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Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.01/A1

Topic: A.01. Neurogenesis and Gliogenesis

Title: Mapping of Neural Progenitors in the Developing Human Hippocampus

Authors: *O. PASTOR ALONSO¹, M. HEFFEL⁴, J. CHU¹, S. LI², M. BAIG⁴, J. HARRIS³, J. GOMEZ⁵, E. J. HUANG⁶, A. ALVAREZ-BUYLLA⁷, C. LUO⁸, M. F. PAREDES⁹;

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Abstract: The human hippocampus (HPC) is a critical brain structure for memory and cognition. Radial glia cells (RGCs) are the foundational neurogenic progenitors that drive the formation of the HPC. However, their cellular features and genetic profiles remain poorly characterized in humans. In this work we sought to define RGCs in the human HPC and map their developmental trajectory. During early gestation, ventricular zone-derived RGCs detached to form the dentate migratory stream (DMS). By mid-gestation, neurogenic populations in the dentate ventricular zone and DMS declined, coincident with the emergence of a diffuse progenitor matrix located between the granule cell layer (GCL) and the hilus, which we term the granular hilar progenitor zone (GHPZ). This final proliferative zone was enriched in immature neurons and RGCs, that start declining after gestational week (GW) 30, paralleling a drop in expression in neurogenic genes and rise in astrocytic transcriptomic signatures. Single-nucleus transcriptomics, across the human HPC from GW 15 to 7 months after birth, identified five subtypes of RGCs. These progenitor groups included a neurogenically primed population (RGC2N), present at mid-gestation but absent thereafter. An astrocytic trajectory was also present from a mid-gestation RGC2A subgroup that transitioned into the RGC3 population that was exclusively present at early postnatal ages. Gene ontology analysis revealed that WNT signaling-associated genes, including the downstream transcription factor LEF1, were enriched in the RGC2A and RGC3 subgroups, suggesting a potential link to neurogenic competence in the human DG. Multimodal spatial transcriptomics showed strong LEF1 expression in the GHPZ during gestation and early postnatal development, which dramatically declined after early infancy, coinciding with the reduction in neurogenesis. Together, these findings reveal the transition of human HPC progenitors from the ventricular zone to a transient hilar-granular matrix, followed by a postnatal depletion of neurogenic capacity and astrocytic fate acquisition. This work provides a developmental blueprint of hippocampal neurogenesis in humans and provides the first demonstration of progenitor states in the human HCX.

Disclosures: O. Pastor Alonso: None. J. Gomez: None. E.J. Huang: None. C. Luo: None. M.F. Paredes: None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.02/A2

Topic: A.01. Neurogenesis and Gliogenesis

Title: Studying cellular diversity of neural progenitors

Authors: *G. GHILONI, F. CREMISI;
Neurosci., Scuola Normale Superiore, Pisa, Italy

Abstract: The neurogenic potential of astrocytes outside the two canonical adult neurogenic niches (the subventricular zone (SVZ) and the subgranular zone (SGZ)) remains a matter of debate. To investigate this potential and the molecular mechanisms involved, we used mouse embryonic stem cells (mESCs) as an in vitro model to recapitulate key stages of corticogenesis, from early neurogenesis to late astrogliogenesis.

We focused on the role of BMP signaling, using fetal bovine serum, a physiological source of BMP4, to modulate pathway activation during defined developmental windows. Exposure to serum during early differentiation stages promoted a shift toward the glial lineage, as shown by an increased proportion of GFAP⁺ cells compared to neurons. Prolonged serum treatment and passaging, enriched the culture in Sox9⁺/Map2⁻ progenitor-like astrocytic cells. Remarkably, these cells retained neurogenic competence, as they were able to differentiate into Map2⁺ and NeuN⁺ neurons upon serum withdrawal or pharmacological BMP inhibition using LDN193189. To assess lineage progression more precisely, we are conducting a longitudinal study based on SATB2/CTIP2 expression ratios, reflecting the balance between upper- and deep-layer cortical neurons. This will be coupled with bulk RNA sequencing of neomycin-resistant progenitors treated at different developmental stages.

Ongoing work includes experiments using spatially controlled Noggin gradients in confined culture systems to further dissect the role of BMP inhibition in regulating astrocyte plasticity. Together, our findings suggest that continuous BMP signaling promotes and stabilizes astrocytic identity but does not eliminate the latent neurogenic potential of astrocyte-like progenitors. This highlights the importance of BMP signaling dynamics in regulating neural lineage competence and provides insights into possible strategies for neural regeneration and reprogramming.

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Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.03/A3

Topic: A.01. Neurogenesis and Gliogenesis

Support: American Lebanese Syrian Associated Charities (ALSAC)
National Institutes of Health (R01NS100939 to YGH)

Title: Investigating the SHH-CDK6 axis in outer radial glia expansion during neocortical folding

Authors: *N. SARODAYA¹, Q. ZHANG², K. M. OLESEN⁴, Y.-G. HAN³;

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Abstract: The remarkable evolutionary expansion of the human neocortex depends on the robust proliferation and diversification of neural progenitors, particularly outer radial glia (oRGs). Despite their pivotal role in cortical growth and complexity, the molecular mechanisms driving oRG expansion remain incompletely understood, limiting our insight into brain development and related disorders. We previously demonstrated that Sonic Hedgehog (SHH) signaling increases both oRG and intermediate progenitor (IP) populations, underscoring its critical role in promoting neocortical progenitor expansion. We also revealed that cyclin-dependent kinase 6 (CDK6) is required for SHH signaling to promote oRG self-renewal through a non-canonical, kinase-independent mechanism. To investigate how CDK6 promotes oRG expansion, we utilized 2D monolayer neural differentiation cultures of human embryonic stem cells, a model where CDK6 mutations disrupted neurogenesis from cortical neural progenitors. Through integrated multi-omic analyses—including ATAC-seq, SLAM-seq, and CUT&RUN—we revealed dynamic, CDK6-dependent transcriptional changes that correlated with chromatin remodeling. These findings suggest that CDK6 regulates chromatin accessibility by binding to the promoter regions of key neurogenic genes. These changes in chromatin accessibility aligned with our bulk RNA-seq and qPCR data, further supporting the functional relevance of these epigenetic modifications. Importantly, mutations in CDK6 cause microcephaly in humans, highlighting its critical, and potentially species-specific, role in cortical development. Collectively, our findings establish a novel SHH-CDK6 axis as a critical regulator of oRG amplification, offering new insight into the molecular control of human neocortical growth and the mechanisms underlying neurodevelopmental disorders.

Disclosures: N. Sarodaya: None. Q. zhang: None. K.M. Olesen: None. Y. Han: None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.04/A4

Topic: A.01. Neurogenesis and Gliogenesis

Support: R21NS129093

Title: Progenitor Competition and Fate Bias in the EGFR-Deficient Mouse Forebrain

Authors: *M. ALIOMRANI¹, X. ZHANG¹, Y. GHAEMI¹, M. OLDHAM², T. GHASHGHAEI¹;

¹Dept. of Mol. Biomed. Sciences, Col. of Vet. Med., North Carolina State Univ., Raleigh, NC;

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Abstract: The transition from neurogenesis to gliogenesis in the developing forebrain is regionally patterned and governed by tightly regulated signaling programs. Our previous studies using Mosaic Analysis with Double Markers (MADM) and conditional Epidermal Growth Factor Receptor (Egfr) mouse alleles demonstrated that EGFR is essential for generating astrocytes and oligodendrocyte precursors in a region-specific manner, particularly in the dorsal forebrain. These findings prompted further investigation into the molecular and cellular mechanisms that govern EGFR-dependent gliogenesis. Here, we used MADM combined with spatially restricted Cre drivers (Nestin-, Emx1-, Nkx2.1-, and Gsx2-Cre) to map the behavior of progenitors in dorsal and ventral domains of the embryonic and early postnatal forebrain. EGFR loss caused a robust reduction in astrocyte and oligodendrocyte production in the dorsal cortex, consistent with a dosage-sensitive requirement for EGFR in gliogenic progenitors. By contrast, ventral and caudal regions retained partial gliogenic capacity, suggesting the presence of EGFR-independent glial sources. Single-cell RNA sequencing at embryonic day 17.5 (E17.5) and postnatal day 5 (P5) revealed a retention of intermediate progenitors and a marked depletion of astrocyte and OPC populations in EGFR-null cortices, accompanied by transcriptional shifts in lineage-biased clusters. In mosaic brains, wild-type progenitors adjacent to EGFR-null cells showed a non-cell-autonomous shift toward astrocyte production, along with upregulation of gliogenic regulators such as Slpr1, Prex1, and Nhs1l. These findings position EGFR as a key regulator of region-specific gliogenesis and reveal how its loss reconfigures progenitor dynamics through both cell-autonomous and non-cell-autonomous mechanisms.

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Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.05/A5

Topic: A.01. Neurogenesis and Gliogenesis

Support: R21NS129093

Title: Egfr_dependent gliogenesis links development to affective behavior

Authors: *Y. GHAEMI¹, M. ALIOMRANI², T. GHASHGHAEI³;

¹Dept. of Mol. Biomed. Sciences, Col. of Vet. Medicine, North Carolina State Univ., RALEIGH, NC; ²Dept. of Mol. Biomed. Sci., North Carolina State Univ., RALEIGH, NC; ³CVM-MBS, North Carolina State Univ., Raleigh, NC

Abstract: We recently showed that a Nes:Egfr-null mouse (the epidermal growth factor receptor, EGFR, is deleted in Nestin⁺ neural stem and progenitor cells) is required for perinatal gliogenesis in a region-specific manner. We identified region-specific glial depletion in circuits such as the cingulate cortex, which modulates approach-avoidance behaviors; the insular cortex, which is responsive to both appetitive and aversive odors; and the lateral and ventromedial nuclei of the hypothalamus, which are involved in mediating odor-induced fear responses. Here we show that EGFR-dependent gliogenesis shapes the development of forebrain circuits critical for reduced exploratory activity and diminished responses to aversive olfactory stimuli. High throughput and AI-aided CFOS mapping following exposure to the predator odor TMT (2,4,5-trimethylthiazoline) reveals blunted activation in forebrain regions critical for fear and salience processing. We discuss our postulate that aversive stimuli may be processed through developmentally early, hard-wired circuits, whereas appetitive odor learning may rely more heavily on later developing or plastic networks. The Nes:Egfr-null model thus provides a tractable platform to dissect how glial-neuronal interactions during early development influence long-term circuit function and sensory-driven behaviors.

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Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

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Program #/Poster #: PSTR148.06/A6

Topic: A.01. Neurogenesis and Gliogenesis

Support: SFI-AN-AR-Pilot-00010018

Title: Transcriptional profiling of mouse midline glial populations required for corpus callosum development

Authors: *E. HOSSEN, J. W. LIM, N. MUNDELL, S. PAL, L. J. RICHARDS;
Neurosci., Washington Univ. in St. Louis, Saint Louis, MO

Abstract: Corpus callosum dysgenesis (CCD) occurs in approximately one in 4,000 human live births and is associated with developmental delay, intellectual disability, and autism spectrum disorder. Previous work has demonstrated that this disorder arises because of defects in the developmental interhemispheric remodeling of the cerebral midline that occurs at gestational week 12 in humans and embryonic day (E) 14 in mice. Interhemispheric remodeling is mediated by specialized astroglia and early neuronal populations of the medial septum. The underlying molecular mechanisms that drive the differentiation of these cell types and their role in corpus

callosum development are largely unknown. Therefore, we utilized single-cell RNA-sequencing (scRNA-seq) of the mouse embryonic midline between E14 and E17 to characterize these populations. To ensure that rare cell types are represented in our dataset, we labeled midline glial populations using intraperitoneal injections of tamoxifen in GLAST-CreER; Ai9 tdTomato transgenic mice. Utilizing fluorescence-activated cell sorting (FACS), we enriched for these rare cell types and performed scRNA-seq on these glial populations along with other tdTomato-negative cell types within this region. Our ongoing analyses have identified cell clusters corresponding to different midline cell types and revealed novel markers for these populations. We also identified ligand-receptor interactions between different cell types that could underlie their function in callosal development. Whilst further studies are required to understand the significance of these interactions, our dataset represents the first developmental atlas of the mouse embryonic midline and contributes to our understanding of these midline cell populations in corpus callosum development.

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Poster

PSTR148: Glial Development

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.07/A7

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH RM1MH138309

Title: Light sheet fluorescence microscopy-based 3D atlas of early postnatal mouse brains to examine emergence of mature oligodendrocytes

Authors: *I. E. BJERKE, J. K. LIWANG, J. PI, L. STAEBELL, Y. KIM;
Penn State Univ., Hershey, PA

Abstract: Developmental 3D mouse brain atlases serve as key spatial framework to quantify and analyze cellular features across the whole brain with cellular-resolution data acquired from light-sheet fluorescence microscopy (LSFM). Previously, we established early postnatal developmental atlas (epDevAtlas) using serial two-photon tomography¹. However, using the epDevAtlas for LSFM data analysis has been challenging due to contrast differences between imaging modalities and deformations caused by clearing techniques. To meet this challenge, we created a set of developmental LFSM based atlas covering every other postnatal day from birth to two weeks of age (P0-P14), and the adult (P56). Brains were cleared using the SHIELD method and imaged with a SmartSPIM microscope using a 3.6x objective lens. Brains were acquired with different cellular markers (e.g., NeuN, Sytox) to facilitate registration to existing atlas templates of different modalities. First, we created symmetric, population-average templates for the different ages using the ANTs registration toolkit². Then, we spatially

registered an average Nissl template³ to our P56 LSFM-NeuN template, thereby importing the CCFv3a annotations into LSFM space. Next, we used iterative registration between temporal neighbors in our template set, achieving a developmental LSFM atlas with dense temporal sampling for the early postnatal stage. Lastly, we validated our anatomical labels using different cell type markers. To demonstrate the utility of the atlas, we quantified mature oligodendrocytes across the brain using MOBP-EGFP mice from different early postnatal time points. We detected GFP positive cells using a deep learning algorithm (Cellpose)⁴, and quantified their distribution across brain regions using our new LSFM based atlas. In summary, our atlas provides an important new resource that will improve both the scale and precision of LSFM data analysis for developing mouse brains.

1. Liwang, J. et al. *epDevAtlas: Mapping GABAergic cells and microglia in postnatal mouse brains*. *bioRxiv* 2023.11.24.568585 (2023) doi:10.1101/2023.11.24.568585. 2. Tustison, N. J. N. et al. *The ANTsX Ecosystem for Mapping the Mouse Brain*. *bioRxiv* 2024.05.01.592056 (2024) doi:10.1101/2024.05.01.592056. 3. Piluso, S. et al. *An extended and improved CCFv3 annotation and Nissl atlas of the entire mouse brain*. *Imaging Neuroscience* **3**, (2025). 4. Pachitariu, M. & Stringer, C. *Cellpose 2.0: how to train your own model*. *Nat Methods* **19**, (2022).
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Poster

PSTR148: Glial Development

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NINDS T32 (NS007473-22)
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AHA Predoctoral Fellowship #902506
Pappendick Translational Research Program Award

Title: Choroid plexus secreted factors support myelination

Authors: *A. HOCHSTETLER¹, L. BYER¹, H. XU², Y. COURTNEY³, B. FUSS⁴, M. LEHTINEN¹;

¹Pathology, Boston Children's Hosp., Boston, MA; ²Pathology, Harvard Med. School/Boston Children's Hosp., Brookline, MA; ³Harvard Univ., Brookline, MA; ⁴Virginia Commonwealth Univ., Richmond, VA

Abstract: The choroid plexus (ChP) is an essential brain barrier which regulates the composition of cerebrospinal fluid (CSF) and instructs normal brain development. While the roles of several ChP-secreted factors in cortical neurogenesis are known, whether the ChP instructs gliogenesis and postnatal brain maturation is less understood. We hypothesized that the ChP secretes signals in a temporally restricted manner which might influence postnatal glial maturation, and that modifying ChP-secreted glial-instructive signals might serve as a novel therapeutic in cases of glial injury. In this study, we focused on perinatal white matter injury, which may arise from a combination of etiologies, including developmental missteps, hemorrhage, trauma, and infection. We and others found the ChP is a key source of Autotaxin, an enzyme with functions as both a lysophospholipase and in actin remodeling, which helps to promote oligodendrocyte differentiation and maturation. In all studies we utilized either CD1, C57Bl/6J, or mixed CD1 x C57Bl/6J mice, both sexes, matched littermate controls, and applied a combination of molecular biology techniques to address our hypothesis. We assessed the expression of and availability of ChP-ATX and CSF-ATX across development using a combination of molecular techniques. We found that ChP-ATX expression and CSF-ATX abundance was upregulated in postnatal development and that ATX in the CSF was enzymatically active. Using a combination of loss-of-function approaches we found that ChP-ATX is essential for postnatal white matter development in mice. Even one-time CSF-ATX inhibition using a small molecule inhibitor caused changes to the periventricular oligodendrocytes compared to saline injected littermate controls. Using models of hemorrhage-induced demyelination in mice, we observed a pronounced decrease in ChP-CSF-ATX levels and activity. In conclusion, our data demonstrate an important role for ChP-secreted factors influencing postnatal brain maturation. Specifically, ChP-ATX secretion is essential for normal myelination, and harnessing this signaling pathway may hold promise for remyelination treatments in white matter injury.

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Poster

PSTR148: Glial Development

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Program #/Poster #: PSTR148.09/A9

Topic: A.01. Neurogenesis and Gliogenesis

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Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
Rachleff family endowment

Title: Cellular import of myo-inositol: a crucial regulator for myelination

Authors: *S. E. RAISSI¹, M. LILLIS¹, K.-J. CHANG², J. R. CHAN¹;

¹Neurol., Univ. of California, San Francisco, San Francisco, CA; ²Neurobio., Univ. of Texas Med. Br., Galveston, TX

Abstract: Schwann cells form myelin membrane in the peripheral nervous system to facilitate rapid action potential propagation. Myelination requires coordinated transduction of Neuregulin 1-mediated phosphoinositide 3-kinase (PI3K)/AKT signaling in Schwann cells, but it is unclear how this cascade mediates differential effects on Schwann cell fate and function. We propose that the tone of this cascade is dependent on the phosphoinositide precursor myo-inositol, which can be either synthesized or taken up from the extracellular environment via myo-inositol cotransporters. While Schwann cells express low levels of the rate-limiting synthesizing enzyme for myo-inositol, they express high levels of the sodium/myo-inositol cotransporter SMIT1 (slc5a3). We therefore asked whether Schwann cells rely on uptake of extracellular myo-inositol to maintain phosphoinositide signaling and promote myelination. We find that mice lacking myo-inositol uptake via SMIT1 exhibit increased immature Schwann cells, deficient PI3K/AKT signaling, persistent peripheral hypomyelination, and motor abnormalities. This hypomyelination is recapitulated in mice lacking SMIT1 selectively in Schwann cells. Together these data indicate Schwann cell uptake of extracellular myo-inositol via SMIT1 is required for peripheral myelination.

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Poster

PSTR148: Glial Development

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Program #/Poster #: PSTR148.10/A10

Topic: A.01. Neurogenesis and Gliogenesis

Support: RF1MH128876

Title: Spatiotemporal Multi-Omics Reveals Epigenetic Memory and Immune Propagation in Brain Development and Demyelination

Authors: *D. ZHANG;
Yale Univ., New Haven, CT

Abstract: Spatiotemporal gene regulation is critical for brain development and immune response, yet how chromatin accessibility, transcription, and protein output coordinate across tissue remains unclear. We used spatial multi-omics and computational modeling to investigate cortical maturation, myelination, and neuroinflammation in the mouse brain. We profiled brain sections across postnatal stages (P0-P21) and a demyelination model using assays that co-measure chromatin accessibility or histone marks, RNA, and protein expression. To integrate across samples and timepoints, we customized *spatialGlue* for spatial domain alignment. Cell types were annotated by label transfer from single-cell references. Generalized additive models

(GAMs) inferred smooth spatial and temporal dynamics for each molecular layer, enabling high-resolution modeling of regulatory changes. In the cortex, chromatin accessibility at key transcription factors (e.g., *CUX2*, *TBR1*) persisted after RNA and protein levels declined, indicating epigenetic memory in postmitotic neurons. These accessible regions remained spatially restricted to their expected layers, suggesting stable, layer-specific regulatory scaffolds during maturation. In the corpus callosum, we observed a lateral-to-medial myelination wave synchronized with projection neuron development and oligodendrocyte lineage progression. Myelin gene activation followed axonal maturation, highlighting tight spatial coordination between neurons and glia. In lyssolecithin-induced demyelination, we found a coordinated repair response involving OPC proliferation, transient CD11c⁺ microglia activation, and remyelination by day 21. Notably, microglial activation extended well beyond the lesion, revealing long-range propagation of neuroinflammatory signals. These immune dynamics were coupled to region-specific chromatin remodeling and histone mark changes during resolution. Together, our findings reveal how spatial gene regulation shapes neural maturation and injury response. Chromatin accessibility persists as a developmental scaffold, myelination follows spatial neuron-glia coordination, and immune activity unfolds across distributed regions. This integrative framework enables systems-level dissection of regulatory mechanisms in brain development and repair.

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Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant R21NS125464
NIH Grant R01NS123080
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Shriners Hospitals for Children 85113-NCA-23

Title: Astrocytic Sox2 regulates locomotor activity and cognitive function through transcriptional control

Authors: *H. CHEN¹, F. GUO²;

¹Univ. of California, Davis, Sacramento, CA; ²UC Davis, Sacramento, CA

Abstract: Astrocytes play essential role in brain development and function. Astrocyte function is anatomically determined by their complex unique morphology, phenotypically reflected by their membrane properties and Ca²⁺ activity, and molecularly defined by their gene expression signature. In response to neurological diseases/injuries, astrocyte transform into reactive

astrocytes, gain neurotoxic and/or neuroprotective functions, and modulate CNS pathophysiology—primarily through transcriptionally regulated gene expression. Our previous studies already proved that Sox2 regulates oligodendroglial development, regeneration, and controls motor coordination. Its function in mature astrocytes remains largely unexplored. To address this, we generated conditional knockout (cKO) mice with astrocyte-specific Sox2 deletion using the Aldh1l1-CreERT2:Sox2^{fl/fl} line induced by tamoxifen. These studies aim to define the role of Sox2 in astrocyte physiology and its contribution to CNS function and behavior. We assessed the mice motor function and spatial learning and memory function by open field test and Barnes maze test. Our preliminary behavioral data demonstrate that Sox2-deficient mice exhibit increased locomotor activity in the open field test and impaired spatial learning in the Barnes maze. Specifically, Sox2 cKO mice traveled significantly longer distances and showed hyperactivity, while also requiring more time to locate the goal box—indicating compromised spatial learning and cognitive performance. To further investigate the underlying mechanisms, 1) We will assess hippocampal long-term potentiation (LTP) to determine the impact of astrocytic Sox2 loss on synaptic plasticity and memory formation. 2) We will employ Cre-loxP-based ribosome-tagging (RiboTag) combined with RNA sequencing to analyze astrocyte-specific gene expression changes following Sox2 deletion. Sox2 cKO-RiboTag mice (Aldh1l1-CreERT2:Sox2^{fl/fl}:lsl-RiboTag) and control RiboTag mice (Aldh1l1-CreERT2:Sox2^{+/+}:lsl-RiboTag) will be generated for this purpose.

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Poster

PSTR148: Glial Development

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Program #/Poster #: PSTR148.12/A12

Topic: A.01. Neurogenesis and Gliogenesis

Title: Glia at motor nerve endings and neuromuscular junctions originate from the same precursor cell

Authors: *R. HASTINGS¹, G. VALDEZ²;

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Abstract: Perisynaptic Schwann cells (PSCs) are critical for the maturation, regeneration, and long-term function of the neuromuscular junction (NMJ). While previous research efforts have shown that PSCs become molecularly distinct from other Schwann cells (SCs) as the NMJ matures, the identity of the progenitor SC from which PSCs emanate remains unknown. To answer this question, we used a stochastic multi-color fluorescent lineage tracing approach to label PSC progenitors in embryonic, newborn, juvenile and adult mice. We then examined PSCs and myelinating Schwann cells (mSCs) in the muscles of the mice in adulthood. We found that when the fluorescent lineage tracer was activated at the embryonic or newborn stage, all PSCs and the last few mSCs leading to an NMJ were the same color. This observation strongly

suggests that both PSCs and adjacent mSCs on the innervating axon are derived from the same progenitor SC. Starting lineage tracing progressively later in life, from the early juvenile to adult stage, led to fewer PSCs and adjacent mSCs sharing the same fluorophore. Thus, precursor SCs associated with NMJs appear to give rise to all future PSCs as well as adjacent mSCs on innervating motor axons. These findings have implications for understanding the role of precursor SCs in the proper maturation of NMJs and their innervating motor nerve endings.

Disclosures: R. Hastings: None. G. Valdez: None.

Poster

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Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant NS127432

Title: Identifying a Combinatorial Regulatory Network for Non-myelinating Schwann Cells

Authors: A. J. HANSON¹, R. RAMESH², D. WANG⁴, *J. P. SVAREN³;

¹Cell. and Mol. Pathology, ²Waisman Ctr., ³Univ. Wisconsin-Madison, Madison, WI;

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Abstract: There are two main types of Schwann cells in the peripheral nervous system—myelinating and non-myelinating. Radial sorting of axons in nerve development results in formation of 1) myelinating Schwann cells that ensheath larger diameter axons, and 2) non-myelinating Schwann cells that form Remak bundles of smaller diameter sensory axons. Formation of Schwann cells is coordinated by a network of transcription factors, that are expressed during certain stages of development to determine cell fate. For example, SOX10 is a transcription factor expressed from the neural crest through mature Schwann cells; it regulates formation of both nonmyelinating and myelinating Schwann cells. A previous study in our lab found Schwann cell-specific SOX10 bound enhancers to be co-enriched with binding sites for nuclear receptor motifs. Two transcription factors in the nuclear receptor family, NR2F1 and NR2F2, are expressed throughout Schwann cell development from neural crest through mature Schwann cells. The siRNA-mediated knockdown of *Nr2f1* and *Nr2f2* in primary Schwann cells revealed downregulation of several important non-myelinating Schwann cell genes. We tested the colocalization of SOX10 with NR2F2 by using Cut&Run assays, and the resulting colocalization of SOX10 and NR2F1/NR2F2 at active enhancers suggests that they work combinatorially. We also found that NR2F2 is primarily expressed in nonmyelinating Schwann cells using immunohistochemistry. Therefore, the combinatorial action of NR2F1/2, SOX10 and other transcription factors may regulate a set of non-myelinating Schwann cell genes that are distinct from myelinating Schwann cell genes. Since transcription factors that maintain the non-myelinating Schwann cell phenotype are poorly understood, we propose a novel combinatorial

regulatory network involved in the development and maintenance of non-myelinating Schwann cells.

Disclosures: **A.J. Hanson:** None. **R. Ramesh:** None. **D. Wang:** None. **J.P. Svaren:** None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.14/A14

Topic: A.01. Neurogenesis and Gliogenesis

Support: California Institute for Regenerative Medicine (CIRM) [EDUC4-12802]
NINDS R01NS126981

Title: Fetal oligodendrocyte precursor cells development is disrupted by inflammation via prostaglandin-dependent mechanisms

Authors: ***H. HORACKOVA**, J. CROSTHWAIT, Y. LIU, D. PHAM-CHANG, A. BONNIN;
Dept. of Pathology and Lab. Med., Univ. of Southern California, Children Hosp. Los Angeles,
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Abstract: Maternal immune activation (MIA) is associated with increased risk of neurodevelopmental disorders, including cerebral palsy in offspring. Our recent data demonstrated that MIA triggered in pregnant mice by the viral mimetic poly(I:C) alters blood-brain barrier (BBB) formation and increased perivascular localization of microglia via prostaglandin-dependent mechanisms at gestational day (GD)15. Prenatal oligodendrocyte precursor cells (OPCs) migrate along blood vessels, suggesting a close interaction between vascular development and oligodendrogenesis.

We hypothesized that MIA-induced BBB alteration might disrupt this interaction resulting in abnormal oligodendrogenesis. Pregnant mice were injected with poly(I:C) on GD13. Fetal (GD15) and postnatal (PD30) offspring brains were analyzed for vascular, immune, and oligodendrocyte markers. We found that in addition to BBB disruption, MIA induced a decrease of OPCs number in the fetal entopeduncular area (EPN), medial ganglionic eminence (MGE), and striatal subventricular zone (sSVZ). MIA also induced increased number and decreased length of PDGFRa⁺ cellular protrusions throughout the EPN and MGE. By PD30, MIA offspring showed reduced numbers of total OLIG2⁺ and PDGFRa⁺ OLIG2⁺ cells, increased MBP immunodensity in the motor cortex, and significantly increased corpus callosum thickness. These findings suggest that MIA might alter oligodendrogenesis via disruption of fetal BBB formation, with life-long consequences on offspring brain oligodendrocyte function.

Disclosures: **H. Horackova:** None. **J. Crosthwait:** None. **Y. Liu:** None. **D. Pham-Chang:** None. **A. Bonnin:** None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.15/A15

Topic: A.01. Neurogenesis and Gliogenesis

Title: Generation of Vascular Leptomeningeal Cells from hiPSCs Using a Directed Differentiation Approach to Improve Blood Brain Barrier Models In Vitro

Authors: *N. AMINI, A. KOKA, M. BRYANT, K. SEARS, R. PADMANABHAN, J. JENSEN;
Trailhead Biosystems, Beachwood, OH

Abstract: Vascular leptomeningeal cells (VLMCs) are a newly discovered cell population found in the blood-brain barrier (BBB). VLMCs are derived from an ectoderm lineage and express common genes shared with oligodendrocyte progenitors such as OLIG1/2 and PDGFRA, and pericytes such as CD44 and CD146 which makes their identification challenging in mixed populations. The blood-brain barrier (BBB) plays an integral role in regulating the transport of compounds into the brain. Consequently, researchers rely on in vitro BBB models to study drug delivery mechanisms. Mimicking the brain's biological environment in these models is crucial for accurately assessing drug function in the human brain. Until now, VLMCs have not been included in human stem cell-based models of the BBB because of a lack of efficient differentiation protocols. By leveraging the power of High-Dimensional Design-of-Experiments (HD-DoE ®) technology, we have developed a directed differentiation protocol capable of generating VLMCs at scale with high purity. Generated cells initially commit to an ectoderm lineage and glial fate, later differentiating to mature VLMCs. The rigorous characterization of the cells confirmed a signature fibroblast-like morphology, alongside the expression of VLMC specific markers such as DCN, LUM, COL1A1 and expected pericyte markers CD44 and CD146. Using bulk RNA-seq, the gene expression profile of VLMCs was compared to that of committed oligodendrocyte progenitors, confirming the expression of shared genes between the two populations as well as distinct markers for each. Immunocytochemistry analysis also showed specific VLMC proteins are expressed in the cells. The robustness of the protocol was validated on two different hiPSC lines and the novel differentiation protocol was then adapted to large-scale bioreactor manufacturing. Functional performance of cells was also evaluated by investigating VLMC inflammatory responses upon LPS stimulation. Cytokine release analysis revealed that VLMCs release pro-inflammatory cytokines in the first 24 hours post-treatment. Furthermore, TEER measurement assays demonstrated that adding VLMCs to conventional in vitro BBB models can influence cellular barrier function. Making VLMCs available to researchers as an additional cell type in the blood-brain barrier region will greatly enhance our understanding of cell-cell interactions within the developing and mature human brain, and bolster efforts in disease modeling and drug discovery for numerous diseases.

Disclosures: N. Amini: A. Employment/Salary (full or part-time): Employment. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ownership interest. A. Koka: A. Employment/Salary (full

or part-time): Employment. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ownership interest. **M. Bryant:** A. Employment/Salary (full or part-time): Employment. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ownership interest. **K. Sears:** A. Employment/Salary (full or part-time): Employment. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ownership interest. **R. Padmanabhan:** A. Employment/Salary (full or part-time): Employment. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ownership interest. **J. Jensen:** A. Employment/Salary (full or part-time): Employment. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ownership interest.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.16/A16

Topic: A.01. Neurogenesis and Gliogenesis

Support: Grants-in-Aid for Transformative Research Areas (A) (JP23H04161)
Grants-in-Aid for Scientific Research (B) (JP23H02658)
JST FOREST (JPMJFR214C)
Grants from AMED-ASPIRE program (JP23jf0126004)

Title: Stepwise maturation of intraventricular macrophages facilitates their entry into the embryonic pallium

Authors: *H. ASAI, Y. HATTORI;
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Abstract: Microglia, the immune cells in the central nervous system (CNS), play diverse roles not only in the pathological states but also in the physiological contexts throughout different stages of life. During embryonic development, they promote the differentiation of neural lineage cells, eliminate excess neural progenitors via phagocytosis, and modulate vascularization. Recent single-cell transcriptomics studies have revealed notable microglial heterogeneity. However, the processes through which microglia acquire their diversity remain poorly understood. We hypothesize that this diversity arises from the complicated events occurring before and after their colonization of the brain. In mice, microglia originate from the extraembryonic mesoderm in the yolk sac around embryonic day (E) 7.5-8.5 and begin colonizing the brain at approximately E9.5, with their population expanding as development progresses. Our studies have shown that developing microglia follow different routes to colonize the brain. Specifically, we previously reported that a distinct subset of microglia is derived from intraventricular CNS-associated

macrophages (CAMs), which frequently infiltrate the pallium around E12. Using intravital imaging, cell tracking, and fate-mapping approaches, we demonstrated that these intraventricular CAMs are provided from the dorsal mesenchyme and enter the ventricles via the commissural plate (CoP), located in the rostral part of the roof plate. To understand the significance and mechanisms of CAMs taking the mesenchyme-CoP-ventricle route before reaching the pallium, we investigated their properties during their migration along this path. Of note, we found that their progenitors acquire high phagocytic activity as they transmigrate through the CoP, which is rich in apoptotic cells. This suggests that exposure to apoptotic cells primes CAM progenitors with specialized phagocytic properties during their passage through the CoP. We hypothesize that this enhanced phagocytic capacity facilitates the CAM infiltration into the developing pallium, which is densely populated with neural progenitors. Taken together, our findings highlight how migratory experiences influence microglial differentiation. Since the subset of microglia derived from intraventricular CAMs account for approximately 10% of the microglial population in the pallium at birth, this may contribute to the emergence of microglial diversity.

Disclosures: H. Asai: None. Y. Hattori: None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.17/A17

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH grant 5R01DA049514-05

Title: Integration of iMicroglia into cortical forebrain organoids enhances upper cortical neuron proliferation and astrogliogenesis

Authors: *A. R. BONGIOVANNI;

Neurosci. Grad. Group, Univ. of Pennsylvania Perelman Sch. of Med., Philadelphia, PA

Abstract: Microglia are the first glial subtype to interact with the developing neurons in the embryonic central nervous system (CNS), and their role in neurogenesis is well profiled. However, the impact of microglia on gliogenesis remains underexplored. Gliogenesis temporally follows neurogenesis and happens in parallel with neuronal maturation. During gliogenesis, oligodendrocyte precursor cells, astrocytes, and oligodendrocytes are produced in this tightly regulated sequential order. Our laboratory utilizes a region-specific brain organoid that recapitulates the organization of the cortical layers. To achieve regional specificity, organoids are generated from neuroectoderm lineage induced pluripotent stem cells (iPSCs) and molecularly guided towards cortical forebrain identity. Cortical forebrain organoids recapitulate gliogenesis by producing astrocytes and oligodendrocytes after neurogenesis. Microglia arise from the mesoderm and do not occur naturally in these pure 3D cultures of ectoderm lineage cells. Thus, we have optimized a protocol for the integration of induced-microglia (iMG) cells into cortical

forebrain organoids. Thus far, results demonstrate that iMG integrated at both early (organoid age = 50 days) and late (organoid age = 80 days) timepoints increased the expression of the putative astrocyte marker GFAP (early timepoint n=12 p=.0003; late timepoint n=14, p=.0181). Integration of the iMG at the late, but not early, timepoint increased the percent of SATB2+ upper layer cortical neurons (n=14 p=.0099) and increased expression of the astrocyte marker, S100 β (n = 6, p=.0178). The thickness of the stem cell-rich ventricular zone as well as cortical plate thickness were unchanged by the iMG. Overall organoid growth during iMG integration was similar to controls. A microglia signature gene highly implicated in oligodendrocyte development and myelinogenesis, CD11c, is upregulated in iMG exposed to organoids (n=3, p=.0016) in comparison to control iMG without organoid exposure. Additionally, organoid exposure increased IL6 expression (n=3, p=.0404), which is a known bidirectional crosstalk signal between microglia and astrocytes. These early results indicate that microglia may have a robust influence on gliogenesis in the developing CNS that can be modeled using iPSC-derived organoids.

Disclosures: A.R. Bongiovanni: None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.18/A18

Topic: A.01. Neurogenesis and Gliogenesis

Support: Community Choice Financial, Inc. to the laboratory of Elaine Mardis

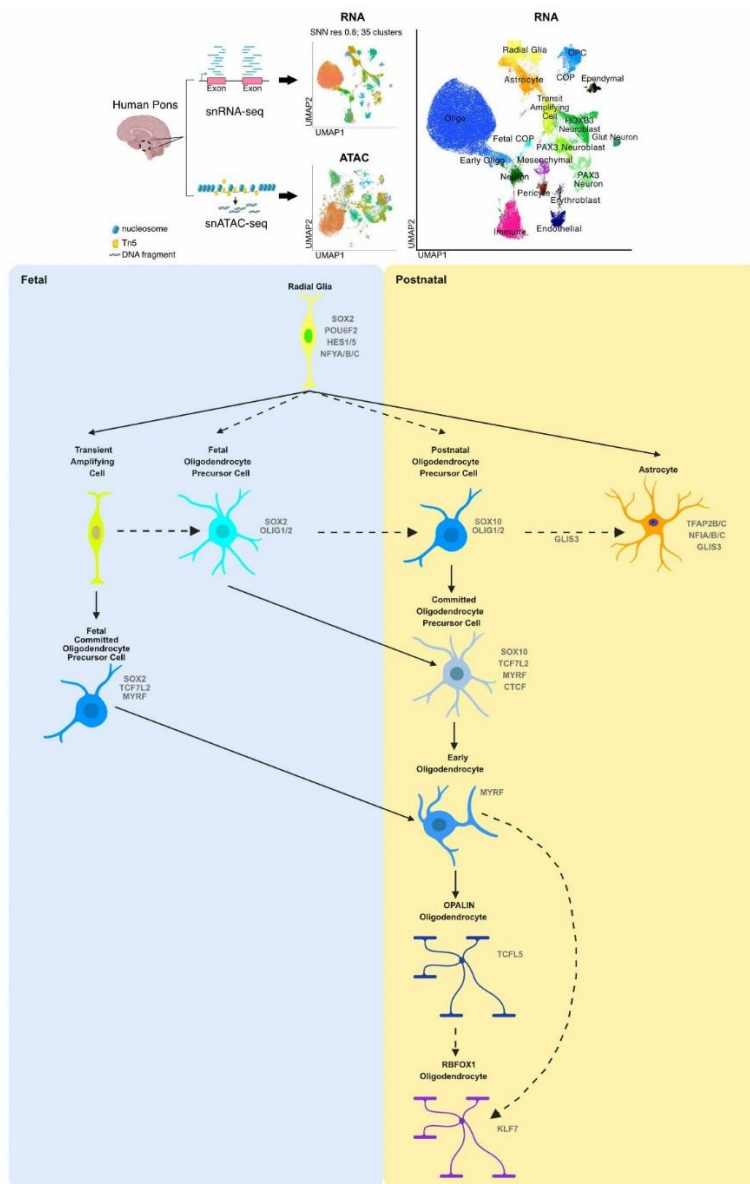
Title: Single Nuclei Multiomic Profiling of the Developing Human Pons Identifies Cell-Type Specific Transcription Factor Patterning

Authors: *T. DING¹, G. SCHWEICKART¹, M. WEDEMEYER²;

¹Steve and Cindy Rasmussen Inst. for Genomic Medicine, Nationwide Children's Hosp., Columbus, OH; ²Nationwide Childrens Hosp. and The Ohio State Col. of Med., Columbus, OH

Abstract: The pons is a relay between the cortex, cerebellum, and the body. The pons is affected by devastating diseases, including diffuse midline gliomas which typically affect children, and multiple sclerosis which predominantly strikes during middle age. Despite a clear relationship between developmental state and disease susceptibility in the human pons, little is known about postnatal pontine development. Here, we present PEDIA-BRAIN, a single nuclei atlas of gene expression and open chromatin assembled from 149,771 nuclei as a reference for normal human pons development. Single nuclei RNA & ATAC sequencing was performed on postmortem pons from 17 human donors ages 0-33 years then combined with publicly accessible single nuclei multiome data from the human fetal hindbrain to generate an encyclopedia of human pons development from the first trimester to early adulthood. Clustering using Harmony, Seurat, and Signac, identified 19 cell types: ependymal cells, radial glia, transit amplifying cells, migrating

neuroblasts, motor neuron lineage cells, astrocytes, oligodendrocyte progenitor, fetal and postnatal committed oligodendrocyte progenitor cells, early oligodendrocytes, mature oligodendrocytes, mesenchymal, immune, endothelial, erythroblasts, and pericytes. Analysis of differentially accessible peaks in each cell type was performed to identify cell-specific enrichment of motifs for regulatory transcription factors. Radial glia are uniquely enriched for YAP1/TEAD binding sites. Astrocytes were enriched for open chromatin with TFAP2B/C binding motifs and a subcluster of astrocytes was characterized by GLIS3 motifs. Accessible chromatin in committed oligodendrocyte progenitors was highly enriched in CTCF, indicative of a period of chromatin remodeling. Clusters of Opalin+ oligodendrocytes were enriched for TCFL5 involved in RNA pol II pausing while RBFOX1+ oligodendrocytes were enriched for KLF7 motifs. Thus, single nuclei multiomic profiling identifies critical transcription factor regulators of cell states in the developing pons.



Disclosures: T. Ding: None. G. Schweickart: None. M. Wedemeyer: None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.19/A19

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF grant 1754513

Title: Structural and functional development of astrocytes in the central nervous system of embryonic zebrafish (*Danio rerio*)

Authors: E. SCOTT, *F. A. ISSA;
Biol., East Carolina Univ., Greenville, NC

Abstract: Astrocytes constitute nearly 40% of the total number of cells in the human brain, and they have been implicated in several neurophysiological roles, including neuroprotection, regulation of neuronal metabolism, maintenance of homeostasis, and synapse formation. However, their structural and functional development remain largely unknown. Here, we used zebrafish as a model organism to map the structural and functional development and innervation pattern of astrocytes during early embryogenesis. Additionally, we characterized how their development is coordinated with the development of dopaminergic system. Zebrafish have emerged as a powerful model organism to study brain function due to flexibility in genetic manipulation, fast embryogenesis, optical transparency that permits prolonged *in vivo* imaging of neural circuits, and a diverse behavioral repertoire that can be readily studied. We generated a double transgenic zebrafish line *Tg(dat:EGFP x slc1a3b:MYRGFP-2A-H2AmCherry)* with targeted expression of mcherry and EGFP fluorescent proteins in astrocyte somata and dopaminergic neurons, respectively, and conducted digital rendering analysis to quantify astrocytes' number and volumetric innervation patterns between 2-7days post fertilization (dpf). Preliminary results show that astrocytes begin development at 2dpf along the dorsal midline of the brain followed by lateral migration of predetermined tracks that envelop specific brain regions by 7dpf. Astrocytes' number increases rapidly between 2-3 dpf, drops by 4dpf, then plateaus between 4-7dpf. This fluctuation correlates with an increase in whole-brain innervation patterns of astrocyte branches. Astrocytes' processes appear to project ventrally with targeted innervation of specific brain nuclei. Notably, astrocytes innervate dopaminergic neurons within the diencephalon and striatum, regions involved in social behavior and spinal motor coordination. *in vivo* calcium imaging using the double transgenic zebrafish line *Tg(elavl3:GCaMP6f x slc1a3b:MYRGFP-2A-H2AmCherry)* with panneuronal expression of GCaMP6f reveals that astrocytes exhibit slower and more gradual calcium dynamics compared to neurons. These differences in calcium signaling highlight the distinct variances and potentially complementary roles astrocytes and neurons play in shaping neural circuit modulation and behavior. The study provides new insights of the structural and functional development of astrocytes and should be of benefit to future studies.

Disclosures: E. Scott: None. F.A. Issa: None.

Poster

PSTR148: Glial Development

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.20/A20

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant 5R35NS105094-08

Title: Transcriptional Control of Astrocytic CEPsh Glia Development in *Caenorhabditis elegans*

Authors: *S. LIU, K. BRADLEY, J. J. TANG, S. SHAHAM;
The Rockefeller Univ., New York, NY

Abstract: Astrocytes are a key glial cell type in the central nervous system, essential for neuronal support, blood-brain barrier regulation, synaptic modulation, and behavioral control. Astrocytes are also implicated in various brain tumors as well as neurological and neurodegenerative disorders. Despite their critical roles, the molecular mechanisms governing astrocyte development remain incompletely understood. The *Caenorhabditis elegans* cephalic sheath (CEPsh) glia are astrocyte-like cells that share anatomical, functional, and molecular similarities with mammalian astrocytes. We leverage the invariant and fully mapped *C. elegans* cell lineage to dissect astrocytic CEPsh glia fate specification at single-cell resolution. Using single-cell RNA sequencing, we generated a lineage-resolved transcriptomic atlas of early CEPsh glia development. We found that CEPsh glia arising from distinct embryonic lineages rapidly converge onto a shared fate within ~1.5 hours after their birth. This convergence is marked by the upregulation of a conserved set of signature genes, many of which—including aquaporins, Na⁺/K⁺-ATPases, and cell adhesion molecules—are also upregulated in developing astrocytes, as revealed by comparative analysis with mouse and human astrocyte developmental atlases. Additionally, we identified conserved transcription factors and components of the Wnt/β-catenin signaling pathway in developing CEPsh glia and their progenitors. These findings underscore the evolutionary conservation of transcriptional programs involved in astrocyte specification. To identify regulators of this shared CEPsh glial fate, we performed a targeted RNAi screen and discovered that the homeodomain transcription factor *ceh-43*, which is expressed across all CEPsh glial lineages, serves as a key determinant of CEPsh identity and function. The mammalian orthologs of *ceh-43*, *DLX1/2*, are established regulators of glia-neuron fate decisions. Through NanoDam, we further identified direct downstream targets of *ceh-43*, including a subset of conserved astrocytic signature genes. These findings suggest that CEH-43/DLX1/2 may participate in a previously uncharacterized transcriptional program that regulates astrocyte development. Together, our findings identify CEH-43/DLX1/2 as a conserved regulator of astrocytic CEPsh glia development and establish *C. elegans* as a powerful model for uncovering principles of astrocyte fate specification across species.

Disclosures: S. Liu: None. K. Bradley: None. J.J. Tang: None. S. Shaham: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.01/A21

Topic: A.06. Developmental Disorders

Support: NIH Grant R01NS094154
NIH Grant R01GM148487
NIH Grant R01AG078794

Title: Neuron-specific overexpression of ACSS2 in mice regulates cellular metabolic cross-talk and influences both animal behavior and neuronal activity

Authors: *T.-L. CHENG¹, F. WU², G. FERNANDEZ-FUENTE³, L. LI², L. PUGLIELLI⁴;
¹Dept. of Med., ²Univ. of Wisconsin-Madison, Madison, WI; ³Uw-Madison Sch. of Med. and Publ. Hlth., Madison, WI; ⁴Med. (Geriatrics & Gerontology), Univ. of Wisconsin Madison, Madison, WI

Abstract: Acetyl-CoA is a versatile molecule involved in energy production, lipid metabolism, and post-translational modification. The acetyl-CoA flux across different cellular compartments such as cytoplasm, mitochondria, nucleus, and endoplasmic reticulum, reflects the metabolic status of cells and serves as a critical regulator of multiple biochemical processes. Cytosolic acetyl-CoA primarily originates from citrate or acetate. Gene duplication events affecting the citrate and acetate pathways are associated with autism spectrum disorder and intellectual disability. Previous studies from our laboratory have revealed that upregulation of the citrate/acetyl-CoA pathway in mice leads to an autistic-like phenotype (PMCID: PMC4925020; PMCID: PMC9014753; PMCID: PMC8823335). To explore the role of the acetate/acetyl-CoA pathway, we targeted Acetyl-CoA synthetase 2 (ACSS2), which converts acetate and CoA into acetyl-CoA. Specifically, we generated mice with neuron-specific overexpression of ACSS2 (ACSS2 nTg). Compared to wild type mice, ACSS2 nTg exhibited reduced locomotion in open field and marble burying tests, along with increased freezing behavior in fear conditioning tests. Cortical neurons from ACSS2 nTg displayed expansion of the somatodendritic compartment with an increased number of dendritic branches. On the multi-electrode array, ACSS2 neurons manifested lower spontaneous activity. Proteomic assessment of the brain revealed widespread changes across multiple pathways, including synaptic transmission, cytoskeleton organization, and mitochondrial function. Taken together, our findings indicate that the acetate/acetyl-CoA pathway can influence metabolic cross-talk across different cellular compartments and regulate neuronal activity and animal behavior, providing a novel molecular mechanism underlying neurological disorders.

Disclosures: T. Cheng: None. F. Wu: None. G. Fernandez-Fuente: None. L. Li: None. L. Puglielli: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.02/A22

Topic: A.06. Developmental Disorders

Support: NIH Grant R01NS094154
NIH Grant R01GM148487
NIH Grant R01AG078794
NIH T32 Biology of Aging and Age related Diseases Training Grant
2T32AG000213-32A1

Title: Overexpression of COASY in the mouse affects both the central and peripheral nervous system

Authors: *S. REID¹, G. FERNANDEZ-FUENTE², L. PUGLIELLI³;

¹Dept. of Med., Univ. of Wisconsin-Madison, Madison, WI; ²UW-Madison Sch. of Med. and Publ. Hlth., Madison, WI; ³Med. (Geriatrics & Gerontology), Univ. of Wisconsin Madison, Madison, WI

Abstract: The endoplasmic reticulum (ER) is important for maintaining proteostasis in the secretory pathway as well as metabolic crosstalk between different intracellular compartments. AT-1 along with SLC25A1 and SLC13A5 maintain the intracellular flux of citrate and acetyl coenzyme A (acetyl-CoA). The COASY protein along with Pantothenic acid produces CoA in the cytosol, which is required for the biosynthesis of acetyl-CoA prior to being transported into the ER by AT-1. Previous models of AT-1 overexpressing mice as well as SLC25A1 and SLC13A5 overexpressing mice have shown autistic-like behavioral phenotypes as well as metabolic responses suggesting that abnormal flux of acetyl-CoA from the cytosol to the ER could be mechanistically related to behavioral and metabolic differences (PMCID: PMC4925020; PMCID: PMC9014753; PMCID: PMC8823335). To expand on these previous findings, we generated two mouse models, one with neuron-specific (nTg) and the other with systemic (sTg) overexpression of the COASY protein. The nTg mice demonstrate many behavioral differences in comparison to wild-type mice, specifically related to locomotion, exploration, and vertical activity. The sTg mice show a clasping phenotype as well as differences in the myelination of axons in the motor branch of the femoral nerve. Overall, our findings indicate that increased production of CoA in the cytosol can affect both the central and peripheral nervous system causing degenerative alterations. They also highlight the fundamental regulatory functions associated with the CoA/citrate/acetyl-CoA pathway.

Disclosures: S. Reid: None. G. Fernandez-Fuente: None. L. Puglielli: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.03/A23

Topic: A.06. Developmental Disorders

Support: International Rett Syndrome Foundation
Pitt Hopkins Foundation
NIH Grant F31MH119699
NIH Grant R01NS112171

Title: Differential mechanism of oligodendrocytes precursor cell and astrocyte maturation mediated by an MeCP2-miR-124 axis in mice modeling Pitt Hopkins Syndrome

Authors: G. ARANTES FREITAS¹, S. D. VERMUDEZ², R. GOGLIOTTI⁴, C. M. NISWENDER³;

¹Pharmacol., Vanderbilt Univ., Nashville, TN; ²Vanderbilt Univ., Waipahu, HI; ³Pharmacol. and Vanderbilt Ctr. for Neurosci. Drug Discovery, Vanderbilt Univ., Nashville, TN; ⁴Loyola Univ. Chicago, Maywood, IL

Abstract: Pitt-Hopkins syndrome (PTHS) is a rare form of autism spectrum disorder and caused by a mutation in the *Transcription Factor 4 (TCF4)* gene on chromosome 18. A known phenotypic overlap between PTHS and Rett syndrome (RTT) indicates that there are possible common signaling pathways between the two disorders. We have found that increasing expression of Methyl CpG Binding Protein 2 (MeCP2), the causative protein in most cases of RTT, can reverse defective behavioral phenotypes found in a mouse model of PTHS (*Tcf4*^{+/-}; Dennys et al., 2024). Additionally, we have found that increasing MeCP2 in the context of *Tcf4* heterozygosity shifts the fate of oligodendrocyte precursor cells to astrocytes. One mechanism that may account for our findings involves the regulation of microRNAs. Among several miRNAs, *miR-124* is known to be regulated by MeCP2 (Jiang et al., 2014; Periyasamy et al, 2018) and is predicted to bind the 3' UTR of both *MECP2* and *TCF4* mRNAs. We generated 4 animal genotypes (WT, *MECP2*^{Tg1/o}, *Tcf4*^{+/-} and *MECP2*^{Tg1/o}; *Tcf4*^{+/-}) and performed RNA-Seq and RT-qPCR, from the PFC, hippocampus, striatum and isolated astrocytes followed by IHC and RNA scope studies for *miR-124*, as well as analysis of oligodendrocyte precursor cells (OPC) and astrocytes. The RNA-Seq identified myelin-associated genes as differentially expressed in *MECP2*^{Tg1/o}; *Tcf4*^{+/-} mice, and IHC results revealed changes of OPC distribution (positive for Olig2), specifically with an increase of immature cells (*Pdgfra*⁺), in *MECP2*^{Tg1/o}; *Tcf4*^{+/-} mice, correlating with a differential increase of astrocyte-related targets, such as Gfap (Glial Fibrillary Acidic Protein). RT-qPCR revealed an overall increase of *miR-124a2* expression in the hippocampus of *Tcf4*^{+/-} mice that was reversed in the *MECP2*^{Tg1/o}; *Tcf4*^{+/-} mice. RNA scope studies showed an increase of *miR-124* in cell nuclei of astrocytes isolated in culture from both *MECP2*^{Tg1/o} and *MECP2*^{Tg1/o}; *Tcf4*^{+/-} mice. Our current results suggest that *miR-124* could be acting altogether with MeCP2 to ameliorate defects caused by *Tcf4* partial deletion,

potentially affecting myelination by OPC differentiation into astrocytes. Further studies are required to determine if *miR-124* is directly contributing to OPCs maturation mediated by MeCP2 overexpression.

Disclosures: G. Arantes Freitas: None. S.D. Vermudez: None. R. Gogliotti: None. C.M. Niswender: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.04/A24

Topic: A.06. Developmental Disorders

Support: NSERC
CIHR
CRC
CFI
ORS

Title: Integrating electrophysiology and proteomics to uncover autism related synapse phenotypes in MDGA2 deficient mice

Authors: *K. PATEL¹, Z. GHASEMI², S. A. CONNOR³;

¹Biol., York Univ., Scarborough, ON, Canada; ³Biol., ²York Univ., Toronto, ON, Canada

Abstract: Autism spectrum disorder (ASD) is characterized by synaptic dysfunction and imbalances in excitation/inhibition (E/I) that impair learning and behavior. MDGA2, a transsynaptic protein that negatively regulates neuroligin-neurexin signaling, has emerged as a candidate ASD risk gene. Here, we combine electrophysiological and quantitative proteomic/phosphoproteomic approaches to investigate how MDGA2 haploinsufficiency (*Mdga2*^{+/-}) alters synaptic plasticity and underlying molecular networks in the adult mouse ventral hippocampus. Preliminary findings show impaired long-term potentiation in *Mdga2*^{+/-} CA1, predominantly in male slices. To further explore the underlying mechanisms that drive this sex-biased phenotype, data-independent acquisition of synaptic proteins and phosphoproteins was performed. Gene ontology enrichment and pathway analysis contextualize dysregulated proteins with various processes, including synaptic vesicle trafficking, gene expression regulation, neuroinflammation, E/I dysregulation, intracellular signaling, and scaffolding and cytoskeletal integrity in male *Mdga2*^{+/-} microdissected CA1. Furthermore, current work is aimed at identifying how female proteomic profiles differ, in an attempt to explain the synaptic basis for male presentation bias in ASD. This research sheds light on physiological impairments underlying ASD phenotypes, while providing insights into changes in synapse protein complement and regulation, which identify multiple nodes for therapeutic intervention. Furthermore, through examining the relationship between sex and ASD, we hope to uncover the

differences in synapse profiles that reduce ASD presentation and severity in females, revealing sex-specific targets for prospective interventions related to MDGA2 haploinsufficiency.

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Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

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Program #/Poster #: PSTR149.05/A25

Topic: A.06. Developmental Disorders

Support: NIH/NIMH Grant F32MH130163
NIH/NIMH Grant R01-MH096847

Title: Syngap1 expression shapes specialized cortical network excitability by either slowing or accelerating the rate of pyramidal neuron subtype maturation

Authors: *R. M. GOLOVIN^{1,2}, S. MICHAELSON², M. ACETI², S. BUTZ^{1,2}, C. ROJAS², D. G. BALAZSFI², J. CHRISTENSEN², T. K. CRESO², C. PAN², T. VAISSIÈRE², C. A. MILLER³, G. RUMBAUGH²;

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Abstract: During mammalian postnatal brain development, a balance must be struck between establishing fully functional networks and restructuring circuits based on the animal's unique environment. One route to accomplish this balance is to establish regional and cell-type specific developmental programs such as the relatively rapid maturation of posterior sensory networks coincides with the relatively slower maturation of anterior motor/movement networks. However, little is known about how this asynchronous development is genetically established or how it impacts adult network-level function. To address these questions, we used a combination of neuronal tracing, single-cell electrophysiology, widefield calcium imaging and quantitative videography to probe the intellectual disability, epilepsy and autism spectrum disorder risk gene, *Syngap1*, across a variety of posterior sensory and frontal associational/motor cortical regions. We find in mice that *Syngap1* expression accelerates the maturation of L2/3 pyramidal neurons (PNs) within primary sensory cortices (SS-bfd and V1) while at the same time delaying the maturation of L2/3 PNs within frontal and associational regions (mPFC and RSP). Within *Syngap1* conditional KO mice, sensory L2/3 PNs show cell-autonomous under elaborated dendritic tree and reduced excitability while in contrast frontal L2/3 PNs show cell-autonomous overelaborated dendritic trees and hyperexcitability. These cellular level developmental alterations of PN subtypes predicted altered specialized network functionality in adult animals. Compared to their littermates, *Syngap1* heterozygous mice have diminished cortical sensory network function following either tactile or visual stimulation. However, these same mutant mice also display elevated neural activity during sensory-independent spontaneous movements within

their frontal motor/movement network. Surprisingly, the level of network activity was relatively balanced across *Syngap1* heterozygous mice and control animals during sensory driven body movements. Together these results highlight cell-type specific maturational effects of an important neurodevelopmental gene and suggest that *Syngap1* may be a central player in establishing proper heterochronic development across cortex by balancing excitability within specialized posterior sensory and anterior/frontal motor/movement networks.

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Poster

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Topic: A.06. Developmental Disorders

Support: NIH-FIC K43TW011920
NIH R01ES010563

Title: Neurodevelopmental sequelae of nickel and manganese in NRXN/NLGN deficient *Caenorhabditis elegans*

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Abstract: Loss-of-function mutations in the *neurexin* (*NRXN*) and *neuroligin* (*NLGN*) families of genes have been established to cause autism spectrum disorder (ASD). However, genetic alterations do not fully account for autism etiology, with the environment considered a major contributing factor. Metals, including nickel (Ni) and manganese (Mn), are prevalent environmental toxicants worldwide that have been strongly linked to ASD pathogenesis. Hence, in the present study, we investigated the impact of *NRXN* and *NLGN* loss-of-function mutation on neurodevelopmental deficits and behavioral phenotypes following Mn and Ni exposures, leveraging a simple, innovative, and affordable invertebrate model, *Caenorhabditis elegans*. Here, we utilized wildtype (N2) worms, as well as worms with loss-of-function in *nrx-1* and *nlg-1* (the worm homologs to human *NRXN* and *NLGN*, respectively). Age-synchronized larval stage-1 worms (N2, *nrx-1*, and *nlg-1*) were treated with Mn and Ni for 1 hour, after which survival and developmental rates were assessed, as well as behavioral patterns and mitochondrial health. Results showed increased sensitivities to Mn and Ni in both strains. Mutant strains also showed a dose-dependent increase in developmental delays when compared to N2, which is exaggerated upon metal exposures. We also report hyper-locomotor activity and increased rate of

body reversal in the *nrx-1* strain, which is indicative of hyperactivity and repetitive behaviors, which was influenced by metal treatments. However, the *nlg-1* strains showed reduced body bends (general locomotion) following metal exposures. Also, our results show altered NaCl and ethanol chemotaxis in both *nrx-1* and *nlg-1* strains, indicating dysfunctions in experience-based behavioral responses from perceived sensory neural transmission. Further, we observed increased clumping and bordering, and defective food leaving behaviors, particularly in the *nrx-1* strain, indicating impaired social dynamics, albeit not clearly impacted by exposures to Ni and Mn. Also, we observe a marked increase in MitoTracker Red® CM-H2XROS fluorescence in N2 wildtype worms following Ni and Mn treatments, indicating elevated mitochondria-derived ROS and mitochondrial dysfunction. Ongoing experiments are assessing mitochondrial health in *nrx-1* and *nlg-1* strains, as well as changes to oxidative stress markers, neurotransmitter systems, and whole transcriptomics. Nevertheless, our available results indicate that Mn and Ni exposures exacerbate developmental and behavioral dysfunctions relevant to autism pathologies in *nrx-1/nlg-1* loss-of-function in *C. elegans*.

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Poster

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Topic: A.06. Developmental Disorders

Support: NIH Grant R01HD110556
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Title: Rfx4, an autism spectrum disorder risk gene, regulates cortical neurogenesis synergistically with notch signaling and rfx3

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Abstract: Regulatory Factor X4 (RFX4) is a transcription factor (TF) that has recently been identified as an autism spectrum disorder risk gene, adding to the large number of TFs that are associated with neurodevelopmental disorders (NDDs). Our prior work defined RFX4 and related TF Regulatory Factor X3 (RFX3) as key regulators of human cortical interneuron (cIN) development; however, RFX4 requirements for human cortical development and pathogenic

mutation contributions to NDD etiology remained unknown. To elucidate the requirements for RFX4 during cortical development, we derived human pluripotent stem cell (hPSCs) models with heterozygous or homozygous RFX4 loss of function (LOF) alleles, specified these as telencephalic-like ventrally or dorsally patterned neural progenitors (V-NPCs/D-NPCs) and subsequently differentiated these into cINs and cortical excitatory neurons (cEXs). In both V- and D-NPCs, dose-dependent RFX4 loss of function (LOF) caused spontaneous neuronal differentiation, due to loss of RFX4-mediated pro-neuronal and synaptic gene repression. This altered gene regulation persisted in neurons, after endogenous RFX4 expression declines, suggesting that disrupting neurogenesis alters later neuronal gene expression and function. We also identified a regulatory relationship between RFX4 and RFX3, with RFX3 requiring RFX4 to bind and regulate synaptic genes in D-NPCs, highlighting potential convergent mechanisms by which RFX3 and RFX4-associated pathogenic mutations may contribute to NDD etiology. We also identified a synergistic relationship between RFX4 and NOTCH signaling, with loss of both additively increasing neuronal and synaptic gene expression, suggesting coordinated regulation of NPC maintenance and neuronal differentiation. Finally, we found that an hPSC model with a homozygous pathogenic mutation in the RFX4 DNA-binding domain exhibited loss of RFX4 genome binding resembling RFX4 homozygous LOF, with subsequently altered gene expression. Together, this work defines RFX4 requirements for human cortical development and identifies convergent RFX3 and RFX4 roles in regulating this process. The identification of shared NDD-associated endophenotypes will both inform our understanding of the etiology of RFX-associated NDDs and provide platforms for developing treatment strategies.

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Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

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Topic: A.06. Developmental Disorders

Title: Mitochondrial DNA Alterations and Exosomal Properties in Autism Disorder: Insights from Cybrid Cell Line Models

Authors: *N. P¹, M. JEEJO¹, M. T. VARGHESE², P. R. HOF³, K. P. MOHANAKUMAR¹, U. RAJAMMA¹;

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Abstract: Autism spectrum disorder (ASD) is a group of neurodevelopmental conditions characterized by deficits in social communication and the presence of repetitive behaviors. Despite a marked increase in ASD prevalence over the past thirty years, the mechanisms

underlying its pathogenesis and the development of effective therapeutic strategies remain poorly understood. Recent research has highlighted the potential impact of mitochondrial DNA (mtDNA) alterations on cellular functions, particularly with oxidative stress, apoptosis, and energy metabolism, key factors in neurodevelopmental disorders. This study aims to investigate the role of mtDNA in the exosomal characteristics of ASD cybrid cell lines. Cybrid cell lines were produced by fusing rho0 cells lacking mtDNA from the SH-SY5Y neuroblastoma cell line with platelets derived from neurotypical individuals and those with ASD. The successful generation of cybrids was validated through long-template PCR, PicoGreen staining, and next-generation sequencing (NGS). We assessed mitochondrial functions in these cybrid cell lines by measuring activities of mitochondrial complexes and analyzing the expression of both mitochondrial and nuclear-encoded genes. Exosomes were isolated using ultracentrifugation, and their characteristics were evaluated through dynamic light scattering (DLS) techniques, with the exosomal marker flotillin-1 confirmed via Western blot analysis. Eighteen cybrid lines of ASD (n=9) and controls (n=9) were established, revealing altered mitochondrial complex I and II activities between ASD and control cybrids. Notably, the expression of ATP6 was elevated in ASD cybrids, while the nuclear-encoded genes NDUFS5 and NDUFS3 exhibited downregulation. DLS analysis indicated that exosomes from ASD cybrids were significantly smaller than those from neurotypical controls, though no differences in zeta potential or polydispersity index were observed. This study elucidates the relationship between mtDNA alterations and the characteristics of exosomes in ASD, highlighting impaired mitochondrial function, altered gene expression, and distinctive exosomal properties. These results provide novel insights into the cellular and molecular mechanisms underlying ASD.

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Poster

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Title: Loss of Katnal2 leads to ependymal ciliary hyperfunction and autism-related phenotypes in mice

Authors: K. KIM¹, *Y. JUNG², E. KIM³;

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Abstract: Autism spectrum disorders (ASD) frequently accompany macrocephaly, which often involves hydrocephalic enlargement of brain ventricles. *Katnal2* is a microtubule-regulatory protein strongly linked to ASD, but it remains unclear whether *Katnal2* knockout (KO) in mice leads to microtubule- and ASD-related molecular, synaptic, brain, and behavioral phenotypes. We found that *Katnal2*-KO mice display ASD-like social communication deficits and age-dependent progressive ventricular enlargements. The latter involves increased length and beating frequency of motile cilia on ependymal cells lining ventricles. *Katnal2*-KO hippocampal neurons surrounded by enlarged lateral ventricles show progressive synaptic deficits that correlate with ASD-like transcriptomic changes involving synaptic gene downregulation. Importantly, early postnatal *Katnal2* re-expression prevents ciliary, ventricular, and behavioral phenotypes in *Katnal2*-KO adults, suggesting a causal relationship and a potential treatment. Therefore, *Katnal2* negatively regulates ependymal ciliary function, and its deletion in mice leads to ependymal ciliary hyperfunction and hydrocephalus accompanying ASD-related behavioral, synaptic, and transcriptomic changes.

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Poster

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Support: This work was supported by the National Science Centre, Poland under research project: OPUS 2023/51/B/NZ4/00856

Title: Neurobehavioral and metabolic alterations in TRAP1 mutant mice: a mitochondria-linked model of autism

Authors: *B. KUZNIEWSKA, D. MALICKA, A. STAWIKOWSKA, M. DZIEMBOWSKA; Lab. of Mol. Neurobiology, Fac. of Biol., Univ. of Warsaw, Warsaw, Poland

Abstract: There is increasing evidence of mitochondrial dysfunction in autism spectrum disorders (ASD), but the causal relationships are unclear. In an ASD patient whose identical twin was unaffected, we identified a postzygotic mosaic mutation p.Q639* in the *TRAP1* gene, which encodes a mitochondrial chaperone of the HSP90 family. Additional screening of 176 unrelated ASD probands revealed an identical *TRAP1* variant in a male patient who had inherited it from a healthy mother. We generated knock-in *Trap1* p.Q641* mice that revealed ASD-related behavioral abnormalities that are more pronounced in males. Accordingly, *Trap1* p.Q641*

mutation also resulted in sex-specific changes in synaptic plasticity. To investigate mitochondrial metabolism in the synapses of Trap1 mutant mice, we performed functional mitochondrial phenotyping of cortical and hippocampal synaptoneurosomes using Mitoplasts (Biolog). We identified altered utilization of tricarboxylic acid (TCA) cycle substrates in Trap1 mutant males, but not in females. Specifically, we observed decreased usage of succinate, the substrate for complex II and increased consumption of pyruvate + malate, substrates for complex I. In addition, we performed high-resolution respirometry of brain mitochondria using O2k Oxygraph (Oroboros). Similarly, we found that in the presence of pyruvate, glutamate and malate, the mitochondria from Trap1 mutant mice respired at a significantly higher rate than the WT mitochondria. Next, targeted metabolomics was performed to quantify amino acid levels in the brains of Trap1 mutant and wild-type (WT) mice. Preliminary data suggest that glutamate and GABA levels are decreased in the hippocampus of male mutant mice, but not in females. Finally, levels of NAD⁺/NADH were measured in the hippocampi of Trap1 WT and mutant mice as indicators of energetic and redox state. Increased NAD⁺/NADH ratio was observed in the hippocampi of Trap1 mutant male, but not female mice. Altogether, our results support the previously observed link between dysregulated mitochondrial metabolism and ASD. Moreover, our findings highlight the need for in-depth analysis of both males and females in mouse models of ASD. This work was supported by the National Science Centre, Poland under research project: OPUS 2023/51/B/NZ4/00856

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Poster

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Topic: A.06. Developmental Disorders

Support: BICAN : R01MH134809
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CHAMP1 : R01HD113594

Title: Genomic profiling of patient-derived CHAMP1 cortical forebrain organoids reveals disrupted neurodevelopmental trajectories

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Abstract: CHAMP1 disorder is an ultra-rare autism spectrum disorder(ASD) like neurodevelopmental condition characterized by intellectual disability, behavioral challenges, and medical comorbidities. Chromosome Alignment Maintaining Phosphoprotein 1 (CHAMP1) encodes for a highly conserved zinc finger protein which has been implicated in mitotic function

and neurodevelopment, including downstream effects such as DNA repair and neuronal migration. To investigate the neurodevelopmental mechanisms disrupted by CHAMP1 loss of function, we generated cortical forebrain organoids from human induced pluripotent stem cell (iPSC) lines harboring a nonsense mutation (c.1489C>T), a frameshift mutation (c.2094delT), a complete CHAMP1 knockout (K3 Champ1^{-/-}), and two neurotypical control lines (K3, 20b). Organoids were cultured and sampled at thirty-day intervals, from days in vitro (DIV) 30 to DIV120. Using single-nuclei RNA sequencing (snRNA-seq), we comprehensively characterized the transcriptional landscapes, cell type diversity, and trajectories of neuronal maturation along a comparable pseudotime axis across genotypes. Our analysis revealed mutation-specific and shared disruptions in gene expression and cellular composition relative to neurotypical controls. Notably, we identified significant transcriptional alterations in genes and pathways involved in synaptogenesis, neuronal maturation, and synaptic transmission, indicating compromised formation and function of synaptic networks. These findings implicate CHAMP1 in the regulation of key neurodevelopmental processes and provide mechanistic insights into how loss of function contributes to neurodevelopmental disorders.

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Poster

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Topic: A.06. Developmental Disorders

Support: Icahn School of Medicine

Title: Exploring Kizuna overexpression as a potential ASD risk factor

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Abstract: Background: The protein Kizuna, encoded by the *KIZ* gene, is essential for centrosome stability during cell division, crucial for neural and cortical development. Our single-nucleus transcriptome and epigenome analysis linked neuronal *KIZ* overexpression to Autism Spectrum Disorder (ASD). Thus, we hypothesize that *KIZ* overexpression during neural development increases ASD risk.

Methods: *In vitro*, primary mouse cortical neurons were transfected with either *pLV-CBh-Scramble* or *pLV-CBh-Kizuna*, an overexpression lentivirus for *mKiz*. Immunofluorescence validated Kizuna upregulation. To dissect the functional role of Kizuna overexpression, P0 neonates received intracerebroventricular (ICV) injections of either *pLV-CBh-Scramble* or *pLV-*

CBh-Kizuna. After three weeks, patch clamp recordings were performed on EGFP-positive pyramidal neurons in cortical layers II-III. To further demonstrate the long-term consequences of Kizuna overexpression, LSL-dCas9p300 mice were injected with *PHP.eB-sgKiz-BFP* or *PHP.eB-sgNTC-BFP* along with neuron-specific Cre via ICV delivery. qRT-PCR confirmed elevated *Kiz* mRNA in *PHP.eB-sgKiz-BFP* mice, confirming successful transcriptional activation.

Results: Kizuna overexpression disrupts neurite development in primary neurons, reducing synaptic branching and extension in *pLV-CBh-Kizuna*-expressing cells. Moreover, anti-Kizuna fluorescence intensity negatively correlated with neurite length, emphasizing Kizuna's essential role in dendrite formation and synapse development through cytoskeletal regulation. Electrophysiological recordings showed that neurons with Kizuna overexpression fired over twice as many action potentials, indicating neuronal hyperexcitability. Our findings point to a simplified dendritic architecture, where reduced membrane integration lowers the threshold for repetitive firing. Mice injected with *PHP.eB-sgKiz-BFP* showed a significant reduction in brain and body weight, accompanied by motor deficits, pointing to disrupted neurodevelopmental progression.

Conclusions: *Kiz* overexpression during early neural development in mice disrupts dendrogenesis, impairs synaptic formation, and induces neuronal hyperexcitability. These defects may contribute to neural circuit dysfunction and ASD-related behavioral phenotypes. Future studies using *in utero* gene manipulation may uncover how centrosomal dysregulation contributes to neurodevelopmental disorders like ASD.

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Poster

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Program #/Poster #: PSTR149.13/A33

Topic: A.06. Developmental Disorders

Title: Characterization of an Emx1-Cre; Wac mouse model during neurodevelopment

Authors: *D. PACHECO CRUZ¹, Z. FERNANDEZ², A. M. STAFFORD³, C. QIAN⁴, D. VOGT⁵;

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Abstract: DeSanto-Shinawi Syndrome (DESSH) is a rare neurodevelopmental disorder caused by mutations in the WW-domain containing adaptor with coiled-coil (Wac) gene. DESSH presents clinically with cognitive and behavioral symptoms that include seizures, autism, ADHD,

and developmental delay. Wac is a high confidence autism risk gene, but vertebrate models to understand the mechanisms underlying its pathology are lacking. Our lab developed a clinically relevant mouse model for DESSH that is a constitutive heterozygous loss of function. This model exhibits susceptibility to seizures, relevant behavioral changes and sex-specific alterations in brain volume. Despite these changes, we were not able to generate a constitutive knockout. Thus, to better understand the role of Wac in cortical development, we have generated an Emx1-Cre conditional model to delete Wac in glutamatergic cortical neurons and glia. Emx1-Cre conditional KOs are viable and exhibit dramatic morphological phenotypes, including agenesis of the corpus callosum, delamination of the hippocampus and microcephaly. Here, we will characterize the molecular, cellular, and morphological phenotypes due to Wac loss of function. Specifically, we will address proliferation, apoptosis, and distinct laminar subtypes in the model, as well as structural changes. Our results will provide a better understanding of the roles of distinct neuronal populations in a mouse model of DESSH.

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Poster

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Topic: A.06. Developmental Disorders

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Title: Elucidating the role of synaptic mitochondria in sex-specific phenotypes of monogenic autism

Authors: B. KUZNIEWSKA¹, M. MAGNOWSKA², A. STAWIKOWSKA², T. WOJTOWICZ³, P. MICHALUK⁴, ***M. DZIEMBOWSKA**²;

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Abstract: Autism spectrum disorders (ASD) are a heterogeneous group of neurodevelopmental conditions affecting approximately 1% of the population, with a pronounced male bias (male-to-female ratio of 4-5:1). Despite intensive research efforts, the etiology of ASD remains poorly understood. Recently we identified a point mutation in the HSP90 family mitochondrial chaperone, TRAP1 p.Q639* in two unrelated male ASD patients (Rydzanicz M., Kuzniewska B. et al., 2024). We generated a corresponding knock-in mouse model, TRAP1p.Q639* mouse (Trap1mut), that displayed social behavior abnormalities. We identified altered dendritic spine morphology and basal synaptic neurotransmission, fewer presynaptic mitochondria and changes in mitochondrial metabolism in the brains of Trap1 mutant mice. Interestingly, observed

symptoms were more pronounced in males than in females. Therefore we focused on studying the properties of synaptic mitochondria in male *Trap1*mut mice. To assess their structural correlates, we performed ultrastructural analyses using transmission electron microscopy (TEM) and serial block-face scanning electron microscopy (SBF-SEM). These revealed synaptic abnormalities and an increased prevalence of mitochondria-lacking presynaptic terminals in male mutants. Complementary functional assays using the genetically encoded mitochondrial calcium sensor mito4x-GCaMP6f indicate impaired calcium buffering in presynaptic mitochondria of male *Trap1*mut mice. Given TRAP1's role in mitochondrial proteostasis, we profiled the synaptic proteomes of male and female TRAP1mut mice. Strikingly, female mutants-but not males-upregulated mitochondrial proteins, including components of respiratory complex I and the mitochondrial import machinery (e.g., Tim22 complex), suggesting a sex-specific compensatory mechanism. In summary, our multidisciplinary approach reveals that TRAP1 loss-of-function disrupts synaptic mitochondrial homeostasis in a sex-dependent manner. These findings implicate mitochondrial proteostasis as a key modulator of synaptic function in ASD and highlight the *Trap1*mut mouse as a valuable model for studying mitochondrial contributions to neurodevelopmental disorders.

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Poster

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Topic: A.06. Developmental Disorders

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Title: Cortical dysgenesis and microcephaly in hiPSC cerebral organoid derived from ddx3x syndrome patients

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¹Neurol., UCSF, San Francisco, CA; ²Loyola Univ. of Chicago Stritch Sch. of Med., Maywood, IL

Abstract: Within the scope of neurodevelopmental disorders, DDX3X syndrome accounts for 1-3% of previously unexplained intellectual disability in females aged under 18 years. As a member of the DEAD box family, the X-linked DDX3X gene encodes an RNA helicase binding protein that expresses various phenotypes of NDD in varying severity and multisystem involvement. Previous research has investigated DDX3X in mice and 2D hiPSC models, but never within hiPSC-derived 3D cerebral layering models. Within this context, we approached investigating DDX3X syndrome via the generation of hiPSC-derived cerebral organoids from three differing discrete mutations of DDX3X, with each patient differing in phenotypic severity

and scope of multiorgan involvement. HiPSC lines (patient and maternal control) were derived from PBMCs and were differentiated into dorsal forebrain organoids. Organoids were analyzed at two different time points, 25 days and 72 days, to investigate the developmental characteristics in both early and mature organoids. Microcephaly was observed within day 25 organoids and continued to deviate in growth towards day 72, in comparison to maternal control organoids. Organoids were sectioned and stained at day 25 and day 72, displaying impaired generation and organization of neuronal progenitor cell populations, and in particular, intermediate progenitor neuronal populations. With this, DDX3X is supported to be a key gene in facilitating early cortical development organization and subpopulation differentiation, which could elucidate an underlying mechanism for microcephaly in patients with DDX3X.

Disclosures: C. Yang: None. C. Bakker: None. E.H. Sherr: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.16/A36

Topic: A.06. Developmental Disorders

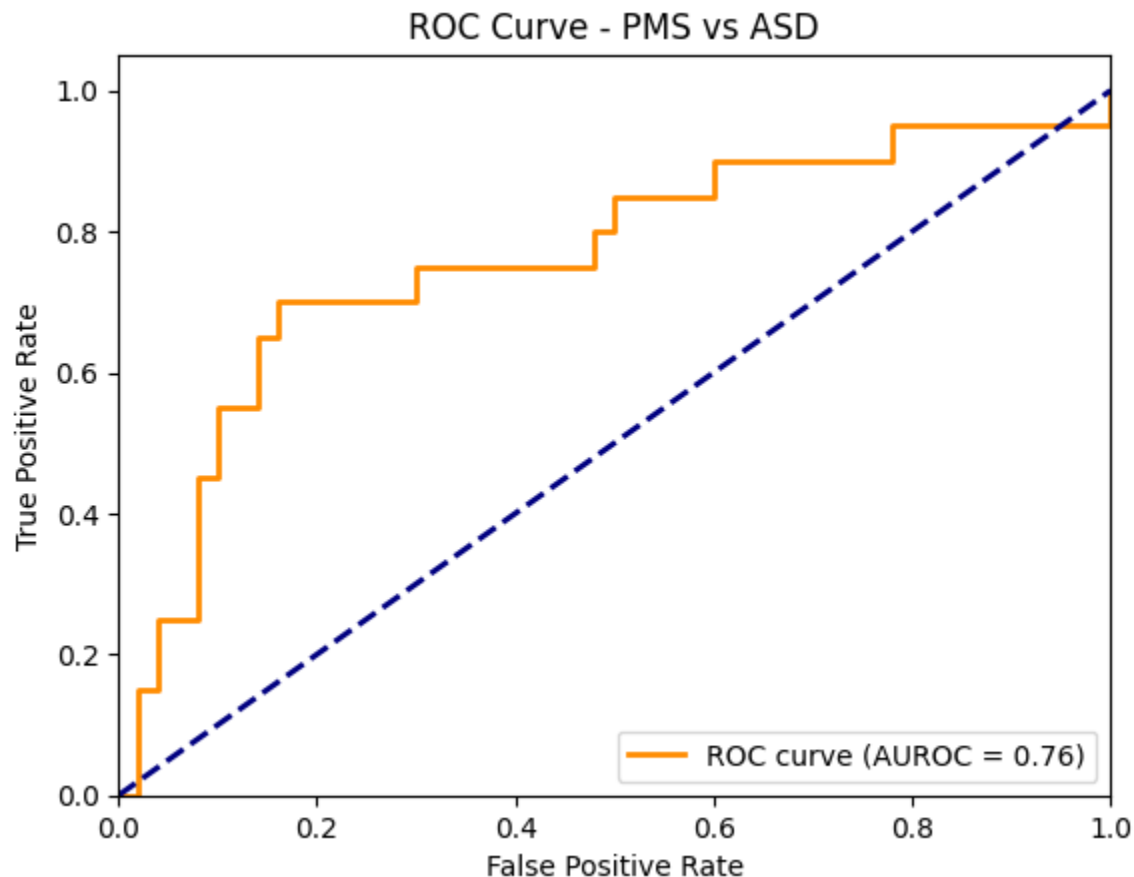
Title: Development of a machine-learning model to differentiate phelan-mcdermid syndrome from autism spectrum disorder using electroencephalogram data

Authors: *S. KOHLI¹, E. S. SCHAFER³, A. KOLEVZON², S. BEKER⁴;

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Abstract: Phelan-McDermid syndrome (PMS) is a rare genetic disorder caused by haploinsufficiency of the *SHANK3* gene on chromosome 22q13.3 which plays an important role in synapse formation and dendritic spine maturation. PMS is among the most common single-gene causes of Autism Spectrum Disorder (ASD), with approximately 60% of PMS patients being diagnosed with ASD. The shared symptomatology includes motor delays, intellectual disability (ID), and impaired or limited language. *SHANK3* mutations may account for up to 2% of individuals with both ID and ASD, and many more cases may remain undiagnosed due to underutilization of genetic testing in the evaluation of ASD. Currently, whole exome sequencing is the diagnostic gold standard but is costly and often inaccessible, delaying diagnosis and limiting access to interdisciplinary care or treatment with novel gene therapies. This study aims to develop a machine learning (ML) model to classify PMS using electroencephalogram (EEG) data to facilitate greater access to molecular genetic testing. EEG data were collected as part of the Rare Diseases Clinical Research Network (RDCRN) consortium using the Auditory Steady State Response (ASSR) paradigm, with a 40Hz auditory stimulus played every 1.1 seconds. Signals were epoched into 1.5 second windows around stimulus onset and transformed using Morlet wavelets to extract power and intertrial coherence features. A support vector machine

(SVM) classifier was trained using a leave-one-out (LOO) approach to classify EEG recordings from PMS and those from ASD. The dataset included 5,821 trials from 50 ASD subjects and 2,187 from 20 PMS subjects. Across all LOO tests, the SVM achieved an area under the receiver operating characteristic curve (AUROC) of 0.76. At Youden's index, the sensitivity was .70, specificity was .84, precision was .63, and F1 score was .67. These findings suggest that EEG-based ML classification may be sensitive to subtle differences in physiological dynamics, and may aid early PMS detection and triage for genetic testing.



Disclosures: S. Kohli: None. E.S. Schaffer: None. A. Klevzon: None. S. Beker: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.17/A37

Topic: A.06. Developmental Disorders

Title: Autism- and Schizophrenia-Associated 3q29 CNV Deletion Drives Transient Hyperproliferation of Neural Precursor Cells During Cortical Neurogenesis

Authors: *X. WANG¹, L. BUCHANAN², X. ZHOU³, S. TOOMEY³, R. M. POLLAK⁴, R. SEBASTIAN⁴, J. G. MULLE⁴, E. M. DICICCO-BLOOM⁵;

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Abstract: The 3q29 deletion is a rare copy number variant that confers increased risk by up to 36-fold for autism spectrum disorder and ~40-fold for schizophrenia. Affected individuals often exhibit delayed development, intellectual disability, and reduced head circumference. To model this deletion, we generated a CRISPR-engineered 3q29 deletion (3q29del) mouse model which displayed a 9% forebrain weight reduction by postnatal day (P) 7, suggesting prenatal origins. We use this model to examine cortical neural precursor cell (NPC) proliferation and underlying mechanisms. Timed-pregnant mice were assessed at E13.5-E16.5. Embryonic cortices were genotyped as 3q29del or wild-type and analyzed via EdU incorporation and immunohistochemistry for Pax6, Ki67, and PH3 to assess proliferation and mitosis. At E14.5 and E15.5, EdU+ cells were elevated in 3q29del embryos (E14.5: 18% increase; $p=0.005$; $N=5$ /genotype; WT from 3 litters, 3q29del from 4 litters; E15.5: 37% increase; $p<0.003$; $N=5-7$ /genotype from 3 litters). No significant differences were observed at either E13.5 or E16.5, indicating a brief window of hyperproliferation. To localize these changes, we divided the cortical wall into 10 horizontal bins extending from the ventricular (bin1) to the pial surface (bin10). EdU+ cells were enriched in bins 2 and 4 in 3q29 deletion embryos ($p<0.03$), which corresponds to the ventricular and subventricular zones (VZ/SVZ) - regions housing actively proliferating NPCs. This enrichment suggested expansion of the proliferative compartment, supported by 15% greater VZ height (Pax6+) and 19% greater VZ/SVZ height (Ki67+). PH3+ mitotic cells were also elevated by 27% at this stage, consistent with NPC hyperproliferation. These findings define a narrow developmental window of transient hyperproliferation in the 3q29del embryonic cortex, which may lead to overproduction of lower layer neurons and disrupt laminar composition. Supporting this, we observed elevated Tbr1+ and reduced Satb1/2+ cells in E15.5 cortical culture in 3q29 group, suggesting a fate bias toward lower layer neuron at the expense of upper layer populations. Ongoing studies assess cell cycle exit and laminar fate markers (Tbr2, Ctip2, Satb2, Cux1) to determine how NPC dysregulation shapes cortical architecture and reduced brain size. Parallel analyses in human cortical organoids with the 3q29 deletion are underway to evaluate conservation of these early mechanisms across species. Taken together, our findings suggest that early disruptions to NPC dynamics alter the trajectory of corticogenesis that may parallel human brain phenotypes in 3q29 deletion carriers and related neurodevelopmental disorders.

Disclosures: X. Wang: None. L. Buchanan: None. X. Zhou: None. S. Toomey: None. R.M. Pollak: None. R. Sebastian: None. J.G. Mülle: None. E.M. DiCicco-Bloom: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.18/A38

Topic: I.05. Working Memory

Support: National Institutes of Health NS127728

Title: Cognitive and synaptic impairment induced by deficiency of Autism risk gene *Smarcc2* and its rescue by Histone deacetylase inhibition

Authors: *P. LI, S. MEN, P. J. PATEL, K. SALEEM, P. ZHONG, K.-W. TAM, Z. YAN;
Physiol. and Biophysics, State Univ. of New York at Buffalo, Buffalo, NY

Abstract: *SMARCC2*, which encodes BAF170, a core subunit of chromatin remodeling BAF complex, is one of the top-ranking risk genes for autism spectrum disorder (ASD). However, the mechanisms linking *SMARCC2* haploinsufficiency to ASD remain poorly understood. *SMARCC2* binds to many other ASD risk genes involved in transcriptional regulation. Knockdown (KD) of *Smarcc2* in prefrontal cortex (PFC) of adolescent mice led to impaired working memory, with largely intact social and anxiety-like behaviors. Genome-wide RNA-seq analysis revealed that the downregulated genes by *Smarcc2* KD were enriched in synaptic transmission. Significant reduction of GABA and glutamate-related genes was also found in PFC of *Smarcc2*-deficient mice by qPCR profiling. In parallel, electrophysiological recordings uncovered the significant impairment of GABAergic and glutamatergic synaptic currents in PFC pyramidal neurons by *Smarcc2* KD. *Smarcc2* binds to HDAC2, and *Smarcc2* KD reduced global histone acetylation and H3K9ac enrichment at synaptic gene *Slc1a3* (EAAT1), *Slc6a1* (GAT1), and *Slc32a1* (VGAT) promoters. Treatment of *Smarcc2*-deficient mice with romidepsin, a class I histone deacetylase (HDAC) inhibitor, restored H3K9ac level, working memory and synaptic gene expression. These findings highlight the critical role of *Smarcc2* in regulating cognitive and synaptic function, suggesting that targeting HDAC could alleviate deficits in *Smarcc2*-associated neurodevelopmental disorders.

Disclosures: P. Li: None. S. Men: None. P.J. Patel: None. P. zhong: None. Z. Yan: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.19/A39

Topic: A.06. Developmental Disorders

Support: NIH Grant K01NS107723
4-VA (Commonwealth of Virginia)
NSF MRI grant DBI-2214633
NSF MRI grant DBI-1725855

Title: Nex1-creERT2 inducible KO of Itgb3 during early postnatal life

Authors: E. VINSON, N. RUSAK, K. JEWELER, A. KALINOWSKI, C. DENZLER, C. GOLDEN, A. DI PIETRO, L. SCOFFIELD, C. LEASE, J.-M. BENEDICT, *G. S. VIDAL;
James Madison Univ., Harrisonburg, VA

Abstract: Autism spectrum disorder and intellectual disability are associated with gene variants for integrin $\beta 3$ (Itgb3), a subunit in the family of integrins, which are classically known as extracellular matrix receptors. Recent evidence from our lab shows that postnatal Itgb3 expression is highest in cortical layer 5 and that it is developmentally regulated within the first 3 weeks of life. Other preliminary data from our lab show that early postnatal behaviors that require somatomotor integration are selectively delayed in conditional Itgb3 KO mice. We utilized the Nex1-CreERT2 driver line to induce conditional KO in excitatory pyramidal neurons localized mainly within cortex and hippocampus. We first characterized the use of the Nex1-CreERT2 driver line in early postnatal ages (P0, P7, and P15) and estimated the timeline of induction by utilizing both a tdTomato Cre reporter line as well as in situ hybridization of Itgb3. Inducible Itgb3 cKO were injected with tamoxifen (experimental group) or vehicle (control group) at P0, P7, or P15, and tested for sensorimotor behaviors that are known to be delayed in the Itgb3 cKO line. Results indicate that, at any early postnatal age, a single injection of tamoxifen causes strong induction of Cre-mediated excision within 3 days. Inducing KO of Itgb3 from excitatory neurons of the cortex and hippocampus during early postnatal life was also shown to delay some sensorimotor behaviors. In sum, we have characterized the Nex1-CreERT2 line during early postnatal life, and also shown that inducible KO of Itgb3 during this period affects behaviors that require sensorimotor integration.

Disclosures: E. Vinson: None. N. Rusak: None. K. Jeweler: None. A. Kalinowski: None. C. Denzler: None. C. Golden: None. A. Di Pietro: None. L. Scoffield: None. C. Lease: None. J. Benedict: None. G.S. Vidal: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.20/A40

Topic: A.06. Developmental Disorders

Support: NIH R01MH116002
NIH RM1MH132648
HHMI Gilliam Fellowship GT16695
NIH R21MH133245

Title: Context-dependent estradiol effects on autism spectrum disorder risk genes

Authors: *A. N. PRUITT¹, L. YANG¹, S. LEE¹, N. BALAFKAN¹, X. LI¹, P. M. DEANS², E. J. HOFFMAN³, K. BRENNAND⁴;

²Psychiatry and Genet., ³Child Study Center, Neurosci., ⁴Psychiatry, ¹Yale Univ., New Haven, CT

Abstract: Autism spectrum disorders (ASDs) are common and complex neurodevelopmental disorders with a well-defined 4:1 male bias in diagnosis, yet the biological basis underpinning the sex bias remains poorly understood. During neurodevelopment, estrogens widely modulate neurogenesis, cellular signaling, gene expression, and neuronal activity. In this study, we tested the hypothesis that the principal biologically active estrogen, 17 beta-estradiol, confers a “female-protective effect” in ASD genetic mutants. Across neural progenitor cells (NPCs) and glutamatergic neurons, we applied CRISPR-based strategies and single-cell RNA sequencing to systematically explore the extent to which 17 beta-estradiol ameliorates the effect of loss-of-function mutations on the transcriptomic landscape across 36 high confidence ASD risk genes. Using in vitro calcium imaging, we assessed how 17 beta-estradiol exposure impacts cell autonomous and network-level glutamatergic neuronal activity in 15 ASD risk genes. Finally, we confirmed the impact of 17 beta-estradiol on extreme discrepancies in rest-wake and visuo-startle behaviors in 3 larval zebrafish genetic mutants. Pooled single-cell transcriptomic analysis revealed that 17 beta-estradiol reversed dysregulated DEGs in 9 overlapping gene mutants between NPCs and glutamatergic neurons, whereas 17 beta-estradiol rapidly ameliorated distinct hypersynchronous patterns of neuronal activity across 5 genes. In zebrafish larvae, we observed rescue of dysregulated sleep patterns in one mutant. Overall, 17 beta-estradiol effects are highly context-dependent, varying across developmental stage and cell type, with genotype-specific impacts on neural gene expression, in vitro neuronal activity, and in vivo behavior in the setting of ASD genetic mutants. This study provides further insight on convergent and divergent gene-by-hormone interactions of functionally diverse ASD risk genes across neurodevelopment, which provides new avenues for therapeutic targets in precision medicine approaches.

Disclosures: A.N. Pruitt: None. L. Yang: None. S. Lee: None. N. Balafkan: None. X. Li: None. P.M. Deans: None. E.J. Hoffman: None. K. Brennand: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.21/A41

Topic: A.06. Developmental Disorders

Title: Modeling the developmental effect of a neuron-specific splicing regulator in human forebrain assembloids

Authors: *H.-Y. CHENG, H.-S. HUANG;
GIBMS, Col. of Medicine, NTU, Taipei, Taiwan

Abstract: RNA splicing regulators play significant roles in neurodevelopment, and are often related to Autism Spectrum Disorder. Although the cellular mechanism remains elusive, few

approaches are available for further investigation in human development due to inaccessibility to primary human tissues. Human cerebral organoids and assembloids provide a potential model for neural circuit formation in the embryonic brain, and therefore serve as a great in vitro platform for human studies. In our work, we adopted a ventral-dorsal forebrain assembloid protocol to study the effect of the regulator's deletion in the human brain. Using a CRISPR/Cas9 edited human iPS cell line with gene-specific nontarget (NT) or homozygous knock-out (KO) edition, we derived the ventral- (vCO) and dorsal-forebrain organoids (dCO). First, we AAV-labelled the vCO and contact them with the homogenic dCO in a stationary condition, creating a ventral-dorsal forebrain assembloids (vdAO). The cryosection of the assembloids are imaged for interneuron migration quantification after a month-long coculture. The migration of the dlx-positive interneurons to the dCO side are differed between KO- and NT-vdAO groups, indicating a disruption of inhibitory-excitatory network related to deletion of the neuron-specific splicing regulator. Furthermore, we conducted calcium imaging to examine the spontaneous calcium transients in the organoid and assembloid cellular network. An amplitude change of the calcium transient was observed in the KO-dCO group, while the frequency or the overall synchronization remained intact. Together, these results suggest a potential function of a neuron-specific splicing regulator in human embryonic brain and provide an insight into the connection of development disorders and RNA splicing in the central nervous system.

Disclosures: H. Cheng: None. H. Huang: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.22/A42

Topic: A.06. Developmental Disorders

Support: NIGMS- GM113109 NIH

Title: Cognitive flexibility in aged *Fmr1* knockout rats

Authors: *B. PLAKKE¹, B. SIVAYOKAN², E. PEREZ-LEBRON¹;

²Psychological Sci., ¹Kansas State Univ., Manhattan, KS

Abstract: Fragile X syndrome (FXS), an X-linked dominant disorder, is the most common single-gene cause for intellectual disability and a leading heritable cause of autism spectrum disorder (ASD). It is caused by a mutation in the *FMRI* gene, which codes for the protein FMRP. This protein is abundant in the neuronal dendrites and play a key role in regulating synaptic plasticity. Loss of this protein in FXS leads to multiple cognitive deficits among which cognitive flexibility impairments are commonly reported. Do aged *FMRI* knockout (KO) animals show impairment in cognitive flexibility? This project was carried out among homozygous and heterozygous KO, and wildtype (WT) rats (at least 8 per group). A touch screen-based categorization task was carried out in these animals to assess cognitive flexibility. Two

categories of Gabor patches differing in frequency and orientation, of which only one is the relevant dimension for categorization, were used in this task. After undergoing shaping procedures to touch the screen for food rewards, the rats were started on the categorization task. The task consists of 80 trials in which 80 different exemplars, 40 from each category, are presented. Each trial consists of four phases. During the first phase, the rats touch a pentagon displayed on the screen to initiate the trial. During the second phase (cue phase), an exemplar is presented on the screen, and the rats are required to touch this exemplar twice to ensure that they are attending to the exemplar. In the third phase (choice phase), identical copies of the exemplar from phase 2 are presented on either side of the screen. The rats decide the category membership of the exemplar by pressing one of the two sides. Eighty percent of all correct choices and twenty percent of all incorrect choices are rewarded during the fourth phase. After 16 days of training on the initial categorization rule, the rule was reversed, and the animals were tested for 8 days on the reversed rule. The experiments were carried out by blind-to-condition researchers. Results showed that while the overall accuracy improved with days of training, both KO and WT rats struggled to reach the criterion of 70% correct for each category. They seemed to rely on a side bias as indicated by the performance when the categorization rule was reversed. While KO and WT exhibited side bias, it was more prominent among the KO rats than WT rats. These findings suggest that aged rats, irrespective of genotype struggle with cognitive flexibility.

Disclosures: B. Plakke: None. B. Sivayokan: None. E. Perez-Lebron: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

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Program #/Poster #: PSTR149.23/A43

Topic: A.06. Developmental Disorders

Support: R03MH133173
NIGMS_GM113109

Title: Motor functioning in FMR1 knockout rats across their lifespan

Authors: *T. MAJI¹, B. SIVAYOKAN², E. PEREZ-LEBRON¹, B. PLAKKE³;
²Psychological Sci., ³Psychological Sciences, Behavioral Neurosci., ¹Kansas State Univ.,
Manhattan, KS

Abstract: Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability and a leading single-gene cause of autism spectrum disorder. This X-linked dominant disease is caused by expansions in the FMR1 gene, leading to the loss of the protein FMRP, which regulates dendritic maturation and synaptic protein synthesis, thereby playing a key role in synaptic plasticity. Its absence results in hyperconnectivity and hyperexcitability, which leads to cognitive and motor deficits. Carriers of the FXS premutation have less extensive expansions in the FMR1 gene and develop a premutation-specific condition known as fragile X-associated

ataxia syndrome, one of the most common single-gene forms of neurodegeneration. This typically presents in mid to late adulthood and is characterized by gait ataxia, intention tremor, Parkinsonian features, peripheral neuropathy, and progressive cognitive impairment. FMR1 knockout (KO) animals also develop varying degrees of motor impairment across their lifespan. How and when do these motor impairments present? Homozygous and heterozygous KO rats and wildtype (WT) rats (at least 8 per group) were used in this project to assess motor functioning across their lifespan. The rotarod test was carried out during postnatal day (P) 70 - (P) 85 and 12 months. Rotarod was started at 5 rpm and accelerated to 40 rpm over 180s. At each time point, the animals were given 2 trials with a 10-minute intertrial interval. The grip strength test was carried out at the ages of 6 months and 12 months. At each time point, the animals were given one trial per day for three consecutive days. The footprint test was used to assess gait abnormalities in these animals at (P) 28 and 6-8 months. The stride length, stride width, and toe spread were manually scored using these footprints. All experiments were carried out by blind-to-condition researchers. Results revealed that the latency to fall from the rotarod was increased during the second timepoint of testing (12-months), $p < .001$, and that all animals stayed on the rod significantly longer during trial 2 than trial 1 during the second but not the first timepoint of testing, $p = .001$. The relative grip strength (grip strength divided by body weight) was higher at the 12-month testing point in all animals, $p < .001$. In the footprint test, the KO rats had shorter stride lengths and wider stride widths than the WT, especially during the second time point of testing. These findings suggest that motor deficits are not apparent when these animals are young but emerge later in life.

Disclosures: T. Maji: None. B. Sivayokan: None. E. Perez-Lebron: None. B. Plakke: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.24/A44

Topic: A.06. Developmental Disorders

Support: SFARI

Title: Disrupted homeostatic plasticity in SCN2A^{+/-} rat model

Authors: *N. DIAZ RODRIGUEZ¹, G. TURRIGIANO²;

¹Brandeis Univ. Grad. Neurosci. Program, Waltham, MA; ²Dept of Biol., Brandeis Univ., Waltham, MA

Abstract: Neocortical circuits maintain both flexibility and stability through synaptic and intrinsic homeostatic mechanisms in response to sensory perturbations. Our laboratory has shown that genes associated with autism spectrum disorders (ASDs), including *Shank3*, exhibit homeostatic plasticity deficits in the primary visual cortex (V1) of rats. Given that multiple ASD-linked genes exhibit impairments in homeostatic plasticity, we hypothesized that V1

homeostatic plasticity might be impaired in other rat models of ASD. Here, we test this hypothesis in a rat model of haploinsufficiency for *SCN2A*, which encodes for a voltage-gated sodium channel (Nav1.2). To mimic human haploinsufficiency, we used Long-Evans rats that were heterozygous for *SCN2A* knockout (*SCN2A*^{+/-}). Experiments were performed during the classic visual system critical period, when visual cortical circuitry is especially plastic. To induce homeostatic plasticity, we chronically suppressed neuronal activity for 24 hours using inhibitory DREADDS (Designer Receptor Exclusively Activated by Designer Drugs) expression in binocular V1 (V1b). Ex vivo acute slice electrophysiology was then used to measure synaptic and intrinsic homeostatic responses from L2/3 pyramidal neurons of wildtype (WT) and *SCN2A*^{+/-} rats. Results demonstrate that L2/3 pyramidal neurons in V1b of *SCN2A*^{+/-} rats exhibit reduced baseline synaptic strength relative to WT controls but retained the capacity for synaptic upscaling following DREADD-induced activity suppression. In contrast, *SCN2A*^{+/-} rats display an elevated baseline intrinsic excitability, but after suppression it failed to further increase excitability via intrinsic homeostatic plasticity. To determine whether this failure to induce intrinsic homeostatic plasticity was due to saturation of the system, we dissociated V1 neurons from WT and *SCN2A*^{+/-} animals and treated cultures for 24 hours with Glyx-13, an NMDAR allosteric modulator known to reduce intrinsic excitability. Electrophysiological recording from DIV10-DIV14 pyramidal neurons revealed that 24 hours of Glyx-13 treatment normalized elevated excitability in *SCN2A*^{+/-} neurons, suggesting that intrinsic homeostatic mechanisms were already maximally engaged under baseline conditions. Altogether, these findings suggest that *SCN2A* is dispensable for synaptic homeostatic plasticity but essential for intrinsic homeostatic plasticity in L2/3 pyramidal neurons. This supports a model in which loss of excitatory synaptic input leads to compensatory intrinsic changes that become saturated in the absence of functional *SCN2A*, potentially contributing to circuit dysfunction in ASD.

Disclosures: N. Diaz Rodriguez: None. G. Turrigiano: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.25/A45

Topic: A.06. Developmental Disorders

Title: Investigation of the Underlying Mechanism of a Disrupted G Protein-Coupled Receptor Involved in Autism Spectrum Disorder

Authors: *C.-Y. LEE, H.-S. HUANG;
Grad. Inst. of Brain and Mind Sciences, Nation Taiwan Univ., Taipei, Taiwan

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder with a global prevalence of approximately 2.8%, according to the National Institute of Mental Health (NIMH). While many ASD-associated genes and their biological pathways have been identified, the complete molecular mechanisms underlying the disorder remain unclear. In this study, we

identified a stop-gain variant in a G protein-coupled receptor (designated as GPCR-A) from an ASD cohort in Taiwan. Variants in GPCR-A have also been reported in other ASD studies (SFARI gene score: 2), suggesting a potential role in ASD pathogenesis. To explore the functional impact of GPCR-A disruption on human neuronal development, we utilized human induced pluripotent stem cell (hiPSC)-based models. Peripheral blood mononuclear cells (PBMCs) from an affected individual were reprogrammed into hiPSCs. In addition, we generated isogenic patient hiPSC lines using adenine base editing (ABE) and obtained hiPSC lines from a healthy control. These hiPSCs are being differentiated into 2D cortical neurons and 3D dorsal forebrain organoids to investigate neurodevelopmental phenotypes. We conducted Sholl analysis, patch-clamp recording and calcium imaging assays to assess potential differences in neuronal structure, excitability, and network activity associated with the GPCR-A disruption. Further experiments, such as miniature postsynaptic potential recordings and transcriptomic studies, are also planned to better understand the downstream consequences of GPCR-A disruption. Through this human neuron-based strategy, we aim to uncover the cellular and molecular mechanisms by which GPCR-A may contribute to ASD, thereby providing insights into the broader genetic architecture of the disorder.

Disclosures: C. Lee: None. H. Huang: None.

Poster

PSTR149: Genetic Models of Autism Spectrum Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.27/A46

Topic: A.06. Developmental Disorders

Support: NIGMS- GM113109 NIH

Title: Restricted repetitive behaviors in FMR1 knockout rats across the lifespan

Authors: *B. SIVAYOKAN¹, B. PLAKKE²;

¹Psychological Sci., ²Psychological Sciences, Behavioral Neurosci., Kansas State Univ., Manhattan, KS

Abstract: Fragile X syndrome (FXS) is an X-linked dominant disorder caused by a triplet repeat expansion in the *FMR1* gene, which codes for the protein FMRP. Though FMRP is ubiquitous, it is particularly abundant in the dendritic spines of neurons, where it plays a key role in regulating protein synthesis in the dendrite and synapses. The loss of FMRP in FXS results in immature dendritic spines and higher spine density, which leads to disrupted synaptic plasticity. Restricted, repetitive patterns of behaviors (RRBs) in FXS are thought to be the result of this disrupted synaptic plasticity in the striatum. RRBs are varied, often disparate behaviors characterized by repetition, rigidity, invariance, and inappropriateness. They are among the core symptoms of ASD and include stereotyped motor movements, ritualized patterns of behavior, inflexible adherence to routines, fixated interests, and hyper- or hypo-reactivity to sensory input. Do RRBs

in FXS manifest differently across the lifespan? Homozygous and heterozygous *FMRI* knockout (KO), and wild type (WT) Long-Evans rats (at least 12 per group) were used in this project. Grooming test, a commonly used behavioral paradigm for assessing repetitive behavior, was carried out at the age of either postnatal day 40 or 12 months. The animals were habituated to a clean arena for 5 minutes. Then, two sprays of 10% sucrose solution were applied on the dorsal coat of the animal to improve palatability and permit persistence of grooming and the animals were allowed to groom for 10 minutes. Nesting removal test was carried out among the older cohort of animals to assess resistance to change. This was conducted in the home cage with regular bedding into which crinkle cut paper was introduced as a nesting material. After 24 hours, the nesting material was removed and the amount of time each animal spent digging was recorded. All tests were carried out by blind-to-condition researchers. Results showed that older animals spent less time grooming than younger animals ($p = .037$), had fewer bouts of grooming ($p < .001$), and a later onset of grooming ($p < .001$). While young and old KO rats spent more time grooming than WT rats, this did not reach statistical significance. However, young but not old homozygous KO had a significantly early onset of grooming than the heterozygous KO ($p = .010$) and WT ($p = .041$) rats. Results of the nesting removal test showed that KO rats spent significantly more time digging than WT rats ($p < .001$). These findings suggest that RRBs are present in both young and old *FMRI* KOs, but manifest differently.

Disclosures: B. Sivayokan: None. B. Plakke: None.

Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.01/A47

Topic: A.06. Developmental Disorders

Support: HIM 2021-022 SSA 1728

Title: Alterations in the striatum and hippocampus of juvenile rats induced by the chronic use of different doses of ADHD drug atomoxetine

Authors: *J. CORONA, J. YAÑEZ ROA;
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Abstract: Atomoxetine (ATX) is a non-psychostimulant drug prescribed for the treatment of attention-deficit/hyperactivity disorder (ADHD). However, it has been shown that ATX produces oxidative stress, mitochondrial damage, cell death and alterations of several signal transduction pathways *in vitro* and *in vivo*. The pathophysiology of ADHD is not entirely known, but oxidative stress and neuroinflammation have emerged as a causal hypothesis. In this study, we aim to determine whether chronic use of three different doses of ATX in the brain tissue of juvenile rats induces impairments. We used rats that were injected intraperitoneally with three different doses of ATX (3, 5 and 10 mg/kg) once a day for 28 consecutive days; Brain sections

were taken from the striatum and hippocampus, which were stained with cresyl violet and the measurement of superoxide by dihydroethidium and GFAP immunostaining. We found that chronic use of three different doses of ATX in juvenile rats decreased the number of neurons in both the striatum and the hippocampus. Moreover, we found that the three doses of ATX increased the number of GFAP+ astrocytes in the striatum and hippocampus. In addition, in the regions mentioned earlier, the three different doses of ATX increased oxidative stress, as seen by elevated superoxide production indicated by dihydroethidium fluorescent signals in both brain areas. We conclude that the chronic use of three different doses of ATX produced increasing neuronal damage which would trigger an increase in the neuroinflammation process and consequently an increasing of oxidative stress in both the striatum and the hippocampus.

Disclosures: J. Corona: None. J. Yañez Roa: None.

Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.02/A48

Topic: A.06. Developmental Disorders

Support: The work is supported by Shota Rustaveli National Science Foundation Research grant #FR-22-1991

Title: Does Cognitive Intervention Effect On Performance Of Children With Attention-Deficit/Hyperactivity Disorder

Authors: *I. KHACHIDZE¹, L. CHANTADZE², K. PARKOSADZE³, N. ZHAMURELI², M. ADVADZE²;

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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with problem of attention and information-processing in children. The link between ADHD and behavioral/neurobiological variations has been extensively investigated and represents aim of our research. Neuropsychological and neurophysiological assessments were conducted to identify effect of a psychological intervention in children with ADHD. The research included 41 children (9 females, 32 male), aged 7-11 years, predominantly inattentive-type ADHD, and conducted in compliance with ethical standards. Various cognitive interventions such as Cognitive Computer Tests (twice per week) and Cognitive Paper Exercises (daily) were implemented over a three-month to evaluate improvements in different types of attention. Neuropsychological and EEG evaluations were performed before and after cognitive intervention: Neuropsychological Computer Assessment Tests (NCAT: Flanker, TOVA, Shifting Attention) measured executive functions, response inhibition and different aspects of attention. Paper-based scales (NPAS:

Vanderbilt/NICHQ, ASEBA/CBCL) captured parent and teacher evaluations. Resting state EEG was recorded with eyes-close followed by eyes-open (3 min. each) and again close conditions (4min). Absolute power spectra (APS) was conducted for delta, theta, alpha, beta frequencies. APS analyzed in frontal, central and parietal regions and compared pre- and post-intervention. Big EEG data collected in Georgia have been uploaded to first online EEG dataset EEGEEGHUB.GE and integrated in EOSC under „Horizon“ grant. NCAT revealed slight improved performance (indicated by increased correct responses and decreased reaction times). NPAS results showed decreased inattention according to parents' assessments and CBLS indicated decreased inattention according to teachers. No significant changes were found in EEG after intervention. No significant reduction in low frequency EEG was observed between pre- and post-intervention, and between eyes-closed and eyes-open conditions. Positive correlation was found between delta and theta. Beta was low in frontal, central, parietal regions and remained same after intervention. Alpha showed minimal modulation between assessments, suggesting that changes in cognitive or attentional state had limited effect on alpha. Cognitive interventions led to some improvements in task performance and attention in ADHD children. No significant changes observed in EEG suggesting that 3 months permanent cognitive training may moderately improve inattention but not impact neurophysiological changes in brain activity.

Disclosures: **I. Khachidze:** 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.; The work is supported by Shota Rustaveli National Science Foundation Research grant #FR-22-1991. **L. Chantadze:** None. **K. Parkosadze:** None. **N. Zhamureli:** None. **M. Advadze:** None.

Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.03/A49

Topic: A.06. Developmental Disorders

Support: This work of the MELD (Multisensory Environments to study Longitudinal Development) is supported by a generous unrestricted gift from Reality Labs Research, a division of Meta.

Title: Behavioral Multisensory Integration Benefits in Children with ADHD

Authors: ***H. VITALI**¹, **M. STURLESE**^{1,2}, **A. PICCINNI**^{3,2}, **A. BARBIERI**^{3,2}, **C. CAMPUS**¹, **M. BERTHOD**², **L. NOBILI**^{3,2}, **M. M. MURRAY**⁴, **M. GORI**¹;

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Abstract: Emerging research suggests that disruptions in multisensory integration (MSI) may play a role in neurodevelopmental conditions, including Attention-Deficit/Hyperactivity Disorder (ADHD). Children with ADHD show difficulties in processing sensory information and generating appropriate responses. While adults with ADHD demonstrate generally faster reaction times as well as further facilitation beyond predictions of probability summation under multisensory conditions than controls (McCracken et al. 2020), it remains unclear whether and how such manifests in children/adolescents with ADHD (Dionne-Dostie et al., 2015; Chmielewski et al., 2018). To address this gap, we are conducting an auditory-visual oddball paradigm in children (8-14 y) with ADHD evaluating the multisensory effect on attentional abilities. The task consisted of 70% standard, 10% auditory oddball, 10% visual oddball, and 10% multisensory audiovisual oddball stimuli. The task was administered in four blocks, for a total of 1000 trials. In two blocks, an auditory stimulus served as the standard, while in the other two, a visual stimulus was used. EEG data were acquired with 64 active scalp electrodes, while reaction times (RT) to oddball events were recorded via keyboard key presses. Although data collection is still ongoing, we conducted preliminary analyses of the effects of multisensory stimulation on behavioral responses in 8 ADHD children. First, a linear mixed model was performed to compare the effect of unisensory and multisensory stimuli on RT. Significant results were found between auditory and audiovisual RTs, as well as between visual and audiovisual RT. This suggests a beneficial effect of multisensory information. Then, to determine whether the observed multisensory benefit was due to statistical facilitation or true MSI, we compared the audiovisual cumulative distribution function (CDF) to the race model given by the sum of the unimodal (auditory + visual) CDFs, which assumes independent processing of auditory and visual stimuli. Violations of the race model inequality were tested via one-tailed t-tests against zero for the first five deciles of the difference between the race model and the audiovisual CDFs. Significant differences were found for all percentiles, revealing the presence of genuine MSI mechanisms. In conclusion, our results show that children with ADHD can integrate multisensory stimuli under attentionally-demanding contexts. Future research is needed to determine whether and how these integrative abilities differ from those of neurotypical peers, and to uncover the underlying neural mechanisms.

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Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.04/A50

Topic: A.06. Developmental Disorders

Support: NIH Grant R01 ES032270

Title: Effect of a rat DRD1-specific conditional knockout of the ADHD risk-gene, latrophilin-3 (Lphn3)

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Abstract: Seven million American children ages 3-17 are diagnosed with attention deficit hyperactivity disorder (ADHD), which is characterized by impulsivity, hyperactivity, and inattention. Additional symptoms include deficits in working memory and executive function. ADHD is highly heritable and associated with a variety of genes and neurotransmitter systems, including the dopaminergic system. Variants in *latrophilin-3* (*LPHN3*), a gene encoding a brain-specific adhesion G-protein coupled receptor, are linked to ADHD. Animal models with *Lphn3* dysfunction exhibit ADHD-like phenotypes, such as hyperactivity, cognitive impairments, and dopamine (DA) dysregulation. We developed a global *Lphn3* knockout (gKO) rat that displayed spatial, egocentric, and working memory deficits, impulsivity, reduced cognitive flexibility, heightened acoustic startle, and altered DA signaling—including upregulated presynaptic markers, such as tyrosine hydroxylase (TH), and downregulated postsynaptic markers, such as dopamine D1 receptors (DRD1). These findings suggest that DA signaling mediates some *Lphn3*-related effects. To dissect this further, we generated an *Lphn3-TH-Cre* conditional knockout (cKO) rat targeting presynaptic DA and norepinephrine neurons. This rat exhibited egocentric but not allocentric learning deficits. However, the role of postsynaptic DA receptors remains unclear. Therefore, we created an *Lphn3-Drd1-Cre* rat to knock out *Lphn3* in *Drd1*-expressing neurons. We used both males and females with 42 Cre control (DRD1^{Cre+/Cre-} *Lphn3*^{+/+}) rats, 30 floxed control (DRD1^{Cre-/Cre-} *Lphn3*^{fl/fl}) rats, 30 wildtype (DRD1^{Cre-/Cre-} *Lphn3*^{+/+}) rats and 43 cKO (DRD1^{Cre+/Cre-} *Lphn3*^{fl/fl}) rats, choosing only one sex per genotype per litter for behavior. The DRD1 cKO rats had few behavioral effects, with nocturnal hypoactivity, increased reactivity to tactile prepulse inhibition, increased latency in straight channel swimming, and a trend toward increased activity in the contextual memory phase of conditioned freezing. In the mirror image version of the Cincinnati water maze, there was a sex × genotype × day interaction with DRD1 cKO males having a faster latency and fewer errors in the first two days of testing. The results suggest that while DRD1 receptors contribute to some effects, they are not the main driver of *Lphn3*-related ADHD-like effects. Instead, presynaptic DA signaling and/or other neurotransmitter systems may play a larger role. Nevertheless, this work contributes to understanding the functional relationship between *LPHN3* and the dopaminergic system and may lead to better treatments for some ADHD symptoms.

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Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

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Topic: A.06. Developmental Disorders

Support: JSPS KAKENHI Grant 23H04979
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JST CREST Grant JPMJCR22P3
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Title: Stabilization of brain dynamics underlies the effects of sustained methylphenidate administration on working memory in adults with ADHD

Authors: *M. UEDA¹, M. SHIMIZU¹, R. AOKI^{2,3,4}, T. ITAHASHI⁵, Y. SHIKAUCHI³, H. NAKAMURA¹, S. TAKAGI^{1,6}, G. SUGIHARA¹, M. NAKAMURA⁵, H. TAKAHASHI¹;
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Abstract: Methylphenidate (MPH) is the first-line pharmacological treatment for attention-deficit/hyperactivity disorder (ADHD), yet approximately 30% of patients show limited therapeutic response. These inter-individual differences may arise from variability in how MPH modulates brain function and cognition, but the underlying neurobiological mechanisms remain insufficiently understood. In particular, little is known about how MPH affects the neural basis of executive functions, such as working memory, at clinically relevant doses. Recent work suggests that brain dynamics may reflect drug effects; however, most studies used single-dose designs that may not generalize to long-term clinical use. To address this gap, we examined the impact of clinical-dose MPH on brain dynamics and objectively measured executive function in adults with ADHD. Twenty-six participants underwent resting-state fMRI and cognitive testing with the Cambridge Neuropsychological Test Automated Battery (CANTAB) twice: once before MPH initiation (or during a drug-free period) and once during a stable period of MPH use. Brain dynamics were quantified via energy-landscape analysis, which models transition probabilities between cortical and subcortical activity states. MPH significantly reduced the occurrence probability of unstable brain states ($p < 0.0002$) and decreased state-transition frequency ($p < 0.05$), indicative of increased network stability. The magnitude of transition-frequency reduction was positively correlated with improvements in spatial working-memory (SWM) scores ($p < 0.01$). Moreover, at both baseline and on-medication sessions, higher individual transition rates were inversely associated with SWM performance (baseline $p < 0.01$; on-medication $p < 0.05$), indicating that intrinsic network instability itself is behaviorally detrimental irrespective of drug status. These findings suggest that clinical-dose MPH stabilizes aberrant brain dynamics in adults with ADHD and that both the absolute level and MPH-induced reduction of neural instability are linked to enhanced working memory, providing a potential neurophysiological marker relevant to cognitive functioning and treatment responsiveness in ADHD.

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Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

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Program #/Poster #: PSTR150.06/A52

Topic: A.06. Developmental Disorders

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AMED 21dm0307008
JST Moonshot R&D Program JPMJMS2292

Title: Differing effects of methylphenidate on attention-related behavior and brain activity in methylphenidate-naive and non-naive ADHD adults

Authors: *M. SHIMIZU^{1,3}, R. AOKI^{5,6,7}, T. ITAHASHI⁶, Y. SHIKAUCHI⁶, H. NAKAMURA³, S. TAKAGI^{4,8}, G. SUGIHARA⁴, H. TAKAHASHI^{4,2}, M. NAKAMURA⁶;
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Abstract: Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. In association with these symptoms, individuals with ADHD show pronounced difficulties especially in the goal-directed, top-down attentional processes. Methylphenidate (MPH) is a widely used pharmacological treatment for ADHD that increases the extracellular dopamine level by inhibiting dopamine reuptake through its action on dopamine transporters. Although MPH has been reported to improve cognitive functions, the influence of prior medication history on its efficacy and its impact on attentional brain regions critical for top-down attention remains unclear. In this study, we examined 36 adults with ADHD using a within-subject design. Participants performed a central cue version of the Posner task during functional magnetic resonance imaging scans before and after MPH administration. Participants were classified into MPH-naive and non-naive group based on prior stimulant use. Behavioral and neural responses were compared across conditions, and correlations between changes in brain activation and symptom improvement were assessed using the Conners' Adult ADHD Rating Scales. MPH administration reduced reaction times across both groups without affecting task accuracy. In the naive group, MPH enhanced activation in the bilateral frontal eye field (FEF) and intraparietal sulcus (IPS) whereas no such acute increase was observed in the non-naive group. However, non-naive participants exhibited baseline activation levels comparable to those of the naive participants after sustained MPH administration at a stable dose. Furthermore, increased FEF activation correlated with symptom reduction exclusively in the naive group. These results suggest that the effects of MPH on the regions within the dorsal attention network depend on the

medication history, supporting the notion that MPH modulates attentional processes through both transient and long-lasting mechanisms. They highlight the importance of considering medication history when evaluating treatment responses in individuals with ADHD.

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Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR150.07/A53

Topic: A.06. Developmental Disorders

Support: Joan Orpella Start-Up Funds Georgetown University Department of Neuroscience

Title: Low synchronizing, low literacy? Investigating reading ability through speech-motor coupling

Authors: ***M. M. WILLIAMS**, C. ODERBOLZ, N. KUMAR, J. ORPELLA;
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Abstract: Reading is a fundamental skill to navigate the modern world. According to the National Assessment of Educational Progress, only 30% of 4th- and 8th-graders met proficient reading achievement levels in 2024. While literacy rates in the U.S. can be attributed to various factors, learning disabilities, and in particular dyslexia (Shaywitz, 2020), play a major role. People with dyslexia show deficits in phonological awareness (Wagner & Torgesen, 1987) and rhythm synchronization (Colling et al., 2017; Bégel et al., 2022; Leong & Goswami, 2014), resembling the characteristics of low speech auditory-motor synchronizers as described by Assaneo et al. (2019). This seminal paper reported a bimodal distribution which characterized participants as high and low synchronizers based on their ability to align their motor output to a speech input. Compared to high synchronizers, low synchronizers also show decreased fronto-temporal functional and structural connectivity (Assaneo et al., 2019; Orpella et al., 2022), similar to people with dyslexia when compared to control participants (Vandermosten et al., 2012; Saygin et al., 2013; Norton et al., 2015). In the current project we investigate the relationship between dyslexia and, more generally, reading skills and auditory-motor synchronization abilities. Participants (ages 18-23.11 years) completed the spontaneous speech synchronization task and were categorized as a high or low synchronizer by computing the phase locking value between the produced speech and the auditory syllable stream (Assaneo et al., 2019, Lizcano-Cortés et al., 2022). We compare typically developing adults to adults with a history of impoverished reading on neuropsychological measures typically diagnostic of dyslexia: phonological awareness (Wagner & Torgesen, 2009; Wagner et al., 1999), rapid

automatized naming (Wolf & Bowers, 1999), and sight-word and phonetic decoding efficiency (Wagner et al., 1999) while controlling for verbal and nonverbal intelligence (Tanaka et al., 2011). Understanding the relationship between auditory-motor synchronization and reading skill can help elucidate the underpinning mechanisms of phonological deficits in dyslexia and may provide a valuable cognitive tool to effectively diagnose or assess risk factor for dyslexia.

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Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.08/A54

Topic: I.04. Executive Functions

Title: Adhd in person learning versus virtual learning using eeg

Authors: *A. L. HICKS¹, V. VELARDE¹, N. N. HETTIARACHCHI², E. E. LEAVER¹;

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Abstract: Attention Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental condition that affects cognitive functioning, particularly attention and executive control, which are critical for academic performance. Prior research suggests that students with ADHD may benefit more from in-person learning environments compared to virtual learning. However, the impact of learning modality on attention, comprehension, and performance remains a subject of debate. This study aims to investigate the effects of in-person versus virtual learning on college students with and without ADHD by measuring sustained attention and cognitive engagement through electroencephalography (EEG). Participants will be divided into four groups: two ADHD groups (one in-person, one virtual) and two neurotypical groups (one in-person, one virtual). All participants will engage in a standardized lesson on a fabricated presentation while EEG data is collected to analyze attention-related brain activity. By comparing EEG spectral changes, response times, and task performance across conditions, this study will provide insights into how learning modality influences sustained attention and cognitive processing in students with ADHD. Findings may inform educational strategies to enhance learning experiences for neurodiverse student populations.

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Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

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Program #/Poster #: PSTR150.09/A55

Topic: A.06. Developmental Disorders

Title: Relationship between adult ADHD symptomatology and oculomotor control in a mixed reality environment

Authors: A. ROSENFELDER¹, M. GONZALEZ¹, A. ESCARZAGA¹, N. BELTRAN², K. D. CARRASCO¹, *A. CARRASCO¹;

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Abstract: Irregularities in ocular movement have been implicated in attention and executive functioning deficits. This association has been supported by reports of atypical oculomotor dynamics among individuals diagnosed with attention-deficit/hyperactivity disorder (ADHD). However, despite the established link between ocular behavior and ADHD, evidence has largely been derived from controlled laboratory tasks, which often do not capture the complexity of real-world environments. To address this gap, the present study examined the relationship between ADHD symptomatology and oculomotor metrics in a naturalistic mixed reality classroom setting. Ninety-four university students participated in the experiment. ADHD symptom levels were assessed using the Adult ADHD Self-Report Scale (ASRS), and eye and head movement data were collected at 200 Hz with a Varjo XR-4 mixed reality headset while participants were immersed in a 360-degree pre-recorded classroom lecture. Linear regression analyses of saccade metrics revealed significant associations with ASRS scores. Specifically, higher ASRS scores were linked to increased mean peak velocity ($p=0.021$), greater mean peak deceleration ($p=0.018$), and larger mean saccade magnitude ($p=0.012$). The slope for mean peak velocity was 17.95 deg/s per ASRS point, and for mean magnitude, 0.091 deg per ASRS point. Analysis of combined gaze measures (integrating eye and head movements) yielded similar findings: higher ASRS scores were associated with increased mean peak velocity ($p=0.022$), greater mean peak deceleration ($p=0.019$), and larger mean gaze magnitude ($p=0.012$), with comparable slope values. These findings suggest a consistent relationship between higher ADHD symptom scores and greater oculomotor instability, reflected in both pure saccadic and combined gaze measures. The employed mixed reality classroom enhanced the ecological validity of previous investigations while permitting the measurement of oculomotor dynamics. This study provides evidence that saccade and combined gaze dynamics are linked to ADHD symptomatology in adults. These findings support the potential for using eye and gaze tracking in mixed reality settings to develop objective biomarkers of attentional control deficits associated with ADHD.

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Poster

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Topic: A.06. Developmental Disorders

Support: NICHD R15HD087937
Alan & Wendy Pesky Research Grant

Title: A Multidimensional approach to understanding reading disability

Authors: *L. A. GABEL¹, P. KAUSHIK², Y.-C. YU², R. BURKE¹, A. BELEJ¹, K. PERETZ³, V. BROWN³, E. GACETTA¹, L. BOYLE⁴;

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Abstract: Family studies show high heritability of reading disability (RD), with several RD susceptibility genes independently validated. Genetic modification of genes like DCDC2 and KIAA0319 in rodents has led to sensory processing deficits and neuroanatomical changes. Our translational research indicates that both genetic mouse models and children with RD exhibit poor maze learning performance, and that DCDC2 variants increase risk. However, these studies did not consider the influence of math ability, nor the potential mediation by domain-general or domain-specific processes implicated in other specific learning disabilities, on the relationship between RD and maze learning performance. In this preliminary study we examined the extent to which visuospatial processing, phonological awareness and math ability influence the relationship between reading impairment and maze performance in kindergarten and second grade children. We also employed multiple machine learning models with oversampling techniques to classify learning impairment based on maze learning performance, achieving over 95% classification accuracy. This approach identifies mediating processes between reading ability and maze learning, and assesses whether maze learning performance in pre-readers can accurately predict future reading ability. These results provide crucial insights into the developmental pathways linking early learning processes to RD and offer a promising approach for the early identification and intervention of children at risk for reading difficulties.

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Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

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Program #/Poster #: PSTR150.11/A57

Topic: A.06. Developmental Disorders

Title: Sex-based neuroanatomical differences in ADHD: A meta-analysis on microstructure abnormalities and symptom variation

Authors: *S. FERGUSON¹, D. O'DEA, Jr.¹, S. E. PLAZA²;

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Abstract: Attention Deficit/Hyperactivity Disorder (ADHD) is a frequently diagnosed neurodevelopmental disorder, affecting about 5-7% of children and 2.5% of adults, and is characterized by persistent inattention, hyperactivity, and impulsivity. Despite its known prevalence, little research explores the link between brain structure, gender, and specific ADHD symptoms. ADHD is associated with the dopamine-regulating COMT (catechol-O-methyltransferase) gene on chromosome 22, which plays a key role in metabolizing dopamine, norepinephrine, and epinephrine. Variations in COMT enzyme activity affect dopamine breakdown in the brain, contributing to ADHD symptoms. Knowing the differences between male and female neuroanatomy, and how it could be linked to symptomatology, is valuable in offering gender specific therapeutic advice. We conducted a systematic literature review of 15 studies published between 2001-2020, and a meta-analysis of cross-sectional and case-control studies, with most using Voxel Based Morphometry (VBM) and functional Magnetic Resonance Imaging (fMRI) on different controlled groups (Female ADHD, Male ADHD, Female Control, and Male Control). We found that children with ADHD often have smaller brain volume, reduced gray matter (particularly in the orbitofrontal cortex, the cingulate gyrus, the caudate nucleus, the putamen, and the cerebellum), and abnormalities in frontostriatal circuits. Of the 15 articles reviewed, 11 primarily focused on microstructures and gray matter, while 4 examined symptom variation. One study suggests that there was a 5.2% change in Gray Matter Volume (GMV) in individuals with ADHD compared to those in the control group, showing a 5.4% reduction in total brain volume. Clusters above 10 voxels were analyzed, showing a decrease in GMV in the orbitofrontal cortex with a cluster size of 8453 mm³; p-value ranging from 0.002 to .004 (Carmona et al. 2005). These microstructural changes differ by sex, potentially influenced by abnormally low levels of dopamine. These low levels of dopamine can cause behavioral sex differences within ADHD individuals. ADHD males exhibit more externalizing behaviors, such as learning disabilities, disruptive behavior, and social dysfunction, whereas females tend to exhibit internalizing behaviors, such as anxiety and depression. We analyzed these structural and behavioral differences using Jamovi to better understand symptom and microstructural (i.e., gray and white matter) variation. Finally, we discussed limitations and future research that could be beneficial for understanding these gender differences.

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Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.12/A58

Topic: A.06. Developmental Disorders

Title: Self-regulation at risk: A dimensional analysis of ADHD traits and gaming disorder symptoms

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Abstract: Gaming Disorder (GD) has been linked to alterations in neurocognitive circuits involved in inhibitory control, emotional regulation, and decision-making, particularly the dorsolateral prefrontal cortex and anterior cingulate cortex. This study aimed to develop and validate an inventory assessing the relationship between gaming and mental health, analyzing its internal structure, construct validity, and measurement invariance. A total of 974 adults (Mean age = 25.40, SD = 8.15) were recruited via non-probability online sampling. Confirmatory factor analysis (CFA) and measurement invariance tests by sex were conducted, along with correlations to mental health measures (emotional, psychological, and social well-being), ADHD symptoms, and depression, anxiety, and stress scales. CFA confirmed a three-factor structure: loss of control, physical-mental well-being, and social well-being. The scale demonstrated measurement invariance by sex and significant associations with mental health variables ($\eta^2 = 0.018-0.183$), supporting its convergent validity. It was also associated with the general ADHD factor ($\eta^2 = 0.161-0.183$), suggesting that GD shares dysregulation mechanisms with neurodevelopmental disorders. Results support conceptualizing GD as a self-regulation problem involving fronto-limbic and reward circuit dysfunction, exacerbated by the intermittent reinforcement features of video games. This inventory offers a valid tool to assess the mental health impact of problematic gaming and to explore underlying mechanisms of cognitive and emotional vulnerability. Future longitudinal studies should examine the directionality of these relationships and potential contextual moderators such as age, gaming habits, or coping strategies.

Disclosures: S. Trejo Garcia: None. L. Llamas-Alonso: None. V. Huerta: None.

Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.13/A59

Topic: A.06. Developmental Disorders

Support: NIH Grant RFA NS18-023 (1UH3NS119844-01A1)

Title: Validating tic detection: Agreement between video- and EMG-based algorithms

Authors: *G. T. LOWOR¹, M. OSEI OPOKU², J. GOMEZ², W. TVENSTRUP², A. NOY⁴, K. FOOTE³, A. GUNDUZ²;

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Abstract: Tourette Syndrome (TS) is a complex neurodevelopmental disorder characterized by motor and vocal tics, varying significantly among affected individuals. Currently, clinicians

primarily rely on subjective clinical assessment scales for tic severity; however, evaluating treatment outcomes for patients with TS requires a more reliable and precise identification of symptoms. This study aims to establish an integrated approach for tic detection based on the capabilities of video and electromyography (EMG) modalities. We hypothesize that both modalities would achieve similar levels of performance in accurately detecting tics. We believe that a multimodal approach for tic detection will provide an objective measure for tic evaluation in TS. Six TS participants (19-32), with their consent, attended three consecutive monthly sessions. During these sessions, participants were asked to rest for 3 minutes, freely tic for 8 minutes, and voluntarily move their hands alternately for 3 minutes while simultaneously recording synchronized videos and EMG data. Corresponding video and EMG recordings of 4 participants were labeled independently as 'Rest,' 'Tic,' and 'Move' using an object detection algorithm and a double-threshold approach, respectively, for each data modality. Both video and EMG modalities were evaluated for comparable detection performances. The overall agreement between video and EMG detectors was moderate at 66.9%. Using video modality as the ground truth, EMG accurately detected 75.3% of instances of "Rest" with an 89% recall, 75.3% precision, and an 81.7% F1 Score. However, the detector faced challenges in detecting tic and voluntary movements, achieving respective accuracy levels of 31.3% and 7.7%, along with a low recall (1.5%) and F1-score (2.8%) for tic detection, indicating frequent false positives. A two-tailed t-test revealed a significant difference in tic frequency computed for each detector for the same session recording ($p = 1.67e-10$), emphasizing the need for improved tic detection methods. Comparably strong correlations were found between time (in months) and tic frequency captured with both video ($R^2 = 0.864$) and EMG ($R^2 = 0.995$), demonstrating temporal consistency of tic detections across months. These findings support the hypothesis that multimodal integration could significantly enhance tic detection accuracy and reliability by emphasizing the limitations of single-modality approaches. Future research should focus on advanced machine learning algorithms that leverage multiple data modalities to improve tic detection, ultimately contributing to improved tic outcomes in TS management.

Disclosures: G.T. Lowor: None. M. Osei Opoku: None. J. Gomez: None. W. Tvenstrup: None. A. Noy: None. K. Foote: None. A. Gunduz: None.

Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.14/A60

Topic: A.06. Developmental Disorders

Title: Investigating the Role of the Somato-Cognitive Action Network in Stimulant Treatment Response in Individuals with ADHD

Authors: *G. J. GRIMSRUD¹, N. BYINGTON², R. J. HERMOSILLO³, K. B. WELDON¹, O. MIRANDA DOMINGUEZ⁴, J. R. COHEN⁵, D. A. FAIR¹;

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Abstract: ADHD is a neurodevelopmental disorder often marked by impaired motor control and impulsivity. Predicting treatment response remains difficult due to clinical heterogeneity. While methylphenidate (MPH) is a first-line treatment, its effectiveness is assessed through a trial-and-error process, underscoring the need for neural markers. Our prior work identified somatomotor changes during a go/no-go (GNG) task after MPH administration. The recently defined Somato-Cognitive Action Network (SCAN)—a system within primary motor cortex integrating body representation and goal-directed behavior—may explain these earlier findings. We tested whether SCAN connectivity changes differentiate MPH responders from non-responders.³⁷ medication-naïve children with ADHD and 32 typically developing (TD) controls (ages 8-12; M = 9.99, SD = 1.35; 33 female) completed two sessions of resting-state and task fMRI. ADHD participants completed one session on MPH and one on placebo; TD participants completed two baseline sessions. Dense functional connectivity matrices (dconns) were generated for each session. For ADHD participants, MPH and placebo dconns were correlated to create vertex-wise heat maps of connectivity change. TD comparisons were computed across sessions. Correlation maps were averaged to generate group-level maps for TD, ADHD responders, and non-responders (NR), with group determined by improved in-scanner GNG performance. We identified regions of greatest change by thresholding to areas of low session-to-session correlation ($r = 0-0.5$) and overlaid such areas with the MIDB Probabilistic Precision Brain Atlas to determine likely network identity and subcortical representation. Children with ADHD who exhibited a behavioral response to MPH demonstrated the greatest changes in functional connectivity within the SCAN, suggesting that prior findings related to somatomotor networks may indeed be attributable to SCAN. In contrast, both TD participants and ADHD-NR showed minimal connectivity change across sessions. As SCAN is represented in the posterior putamen, we hypothesize that MPH-induced increases in striatal dopamine may modulate SCAN connectivity subcortically, influencing cortical dynamics in responders. Future work will explore this by examining differences in subcortical SCAN representation and subcortical-cortical connectivity between groups. Further research is needed to investigate alterations in SCAN connectivity associated with more meaningful clinical measures.

Disclosures: G.J. Grimsrud: None. N. Byington: None. R.J. Hermosillo: None. K.B. Weldon: None. O. Miranda Dominguez: None. J.R. Cohen: None. D.A. Fair: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Turing Medical Technologies Inc..

Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.15/A61

Topic: A.06. Developmental Disorders

Support: Healthy Brain Network (HBN) dataset, provided by the Child Mind Institute

Title: Rethinking ADHD Diagnosis with fMRI functional connectivity data: Generalization and Bias Through a Hypergraph-Family Systems Lens

Authors: *Z. CHEN^{1,2}, J. CHEN^{2,3}, Y. QI⁴, W. SHEN⁵, Y. ZOU⁶;

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Abstract: Background: Attention-Deficit/Hyperactivity Disorder (ADHD) is increasingly understood not solely as a unitary neurobiological condition but as a context-dependent manifestation influenced by socio-familial factors. It remains unclear to what extent differences in parental education and associated family-system dynamics modulate children's brain functional connectivity—and, consequently, how these neural alterations affect the accuracy of machine-learning ADHD classifiers.

Methods: We integrated quantitative metadata (parental education, occupation, APQ) and resting-state functional connectivity (200 brain regions) from N=910 (with 626 ADHD children) participants (age 6-21) provided by the Healthy Brain Network (HBN), the signature scientific initiative of the Child Mind Institute, and the Reproducible Brain Charts project (RBC). First, we projected all socio-behavioral features into a low-dimensional “family-behavior-parenting” vector space via autoencoder, then applied Deep Embedded Clustering (DEC) to identify 3 developmental risk phenotypes. Next, we extracted both traditional pairwise connectivity and high-order hypergraph features via Safe Ridge Solver, yielding composite hyperedges reflecting group-wise co-activation patterns. Finally, we trained TabPFN classifiers on pairwise connectivity and hypergraph features to predict ADHD diagnosis.

Results: Hypergraph-enhanced models achieved superior accuracy compared to pairwise connectivity models. Within high-education families, classifiers generalized well, but performance dropped in low-education clusters, indicating structural bias. Notably, hypergraph-selected ROIs differed markedly across family types, suggesting distinct neurodevelopmental patterns.

Conclusions: Our findings demonstrate that hypergraph-based brain features capture ADHD-related network disruptions more robustly than traditional connectivity, and socio-familial context, particularly parental education and family system typology, critically influences both brain phenotypes and machine-learning generalizability. These results underscore the need for “structural fairness” in neuroimaging-based diagnostic tools and support a compositional model of neurodevelopmental diversity.

Disclosures: Z. Chen: None. J. Chen: None. Y. qi: None. W. Shen: None. Y. Zou: None.

Poster

PSTR150: ADHD Behavioral Analyses, Interventions, and Molecular Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.16/A62

Topic: A.06. Developmental Disorders

Support: Ontario Graduate Scholarship

Title: Restricted and repetitive behaviours are associated with the noradrenergic system in neurotypical and neurodiverse children: A neuromelanin-MRI study

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Abstract: Background: Children with autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) can exhibit restricted and repetitive behaviours (RRBs), which are mediated by alterations in dopaminergic (DA) and noradrenergic (NE) processes. Advancements in neuromelanin magnetic resonance imaging (NM-MRI) has offered a unique and non-invasive way to examine dopamine and norepinephrine concentrations in the human midbrain, reflected in NM signal changes in the substantia nigra (SN) and locus coeruleus (LC).

Objectives: To probe midbrain DA and NE functioning in children with and without neurodevelopmental disorders (NDDs) using NM-MRI to enhance our understanding of neuropathophysiological mechanisms underlying RRBs. It was hypothesized that participant age and RRBs would be predicted by NM-MRI signal intensity in the SN and LC, indicative of aberrant DA and NE system functioning in children with NDDs. **Importance:** Identifying early biomarkers of RRBs among children with NDDs will aid in the future development of targeted therapeutic interventions. This research will enhance our ability to support children with NDDs in both clinical and educational settings, ultimately improving their learning experiences and long-term developmental trajectories. **Method:** A sample of 86 participants between the ages of 9-months-old and 21-years-old (46 males, $M_{age} = 9.69$ years, $SD = 5.27$ years) including children with ADHD ($n=32$, 18 males, $M_{age} = 12.63$ years), ASD ($n=11$, 6 males, $M_{age} = 10.73$ years), and typically developing children ($n=43$, 22 males, $M_{age} = 7.24$ years) 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). RRBs were assessed using the Repetitive Behaviors Scale - Revised (RBS-R) and the Repetitive Behavior Scale for Early Childhood (RBS-EC). **Results:** Participant age was significantly predicted by NM-MRI signal intensity in the SN ($\beta=.792$, $p<.001$) and LC ($\beta=.609$, $p<.001$). Further, higher LC NM-MRI signal intensity significantly predicted more severe stereotypic behaviour ($\beta=.908$, $p<.05$), self-injurious behaviour ($\beta=.156$, $p<.05$), compulsive behaviour ($\beta=1.23$, $p<.05$), ritualistic behaviour ($\beta=1.57$, $p<.05$), and restricted interests ($\beta=.895$, $p<.05$). **Conclusion:** This study helps to establish neuromelanin concentration in the locus coeruleus as a candidate biomarker for RRBs among children with NDDs, highlighting the importance of targeting the NE system when developing therapeutic interventions.

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

Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.02/B2

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

Support: U19 NS107616-06
R01 MH119136-05
The PEW Charitable Trusts
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Title: Astrocytes mediate a local positive feedback loop for oxytocin

Authors: ***M. SELLES**¹, M. COOPER², F. LIMONE³, A. AHMED⁴, S. A. LIDDELOW⁵, R. C. FROEMKE⁶, M. V. CHAO⁷;

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Abstract: The world is undergoing an epidemic of loneliness and isolation, underscoring the importance and urgency for understanding the neural mechanisms of social interactions. While there is a growing amount of evidence showing the relevance of oxytocin for social behaviors, less is known about how social interactions - or the lack of them - affect oxytocin neurons. We found a sex-specific effect of long-term social deprivation, decreasing oxytocin levels and delaying affiliation upon reunion in male mice. This phenotype was rescued by stimulation of the endogenous oxytocin system with chemogenetics and by delivery of exogenous oxytocin during the isolation period. Moreover, both approaches induced an upregulation of endogenous oxytocin expression, a phenomenon that we named the **local oxytocin positive feedback loop**. At a cellular level, conditional knock-out studies revealed that **astrocytes are key mediators** of this loop. To investigate the underlying molecular mechanisms regarding the crosstalk between oxytocin neurons and astrocytes, we are combining chemogenetics and fiberphotometry with calcium imaging and RNAsequencing. We found that oxytocin upregulates calcium levels in astrocytes, and are currently investigating molecules involved in this response that can loop back to oxytocin neurons to upregulate its expression. In summary, we found a local positive feedback loop for oxytocin that is dependent on neuron-glia communication in which **astrocytes can sense and modulate the oxytocin system**. This mechanism is relevant for social interactions and represents a potential therapeutic target for disorders and diseases involving social dysfunction - such as autism spectrum disorder and Alzheimer's disease.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.03/B3

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

Title: Factors modulating basal Ca^{2+} and activity-dependent Ca^{2+} influx in dendrites of oxytocin magnocellular neurons in mouse PVN

Authors: *N. ALSHAKHSHIR, S. W. HARDEN, C. J. FRAZIER;
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Abstract: Oxytocin magnocellular neurons (OT-MCNs) release oxytocin (OT) from their axon terminals, soma, and dendrites. Evidence suggests dendritic release as a major source of brain OT, stimulated by activity-dependent Ca^{2+} influx into dendrites and potentiated by Ca^{2+} release from intracellular stores. This project investigates mechanisms that regulate dendritic Ca^{2+} homeostasis involved in modulating dendritic release. NMDA receptors, which are Ca^{2+} -permeable, require both glutamate binding and membrane depolarization for Ca^{2+} influx, making them excellent coincidence detectors. We aimed to test the hypothesis that OT-MCNs express extrasynaptic NMDA receptors on their dendrites that contribute to activity-dependent Ca^{2+} influx underlying dendritic release of OT. We further aimed to test the effect of endogenous ligands known to stimulate dendritic OT release on both basal and activity-dependent Ca^{2+} influx. Experiments were conducted using electrophysiological and optical approaches in PVN OT-MCNs in brain slices extracted from male and female OT-tdTomato reporter mice. NMDA application in Mg^{2+} -free medium increased dendritic Ca^{2+} signals along the dendritic length in both sexes. However, male dendrites exhibited a greater response beginning around 100 μm from the soma, with progressively larger signals at more distal locations. The response in males was largely attenuated by a GluN2C/2D subunit blocker and unaffected by a GluN2B blocker, whereas in females, it was slightly and similarly reduced by both blockers. Furthermore, we found that several endogenously available ligands (OT, norepinephrine, and α -MSH) increased dendritic basal Ca^{2+} , while OT and CRH enhanced dendritic conductivity. The results reveal widespread expression of extrasynaptic NMDA receptors along dendrites, with sex-dependent differences in expression levels and subunit composition, and suggest that modulation of basal Ca^{2+} and dendritic conductivity in dendrites may impact later activity dependent release of OT. Further experiments will attempt to test that hypothesis directly.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.04/B4

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

Support: NRSA 1F31NS127592
 VA I01 BX006921
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 Lacroute Fellowship
 5T32GM141938

Title: Functional role of endogenous opioid peptide met-enkephalin on network dynamics in the mouse hippocampus

Authors: *N. WARIKOO^{1,2}, A. ANDERSON¹, C. DONG^{3,4}, L. TIAN^{3,5}, E. SCHNELL^{2,1};
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Abstract: Opioid drugs potently control neuronal circuitry throughout the brain through their actions at opioid receptors. Endogenous opioid peptides, such as met-enkephalin (ME), are produced, packaged, and released by neurons, but their contributions to neural network dynamics are less known. Here, we utilize optogenetics and electrophysiology in mouse brain slices to interrogate the effects of ME in the hippocampal circuit. Bath application of ME causes network disinhibition in the dentate, as assessed by its ability to increase the ratio of excitatory to inhibitory evoked synaptic currents in granule cells after electrical stimulation of molecular layer inputs. Further investigation revealed that ME preferentially acts at inhibitory synapses, likely by inhibiting GABA release from presynaptic terminals, while having no effect on excitatory transmission. Similar results were obtained in region CA3, suggesting a broader role for enkephalin on network disinhibition. Ongoing studies aim to understand the effect of electrically evoked endogenous opioid peptide release on PV-mediated inhibition in region CA3. Additionally, we virally expressed the novel opioid biosensor deltaLight in mouse hippocampus and found that it reliably detects exogenously applied opioid peptide ME in a concentration-dependent manner. Ongoing studies aim to visualize endogenous opioid peptide release in healthy and translationally modeled epileptic brain slices, to understand how endogenous opioids modulate circuit excitability in brain disease.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.05/B5

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

Title: An intriguing puzzle of cortical cholecystokinin gene expression

Authors: *S. J. SMITH^{1,2};

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Abstract: Single-cell RNA-sequencing (scRNA-Seq) data offer extraordinarily panoramic perspectives on the brain's myriad neuropeptide signaling networks. This poster presents an analysis of such data from a published scRNA-Seq data from mouse cortex (PMC8195859). This analysis exposes high expression of at least 20 different Neuropeptide Precursor Protein (NPP) genes and 34 conjugate Neuropeptide-selective G-Protein Coupled Receptor (NP-GPCR) genes, expressed in varied but highly cell type specific patterns. Very nearly every neuron sequenced showed expression of at least one NPP (99.3% of neurons) and at least one NP-GPCR gene (99.9% of neurons). These data suggest that many distinct neuropeptide (NP) networks interconnect cortical neurons locally and very densely, with connectivity determined by differential expression of NPP and NP-GPCR genes, by anatomical details, and by the physics of interstitial neuropeptide diffusion. We focus here on expression patterns of two genes related to signaling by the neuropeptide cholecystinin (CCK): (1) *Cck*, which encodes the NPP from which active CCK is produced post-translationally, and (2) *Cckbr* encodes an excitatory (Gq/11-coupled) NP-GPCR selective for active CCK. CCK has attracted much because of observations linking CCK signaling in brain to appetite, anxiety, memory and brain cancers. Consistent with earlier studies (reviewed in PMC3005241), we find that *Cck* transcripts are by far the most abundant NPP transcripts in mouse cortex. We also find that *Cck* transcripts abound in by far the largest fraction of neurons (81.9% of all neurons sequenced; 91.2% of all glutamatergic pyramidal cells) and that they rank very highly in abundance (99.9th percentile) as compared to all 19,750 genes mapped in our resource dataset. Furthermore, co-expression of the *Cck/Cckbr* pair is also quite striking, being observed in 72.1% of all glutamatergic pyramidal cells. This co-expression is all the more notable because it is very uncommon for the CCK-positive GABAergic neurons. These patterns of *Cck* and *Cckbr* gene expression are especially intriguing because of prospects we outline here for regenerative signaling modalities portended by the transcriptomic and ultrastructural data. They are nonetheless very puzzling because even though CCK peptide is readily detectible by immunostaining in a subset of cortical GABAergic neurons, such detection has not been reported for the glutamatergic pyramidal neurons. We outline several possible resolutions and argue that new research aimed at solving this puzzle is likely to shed very bright new light on cortical plasticity mechanisms.

Disclosures: S.J. Smith: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Aratome, LLC.

Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.06/B6

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

Support: UVA Brain Institute

Title: Bdnf signaling as a dual-rheostat mechanism for AgRP neuron plasticity in response to caloric state

Authors: *Y. CALHAN, E. GODSCHALL, A. D. GULER, C. D. DEPPMANN;
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Abstract: The hypothalamus orchestrates feeding behavior to maintain energy homeostasis, but the molecular mechanisms allowing this system to adapt across different metabolic states remain poorly understood, a critical gap given the rising prevalence of metabolic disorders. Here we reveal a novel dual-rheostat mechanism wherein BDNF signaling through two opposing receptors, TrkB and p75NTR, differentially regulates AgRP neuron plasticity depending on caloric state. Caloric restriction (CR) transiently increases BDNF expression in the paraventricular hypothalamus (PVH) while selectively upregulating TrkB receptor expression in AgRP neurons. In contrast, high-fat diet (HFD) sustains elevated PVH BDNF expression while robustly enhancing p75NTR expression in these same neurons. These opposing molecular adaptations drive unexpected structure-function relationships: CR increases AgRP→PVH fiber density without enhancing feeding responses, while HFD decreases fiber density yet paradoxically amplifies AgRP-driven orexigenic capacity. Genetic evidence confirms this model: deleting p75NTR from AgRP neurons increases PVH fiber density yet blunts feeding responses, while TrkB deletion decreases innervation but amplifies orexigenic capacity, demonstrating that each receptor controls distinct aspects of the adaptive response. Thus, BDNF signaling via TrkB and p75NTR forms an adaptable dual-rheostat system that uncouples structural connectivity from functional output, enabling hypothalamic circuits to precisely calibrate feeding behavior according to metabolic demand, a mechanism that may be targeted to address disorders of energy balance.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.07/B7

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

Support: FONDECYT 1221508

Title: Effects of β -hydroxybutyrate on neuroendocrine neurons and feeding behavior

Authors: *V. A. SEPULVEDA¹, L. AGUAYP², M. GARCIA ROBLES³;

¹Biología Celular, Univ. de Concepción, Concepción, Chile; ²Univ. de Concepción, Concepción, Chile; ³Cell Biol., Univ. of Concepción, Concepción, Chile

Abstract: Introduction: The hypothalamus is a key regulator of energy homeostasis, integrating peripheral signals such as glucose through specialized glial cells called tanycytes. Under low-glucose conditions, we have shown that tanycytes increase the secretion of β -hydroxybutyrate (β HB), the primary ketone body produced in mammals, to the medium. While long-term intermittent fasting has been associated with appetite suppression, our findings suggest that acute increases in β -HB levels can depolarize POMC neurons in the arcuate nucleus and promote food intake. On the other hand, the role of the β HB receptor HCAR2 (also known as GPR109A), a Gi/o protein-coupled receptor, in the regulation of appetite remains largely unexplored. Here we explore HCAR2 distribution in the brain and the effect of β HB icv injection on food behavior. Material and Methods: We used coronal brain slices from C57BL/6 mice to characterize HCAR2 expression across various brain regions using qPCR, western blot, in situ hybridization (ISH), and immunofluorescence. To determine HCAR2 expression specifically in hypothalamic neurons, we examined its colocalization with POMC-eGFP and NPY-eGFP neurons in transgenic mice and performed fluorescence-activated cell sorting (FACS) followed by qPCR to quantify HCAR2 mRNA levels in isolated POMC and NPY neurons. To assess neuronal activation, we conducted c-Fos immunofluorescence in transgenic mice following icv injection of β HB, focusing on POMC and NPY neurons. Finally, we evaluated feeding behavior after icv β HB administration. Results: We examined HCAR2 expression in several brain regions, detecting it in the cortex, hippocampus, cerebellum, and hypothalamus. We demonstrated its colocalization with NPY and POMC neuron populations in the arcuate nucleus. Cell sorting and qPCR allowed us to show that NPY and POMC neurons expressed good levels of HCAR2. Furthermore, icv injection of β HB increased c-Fos expression in NPY neurons. Interestingly, icv administration of 10 μ L of 50 mM β HB significantly increased cumulative food intake up to 4 hours post-injection. Additionally, a significant reduction in meal interval duration was observed, suggesting a decrease in satiety. Discussion: As β HB presents a potent orexigenic effect, we can hypothesize that local synthesis of β HB by tanycytes can stimulate NPY neurons via extracellular β HB. Since HCAR2 is a Gi-coupled receptor, the activation of NPY neurons may occur through an indirect pathway, ultimately influencing food intake.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.08/B8

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

Support: VA I01 BX006921
NIH NINDS R01 NS126247

Title: Enkephalin upregulation in the mouse hippocampal dentate gyrus after seizures

Authors: *C. P. TRAN^{1,2}, A. N. ANDERSON^{1,2}, N. WARIKOO^{1,2}, E. SCHNELL^{1,2};
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Abstract: Hippocampal dentate granule cells express a variety of peptide neurotransmitters, including the endogenous opioid peptides dynorphin and enkephalin. Although dynorphin appears to be constitutively expressed in granule cells, enkephalin expression appears sparse in healthy mouse hippocampus but is increased in epileptic hippocampus. To understand the timecourse of enkephalin expression during the development of epilepsy, we are using a variety of translational models of seizures and epilepsy in mice and quantifying enkephalin levels using RT-PCR, in situ hybridization, or immunohistochemistry. We found that the timecourse, variability, and duration of enkephalin upregulation depends on the specific seizure model used, and most notably, the duration and intensity of the initial seizure events. Using pentylentetrazol (PTZ) injected intraperitoneally, mice experienced seizures of variable duration and intensity with inconsistent and short-duration increases in enkephalin expression. Kainic acid injections (either intraperitoneal or intraparenchymal) more consistently induced enkephalin upregulation, and enkephalin expression remained elevated for a longer duration. Pilocarpine-induced status epilepticus caused an efficacious and long-lasting increase in enkephalin expression but was a less consistent model due to variability in achieving status epilepticus between mice. Ongoing studies aim to more completely define the timecourse of these changes, and to clarify patterns of enkephalin expression using Proenkephalin-Cre::reporter mice. Through this work, we hope to identify patterns of enkephalin upregulation which will be helpful to understanding the functional roles of enkephalin in hippocampal circuits during epileptogenesis.

Disclosures: C.P. Tran: None. A.N. Anderson: None. N. Warikoo: None. E. Schnell: None.

Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.09/B9

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

Support: NIH/NIDA DA049257

Title: Intranasal Galanin Nanoparticle Delivery Reduces Latency to Flurothyl-Induced Seizures in Mice

Authors: *E. GUO¹, B. S. PATE¹, D. WEINSHENKER²;
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Abstract: Galanin is a 29-amino acid neuropeptide whose receptor (GalR1) is co-expressed with μ -opioid receptors in reward-associated brain regions including the ventral tegmental area (VTA) and rostromedial tegmental nucleus (RMTg). Past literature has shown

intracerebroventricular(ICV) galanin delivery to the VTA attenuates morphine-induced conditioned place preference(CPP), demonstrating promise for opioid use disorder treatment. However, galanin cannot pass the blood-brain barrier (BBB), representing a major obstacle for clinical translation. Because other neuropeptides have been successfully delivered to the brain via intranasal administration, we investigated whether intranasal galanin-loaded nanoparticles can bypass the BBB. CPP is a multi-day, labor-intensive paradigm that is too inefficient for exploratory drug delivery testing. Galanin has anticonvulsant effects in mice, so we used seizure susceptibility as a simple and fast bioassay to assess whether intranasally delivered galanin can influence a brain-mediated, clinically-relevant behavior. Galanin was encapsulated in bovine serum albumin(BSA) nanoparticles using a Tween-based method at optimized ratios that have been validated for oxytocin administration. Adult C57BL/6J mice received intranasal galanin-loaded nanoparticles [DW1] or empty nanoparticle [DW2] controls. Two hours post-administration, mice were exposed to flurothyl vapor to induce generalized tonic-clonic seizures (GTCS), and onset latency was measured. Galanin-treated mice demonstrated a borderline significant reduced seizure latency compared to controls (429.0 vs 564.3 seconds; n=13; p=0.055). This proconvulsant effect, while the opposite of predicted based on other galanin seizure studies, provides evidence that intranasally delivered galanin can successfully cross the BBB and modulate behavioral changes. These findings establish intranasal nanoparticle delivery as a viable non-invasive route for CNS galanin delivery. Future studies will quantify brain galanin levels via ELISA and evaluate whether intranasal galanin attenuates morphine-induced conditioned place preference, bridging preclinical findings toward therapy for opioid use disorder.

Disclosures: E. Guo: None. B.S. Pate: None. D. Weinshenker: None.

Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.10/B10

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

Support: CONAHCYT 1008205

Title: Localization and functionality of cb1 and cb2 receptors in mice globus pallidus neurons

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Abstract: The endocannabinoid system plays a critical modulatory role in basal ganglia (BG) function, yet its cellular specificity within the globus pallidus (GP) remains poorly understood. Whether cannabinoid receptors CB1 and CB2 are differentially expressed and functionally active

in the two principal GP projection neurons—prototypical and arkypallidal—has not been fully elucidated. This study aimed to investigate the localization and synaptic roles of CB1 and CB2 receptors across these distinct neuronal populations. We conducted immunofluorescence analysis using parvalbumin and Foxp2 as molecular markers to distinguish prototypic and arkypallidal neurons, respectively, and mapped the rostrocaudal distribution of CB1 and CB2 receptors in the GP of P12-P14 C57BL/6 mice. Additionally, we performed whole-cell patch-clamp recordings in acute brain slices to assess the pharmacological effects of selective CB1 (ACEA) and CB2 (GW833972A) agonists on GABAergic synaptic transmission at pallid-nigral and pallid-striatal synapses. Our results reveal a robust co-expression of CB1 and CB2 receptors in approximately 80% of prototypic neurons throughout the GP. Electrophysiological recordings showed that activation of both receptors reduced the evoked inhibitory postsynaptic currents (eIPSC) amplitudes at pallido-nigral synapses via a presynaptic mechanism. Arkypallidal neurons also co-expressed both receptors; however, preliminary data suggests that CB2 activation does not modulate GABA release at pallido-striatal synapses. These findings suggest a selective involvement of cannabinoid receptors in modulating GP output, particularly within the indirect pathway via prototypical neurons. This cellular and functional specificity may have important implications for therapeutic strategies targeting motor disorders involving BG dysfunction.

Disclosures: C. Castillo-Chávez: None. I.O. Conde Rojas: None. J.A. Fuentes: None. F.J. Paz: None. F. Rodriguez Cruz: None. G.B. Floran: None.

Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.11/B11

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

Support: CAPES #88887.666324/2022-00
FAPESP #2017/27131-9
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FUSP/ Institute of Chemistry #403601

Title: Sars-cov-2 infection promotes impairments and increases neuroinflammation in astrocytes derived from hipsc from autistic patients

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Abstract: During the COVID-19 pandemic, families of individuals with Autism Spectrum Disorder (ASD) reported worsening of autism-related symptoms following SARS-CoV-2 infection. This led to the hypothesis that COVID-19 may aggravate pre-existing neuroinflammation in autistic individuals, contributing to increased stereotypies and aggression. Despite the clinical relevance, data on the pandemic's impact on ASD remains limited. It is therefore essential to further investigate the impact of COVID-19 on this population, especially considering that such global events often involve social isolation, disruption of routines, and separation, factors known to affect the clinical condition of autistic individuals negatively. We used astrocytes derived from human-induced pluripotent stem cells (hiPSCs) from autistic patients to infect them with SARS-CoV-2 at two multiplicity of infection (MOI) levels (0.05 and 0.5). We analyzed cell death by CASP-3 expression, glutamate optical density, and inflammatory cytokines by Luminex assays. Statistical analyses were performed using the t-test and Two-way ANOVA with a p-value < 0.05. Based on the pre-existing inflammation in astrocytes derived from autistic patients, we investigated the effects of SARS-CoV-2 infection on these cells. First, we observed morphological changes and cell death in astrocytes at 72 hours compared to the MOCK control, as shown in the bright-field images, immunofluorescence assays, and CASP-3 expression. By glutamate optical density, we observed a statistically significant difference between 24 hpi and 48 hpi, with cell death after this time point. Considering genes E, RdRp, and N, there is no evidence of viral replication in astrocytes derived from autistic children. In contrast, analyzing cytokines revealed a pro-inflammatory profile, marked by elevated IL-6, RANTES, TNF α , MCP-1, IFN γ , and IL-4 levels in the culture supernatant of astrocytes derived from autistic children compared to those derived from neurotypical children. IL-6 is a biomarker for COVID-19 severity, but it is also increased in ASD. Considering that, we hypothesize that SARS-CoV-2 infection could worsen the ASD symptoms. We observed that SARS-CoV-2 infection in astrocytes derived from autistic children presented an exacerbation of the neuroinflammation profile. These findings reveal that SARS-CoV-2 disrupts astrocyte function, leading to neuroinflammation and cell death that may underlie the neurological sequelae of COVID-19 in the autistic population.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.12/B12

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

Support: Zachry Foundation Endowment for Alzheimer's Clinical Care and Research
Greehey Family Foundation Endowment for Alzheimer's Research

Title: Genomic variations in the small conductance calcium activated potassium channel SK3 impact on dopaminergic function

Authors: L. PADILLA¹, A. S. KOKENGE², J. MARTINEZ², C. DEL VAL³, I. ZWIR⁴, D. B. NEIDRE⁵, *G. A. DE ERAUSQUIN⁶;

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Abstract: We analyzed splicing variants and structural mutations of KCNN3 to predict their functional impact. Of five splicing variants of the KCNN3 gene, four are in coding regions. Variants ENST00000618040.4 and ENST00000271915.9 encompass 746 and 731 amino acids, respectively, whereas EST00000361147.8 and ENST00000358505. encompass 426 and 418 amino acids respectively. Variants ENST00000618040.4 and ENST00000271915.9 have nearly identical sequences, differing only by a segment insertion in position 484. Variants ENST00000361147.8 and 154 ENST00000358505.2 are also nearly identical, except for positions 309-314. Three dimensional structures obtained using AlphaFold reveal visible differences in the protein conformation as the result of each variant. Analysis of the short variants and their coding regions with more detail using Ensembl database revealed absence of the motif required for potassium channels, resulting in loss of function. The two longer variants express all the segments for that motif and are both functional despite the segment insertion. Structural variants were studied in Ensembl in an effort to study the documented mutations that have a known pathogenic effect and further analyzed with SIFT. From the 2394 reported variants, 13 variants were identified that were predicted as pathogenic with SIFT and were backed by publications. 13 pathogenic variants result from missense mutations, in which the resulting protein is largely the same but will encode a different amino acid at a given position due to a nucleotide substitution. In all cases, the consequential effects depend on the specific location and role of the amino acid being changed.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.13/B13

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

Title: Neuron-specific regulation of extracellular vesicle secretion and content by NSG family members NSG1 and NSG2

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Abstract: Members of the neuron-specific gene family (NSG1-3) are small adaptor proteins that regulate trafficking and processing of multiple proteins throughout the secretory and endosomal pathways, including AMPA receptors, Neuregulin-1 and Sortilin-1. Previous research showed the presence of NSG1 in intraluminal vesicles of multivesicular bodies as well as binding to L1CAM, a protein known to be present in extracellular vesicles (EVs). Further, Proximity-based proteomic analysis of all family members showed that NSG1-3 biotinylated a plethora of proteins present in EVs including CFL1, CLTC1, ENO1, GAP43, and FLOT1. Here we directly examined whether NSG1-3 had a potential role in transcellular signaling via secretion of EVs from neurons. We found both NSG1 and NSG2 proteins were present in abundance in EVs isolated from human and mouse neurons, but not from other cell types including astrocytes. Surprisingly, NSG3 was not present in EVs from any cell type tested. Differential centrifugation and filtration of various types of EVs showed that NSGs are not present in apoptotic vesicles, and were contained in EVs < 200nm in diameter, suggesting their enrichment in small EVs. Using primary cultures from knockout animals of individual and combinations of NSG1-2, we further determined that both EV abundance and content were significantly regulated by NSG1-2. Interestingly, loss of NSG1 significantly reduced overall EV abundance, while NSG2 had a significant effect on RNA content. Further, we found robust changes in transcripts that were previously shown to be altered in EVs taken from models of Alzheimer's disease. Together, these data point to a significant role of NSG1 and NSG2 on the secretion and content of EVs, specifically derived from neurons, which may have implications for neuronal plasticity and degeneration.

Disclosures: L. Vega: None.

Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.14/B14

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

Support: NIH DIRP ZIAMH002797

Title: Exploring the dynamics of brain extracellular space

Authors: *S. PAJEVIC;

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Abstract: The brain's extracellular space (ECS) is a narrow and dynamic microenvironment that plays pivotal functional roles in intercellular communication, ionic homeostasis, and transport of nutrients/metabolic waste via elaborate glymphatic system. The intricate geometry and composition of the ECS are active areas of research; however, existing dynamical models primarily focus on convective and diffusive transport. Here, we address a novel ECS dynamical mechanism that involves gap junction (GJ) plaques (GJP), forming tight binding between apposing cells. Typically, open GJ channels enable fast diffusion of ions and small molecules, facilitating direct intracellular communication and the formation of functional syncytia between neurons or astrocytes. However, in the ECS, the GJP are ionic traps, not only in the context of the Stern layer but also beyond. We argue that in such narrow, 2-4 nm wide ECS space, Gouy-Chapman (GC) diffuse layer cannot form and that even the improvements on GC theory that include finite size of water molecules and ions, e.g. the Bikerman model, are not sufficiently accurate to describe the electric potential within such narrow space with low water dielectric constant. We study theoretically a set of biologically plausible potentials in 1D and 2D, as well as their tensored 3D equivalents. In particular, we explore different 2D lattice configurations, which, in our idealization of the problem, can form higher-order, superlattice-like configurations at larger spatial scales. At the local level, they can facilitate weakly bound electronic states, enabling stochastically and externally driven conduction while having sufficiently large energy gaps to support stable collective modes. We compare the characteristic thermal mixing time to other times (e.g., braiding, attempt) in different settings (2D vs 3D; open vs closed channels) and argue that topologically stable modes can exist on physiologically relevant time scales. We argue that even when only a tiny fraction of the density matrix is off-diagonal, it can have a consequential role on neural properties. We show this by hierarchical decomposition into different modes (bosonic, fermionic, anyonic, skyrmion-like, etc), elucidating the connection with integrative and discriminative properties. Our idealized model's role is to elucidate the basic principles of this mode of operation, relevant for the regions rich in GJP, e.g., TRN sectors. Currently, direct experimental investigations of such narrow ECS space and relevant nuclei with abundant GJ coupling are scarce. We expect that enhanced characterization of the ECS and its lattices will yield more accurate and testable predictions.

Disclosures: S. Pajevic: None.

Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.15/B15

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

Support: NSF Grant IOS-2338915

Title: Opposing Effects of Anandamide on Nociceptive vs. Non-Nociceptive Synapses: A Concentration-Dependent Effect?

Authors: *B. D. BURRELL;

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Abstract: Despite considerable interest, effective analgesic treatments using cannabinoids have yet to be developed. A critical barrier is that cannabinoids have both anti-nociceptive and pro-nociceptive effects, but it is not clear how to access the former without the latter. In prior studies using the medicinal leech, *Hirudo verbana*, we have studied opposing effects of endocannabinoids (eCBs) on nociceptive and non-nociceptive synapses in detail. Both 2-arachidonoylglycerol (2-AG) and N-arachidonylethanolamide (AEA) depress nociceptive synapses, an anti-nociceptive effect that can be reproduced by low frequency stimulation (LFS) of non-nociceptive afferents. 2-AG and AEA also potentiates non-nociceptive synapses via disinhibition, a pro-nociceptive effect that can be reproduced by high frequency stimulation (HFS) of nociceptive synapses. Furthermore, LFS only produces eCB-dependent depression of nociceptive synapses, while HFS only produces eCB potentiation of non-nociceptive synapses. How does activity selectively produce one form of eCB-mediated modulation, but not the other? One possibility is that opposing effects of eCBs are concentration-dependent, e.g., low levels elicit depression while high levels elicit potentiation. To test this idea, 1 nM to 10 μ M AEA was applied to the *Hirudo* CNS with changes in nociceptive and non-nociceptive synapses observed 30 mins after washout. AEA $\geq$ 10 nM elicited both depression in nociceptive synapses and potentiation in non-nociceptive synapses, suggesting no concentration-dependent mechanism, at least for exogenously applied AEA. AEA-mediated potentiation was blocked by both inhibitors of TRPV channels and CB1 receptors. On the other hand, AEA-mediated depression was not blocked by either TRPV or CB1 inhibitors. Interestingly, LFS (which normally does not elicit eCB-mediated potentiation) did potentiate non-nociceptive synapses when LFS was combined with a FAAH inhibitor (FAAH breaks down AEA). These findings suggest that when exogenously-applied, different AEA concentrations do not have different pro- vs. anti-nociceptive effects. However, activity can regulate AEA synthesis and release spatially so that AEA levels are locally controlled to produce either nociceptive synaptic depression or non-nociceptive potentiation.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR151.16/B16

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

Support: European Research Council, AVIAN MIND, ERC-2020-ADG, LS5, GA No. 101021354
Ruhr University Research School, funded by Germany's Excellence Initiative [DFG GSC 98/3]

Title: Calcium-binding protein distributions in different sensory- and motor-related areas of the pigeon (*Columba livia*)

Authors: *K. HASELHUHN¹, O. GUNTURKUN³, N. ROOK²;

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Abstract: For over a century, the unique structure of the avian brain has captivated neuroscientists, particularly due to the remarkable cognitive abilities exhibited by birds despite their distinct forebrain architecture. In contrast to the six-layered neocortex that underpins higher-order processing in mammals, the avian forebrain was thought to be organized in a nuclear configuration, comprising the dorsal ventricular ridge (DVR) and the visual Wulst, a quasi-laminar structure. The Wulst stems from the dorsal pallium and thus is considered to share genetic, and some structural and functional parallels with the mammalian neocortex. In contrast, the DVR was thought to be composed of several discrete nuclei that all have no obvious mammalian homologue. However, emerging evidence suggests that both the Wulst and sensory domains within the DVR exhibit laminar and columnar organizational features reminiscent of cortical architecture. Despite these insights, the neurochemical characterization of the DVR and Wulst remains relatively underexplored. In this study, we examined the distribution of the calcium-binding proteins calbindin (CB), calretinin (CR), and parvalbumin (PV), and their relationship to GABA, across sensory domains of the DVR and the Wulst, comparing their expression patterns with those observed in mammalian cortical layers. Notably, we found that calretinin, which is characteristically absent from layer 4 of the mammalian neocortex, was similarly absent from the primary input layer of the visual Wulst, while calbindin and parvalbumin can be found. In contrast, all three calcium-binding proteins were robustly expressed in the entopallium, nucleus basalis, and field L2, regions that are the primary input areas of the DVR. These findings show that the visual Wulst as a true homologue of the neocortex shares numerous similarities at the neurochemical level. In contrast, the DVR exhibits convergent features at the architectural level but is more distinct in terms of chemoarchitecture. In motor- and executive-related areas, like arcopallium, striatum and nidopallium caudolaterale (NCL), CR is mostly dominant, but CB shows a high overlap with GABA, suggesting a regulatory role in motor inhibition. The analyzed areas also show that co-expression of all three calcium-binding proteins is rare, while dual expression in all combinations is more common. This could be due to the different functions of the areas, as it is more common to have PV, a slow calcium buffer, overlap with CB or CR, which are both acting as fast calcium buffers.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

Location: SDCC Halls B-H

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Program #/Poster #: PSTR151.17/B17

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

Title: Slow axonal transport of clathrin cargoes is facilitated by rab vesicles

Authors: *R. SHARMA¹, A. BHATT¹, L. A. PARRA², S. ROY³;

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Abstract: Proteins and macromolecules are transported in axons and synapses via fast and slow axonal transport, which operate at different rates. Pulse-chase radiolabeling studies show that the composition of these transport types varies. While fast transport carries vesicles and mitochondria, cytoskeletal and soluble (or cytosolic) proteins are conveyed in slow axonal transport. Here we show that surprisingly, clathrin - a protein known to move in slow axonal transport - is conveyed as vesicles that also contain other endocytic proteins such as AP-2 and FCHO, as well as multiple Rab proteins. The biogenesis of clathrin transport-carriers depends on an intact ER-Golgi network, and the transport of individual particles resemble a stop-and-go motion that has been seen with cytoskeletal polymers moving in slow transport. We also developed a RUSH (Retention Using Selective Hooks) assay to capture clathrin transport carriers or synaptotagmin-1 vesicles in the neuronal soma and then release them into the axon at specific time points. This confirmed the slow overall movement of clathrin and allowed us to identify specific Rab proteins involved in this process. Super-resolution imaging indicated that these clathrin cargoes do not colocalize; instead, they appear to "piggyback" on vesicles containing Rab4. Furthermore, the non-endocytic clathrin pool in non-neuronal cells is found to specifically associate with Rab4-containing vesicles. Overall, our findings challenge the prevailing belief that vesicles can only move via fast axonal transport and provide a mechanistic understanding of a unique cargo complex conveyed through slow axonal transport.

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Poster

PSTR151: Molecular Signaling: Diversity and Mechanisms

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Program #/Poster #: PSTR151.18/B18

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

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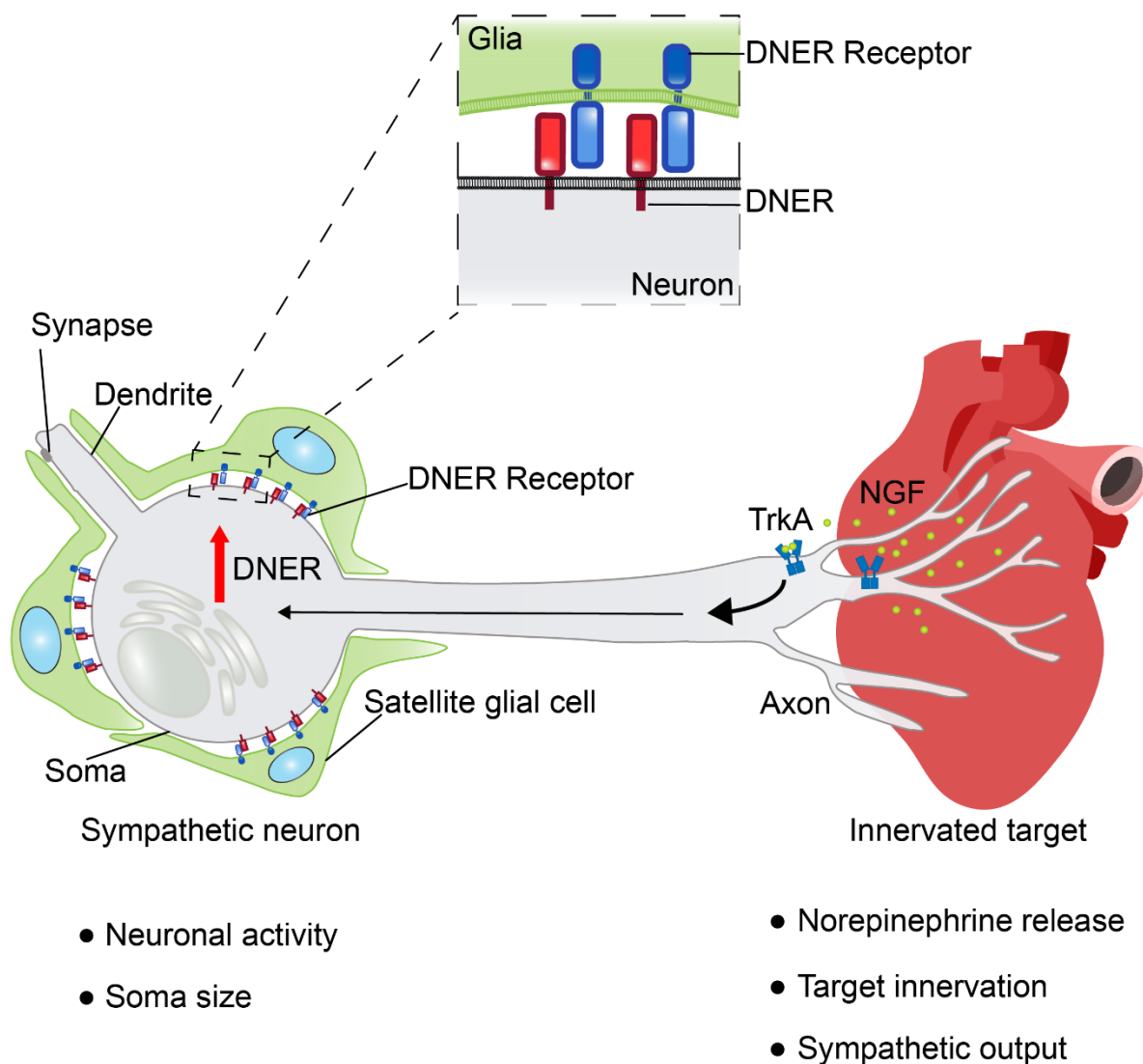
Title: Retrograde control of sympathetic neuron-satellite glia interactions by target-derived NGF signaling

Authors: *R. KUMARI¹, B. W. JONES³, R. KURUVILLA²;

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Abstract: Satellite glial cells (SGCs) are the major glial cells in sympathetic ganglia, contacting neuronal cell bodies. The intimate association of SGCs with sympathetic neurons ideally

positions these glia as critical regulators of neuronal homeostasis, architecture, and function. However, how these neuron-glia interactions are established remains unclear. Here, we identify a contact-mediated pathway triggered by retrograde signaling from innervated sympathetic targets that underlies neuron-SGC interactions, neuronal morphology, and functional output. We found that neuronal expression of a transmembrane protein, Delta/Notch-like EGF-related receptor (DNER), is dependent on signaling by target-derived nerve growth factor (NGF). Neuronal DNER deletion disrupts neuron-SGC contacts, and results in aberrant neuronal morphology, including decreased soma size and hyper-innervation of targets in mice. DNER mutant neurons have elevated activity, and mice lacking neuronal DNER exhibit increased heart rate and thermogenesis, indicative of enhanced sympathetic tone. These results suggest a mechanism whereby innervated targets control assembly of functional neuron-glia units in the sympathetic nervous system.



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Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.01/B19

Topic: B.05. Synaptic Plasticity

Support: YS-24-194

Title: Chronic Inhalation of Toluene Induces Long-lasting Synaptic Changes in the Adolescent Rat Brain: An Electron Microscopy Study

Authors: *N. POCHKHIDZE^{1,2};

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Abstract: Toluene is a common inhalant known to affect brain function, especially during adolescence when the brain is still developing. This study looked at how chronic exposure to toluene changes the structure of synapses—the connections between nerve cells—in adolescent male Wistar rats. Rats were exposed to 2000 ppm of toluene for 5 minutes each day over 40 days. To understand the effects, we tested their behavior and examined their brain tissue using electron microscopy to see detailed changes in synapses. Our findings showed clear damage to the synapses, including fewer synaptic connections, irregularities in synaptic vesicles, and swollen mitochondria inside nerve endings. These changes were mainly seen in parts of the hippocampus important for learning and memory. Rats exposed to toluene performed worse on memory tests, suggesting the synaptic damage may underlie their cognitive problems. This work helps explain how repeated exposure to inhaled toluene can harm the brain during critical developmental stages. Knowing this can guide efforts to prevent and treat brain damage caused by solvent abuse.

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Disclosures: N. Pochkhidze: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.02/B20

Topic: B.05. Synaptic Plasticity

Support: R01-20230205-#30v2

Title: The Role of the Activity-Dependent Mechanisms in Corticolimbic Circuits on Maternal Behavior: Role of Microtubules and GRP+ Circuits in the mPFC

Authors: *C. VELAZQUEZ DELGADO;
Rutgers Univ., Highland Park, NJ

Abstract: Maternal behavior relies on neuroplasticity within the corticolimbic system, including the medial prefrontal cortex (mPFC), hippocampus (HPC), and basolateral amygdala (BLA). Microtubules (MTs) are crucial for neuronal structure and synaptic function, and their regulation via stathmin, a MT-destabilizing protein, is essential for adaptive plasticity. Phosphorylation of stathmin (Ser16/25) increased peripartum in wild-type (WT) mice, inhibiting its MT-destabilizing activity. To investigate MT-dependent mechanisms in maternal behavior, we used a gain-of-function Stat4A mutant, which irreversibly binds tubulin, depleting free tubulin and destabilizing MTs selectively in GRP+ neurons. Stat4A mothers exhibited deficits in MT stability, synaptic GluA2 levels, and dendritic spine plasticity in the HPC, suggesting impaired synaptic remodeling required for maternal adaptations. RNA-seq analysis of the mPFC revealed distinct transcriptional changes in Stat4A mothers, particularly in genes related to synaptic vesicle membrane composition, postsynaptic protein localization, and MT depolymerization. Additionally, chronic corticosterone (Cort)-induced maternal stress reduced MT stability and stathmin phosphorylation, indicating a convergent mechanism underlying maternal deficits. Importantly, blocking GluA2 endocytosis via TAT-GluA23 γ peptide in the mPFC rescued pup retrieval in Stat4A mothers, restoring maternal care. These findings highlight the critical role of MT integrity in synaptic plasticity and maternal behavior, providing insights into molecular pathways that regulate parenting

Disclosures: C. Velazquez Delgado: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.03/B21

Topic: B.05. Synaptic Plasticity

Support: HRZZ IP-2024-05-5754

Title: Tempo and mode of dendritic spine morphological changes depending on synaptopodin presence in hippocampal granule cells following complete perforant pathway transection in wild-type mice

Authors: *M. ZELIC, F. BOŽIC, D. SMILOVIC, M. VUKSIC;
Croatian Inst. for Brain Res., Zagreb, Croatia

Abstract: Traumatic brain injury and a plethora of neurodegenerative diseases cause neuronal damage at the site of the lesions but also in distant cortical areas due to axonal damage and reduction of input through denervation. Classical neuroanatomists employed the transection of the perforant pathway fibers in animal models in order to study the principles of neuronal reorganization and dendritic plasticity within the dentate gyrus of the hippocampal formation. In this research, we combined the stereotactical entorhino-hippocampal denervation in C57BL/6 male young adult mice with intracellular fluorescent dye injections, immunofluorescence and confocal imaging to study the response of granule cells' dendritic spines in the denervated outer molecular layer (OML) and non-denervated inner molecular layer (IML) of the dentate gyrus within the first-month post-lesion. A particular correlation was found between the spine content of synaptopodin (SP), a protein necessary for spine apparatus formation and actin-related structural plasticity, and spine density and size measurements. Specifically, this study shows that in the OML, SP-negative spines are rapidly eliminated during the first 3 days post-denervation, with complete recovery of total spine density by 14 days post-lesion. During the period of reduced spine density, the remaining population of SP-negative spines exhibits a structural plastic response by increasing total spine head volume, measured as the maximum area in a two-dimensional cross-section. Simultaneously, the population of SP-positive spines shows an increased resilience to denervation with significantly lower changes in structural plasticity. Their spine head size remains the same during the one-month post-denervation period, while they also exhibit an increase in overall density. These findings imply that synaptopodin could be linked to granule cell spine adaptability to the loss of input and that SP-positive spines demonstrate increased stability without significant structural plasticity. In contrast, SP-negative spines demonstrate a highly dynamic response as they compensate for the reduction of synaptic input by expanding their receptive volume.

Disclosures: M. Zelic: None. F. Božic: None. D. Smilovic: None. M. Vuksic: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.04/B22

Topic: B.05. Synaptic Plasticity

Support: NSF Cooperative Agreement #OIA-2242771
NASA West Virginia Space Grant Consortium, Grant #80NSSC25M7079

Title: Silver nanoparticle-induced disruption of the tripartite synapse in rat brain

Authors: *E. S. WILLIAMS, R. N. SMITH, A. M. BORA, N. SPITZER;
Biol. Sci., Marshall Univ., Huntington, WV

Abstract: The antibacterial properties of silver nanoparticles (AgNPs) and low eukaryotic toxicity of silver has led to their incorporation in consumer products such as wound dressings and cosmetics. AgNPs can be released into the environment during product use and manufacturing, leading to possible exposure of animals by ingestion or inhalation. AgNPs cross the blood-brain barrier (BBB) and once inside, bioaccumulate and persist in brain tissue. Previously we found that AgNP exposure induces disruption of the F-actin cytoskeleton and neurite collapse in cultured neural cells. Since proper synaptic function relies on structural integrity, disruptions in the cytoskeleton can lead to imbalanced synaptic plasticity. Astrocytes play a crucial role in modulating tripartite synaptic signaling with their peripheral astrocytic processes (PAPs). These functions rely on the actin cytoskeleton, as it enables structural changes in PAPs and facilitates bidirectional communication. AgNPs cross the BBB and bioaccumulate, but their impact on astrocytic function remains unknown. Given the role of astrocytes in maintaining synaptic morphology, we tested the hypothesis that the bioaccumulation of AgNPs leads to a disruption in tripartite synapse microarchitecture. Male and female Sprague-Dawley rats were treated daily with Control (0 mg/kg), Low AgNP (25 mg/kg), and High AgNP (100 mg/kg) doses for nine consecutive weekdays. Following treatment, brains from half of the rats were collected (immediate group). Brains were collected from the other half after an additional month of standard conditions (bioaccumulation group). Using immunohistochemistry for the presynaptic marker Bassoon and the PAP marker Ezrin, we found a significant decrease in the percentage of presynaptic and PAP colocalizations in the hippocampus and striatum of rats following immediate oral AgNP exposure. This significant decrease in percent colocalization of presynaptic and PAP markers was still present in the hippocampus and striatum of rats following exposure to bioaccumulated AgNPs. These data suggest that AgNP exposure could disrupt tripartite synapse microarchitecture by preventing tripartite synaptic elements from maintaining proper apposition and lead to improper synaptic functioning, which has been implicated in neurodegeneration. Given the hippocampus' essential role in learning and memory, and the striatum's involvement in motor control, these disruptions may impair cognitive and motor functions. This work could be used to guide the regulation of AgNP usage and disposal during the manufacturing process.

Disclosures: E.S. Williams: None. R.N. Smith: None. A.M. Bora: None. N. Spitzer: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.05/B23

Topic: B.05. Synaptic Plasticity

Title: Visual associative learning promotes remodeling of spines in the mouse primary visual cortex

Authors: *M. FARIBORZI¹, A. RIBIC²;

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Abstract: Excitatory synapses on cortical pyramidal neurons can be visualized as spines, dendritic protrusions that contain the postsynaptic apparatus. When labeled with calcium indicators such as GCaMP6, spines in the primary visual cortex (V1) display visually-evoked activity and orientation preference (Opref) for grating stimuli. Orientation preference of spines is thought to reflect the preferences of their synaptic inputs and contributes to the orientation preference of their host neurons. Previous studies have shown that learning to discriminate oriented visual cues through associative tasks changes the orientation preference of V1 neurons. However, it is unknown if neurons alter their preference due to changes in synaptic inputs. To address this, 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 (60°) has no consequence. Mice were injected 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 of anesthetized mice throughout training and found that trained mice had a higher proportion of spines tuned to task-relevant orientations. Our results therefore suggest that visual discrimination learning induces robust changes in synaptic inputs of pyramidal neurons, resulting in increased representation of trained cues in the V1. Our future studies will address the input origin of newly formed spines to deepen our understanding of the circuit mechanisms of learning.

Disclosures: M. Fariborzi: None. A. Ribic: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.06/B24

Topic: B.05. Synaptic Plasticity

Support: DFG SFB1286/A03
EU grant agreement No 835102

Title: Rewiring the Matrix: Neuron-Glia ECM Exchange via Extracellular Vesicles

Authors: *S. V. GEORGIEV^{1,2}, S. O. RIZZOLI^{2,1,3}, V. F. VIALOU⁴, S. ROBERT⁴, R. LERCHUNDI⁴;

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Abstract: The brain extracellular matrix (ECM) is a lattice-like structure that fills the intercellular space. Traditionally viewed as a stable scaffold, the ECM is thought to undergo rare

remodeling via matrix metalloproteinase (MMP)-mediated cleavage and *de novo* protein synthesis. However, rapid structural changes at synapses suggest that additional, faster remodeling mechanisms probably exist. Using nanoscale imaging, by conventional super-resolution optics and expansion microscopy, along with molecular biology tools and biochemical assays, we discovered a novel mechanism of ECM remodeling, which requires the interaction of the ECM with extracellular vesicles (EVs), and is a critical component of neuronal signaling. We focused on the proteoglycan neurocan (Ncan), which is initially secreted by astrocytes and localizes to their surfaces in early development. Over time, Ncan is transferred to neurons via EVs, and continues to shuttle between cell types during later developmental stages. Blocking EV release with specific drugs or mutations, or suppressing neuronal activity, leads to Ncan accumulation in glia, indicating that this transfer is both EV- and activity-dependent. Our findings challenge the prevailing view of ECM remodelling, highlighting a previously unknown mechanism of dynamic transcellular molecular exchanges within the CNS, which is dependent on synaptic activity and EV shuttling between neurons and glia.

Disclosures: S.V. Georgiev: None. S.O. Rizzoli: None. V.F. Vialou: None. S. Robert: None. R. Lerchundi: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.07/B25

Topic: B.05. Synaptic Plasticity

Title: Short- and medium-term effect of propionic acid on synaptic architecture in rat amygdala: relevance to autism

Authors: *M. ZHVANIA;

Ilia State University, Ivane Beritashvili center of Exptl. Biomedicine, Tbilisi, Georgia

Abstract: Autism spectrum disorder (ASD) is a neurological and developmental disorder, characterized by social communication deficits, restricted interests and stereotyped, repetitive behavior. Although ADS is a common disorder, the precise mechanisms underlying its onset and progression are not completely understood. Propionic acid (PPA), short-chain fatty acid, generated in the gut, is known to be involved in a number of neurodevelopmental disabilities, including ASD. Social brain dysfunctionalities and emotional disturbances are often associated with altered levels of PPA. Amygdala, limbic region, which plays one of the key roles in social cognition and emotional processing, is a one of the most vulnerable to PPA treatment. We have previously shown that intraperitoneal injection of moderate dose of PPA provokes immediate, mild effect on social motivation, emotional status and the structure of amygdala of adolescent male Wistar rats. In the present electron microscopic study, we elucidate short- term effects (5 and 10 days after treatment) of moderate dose of PPA administration (175 mg/kg) on synaptic

architecture of rat amygdala. Namely, the diameter and depth of active zone of synapses, the volume and area of presynaptic and postsynaptic mitochondria, the distance between presynaptic mitochondria and presynaptic active zone and the distance between postsynaptic mitochondria and active zone were evaluated. In almost all parameters, time-dependent significant alterations were revealed. The most affected was the active zone of synapse, the diameter and the depth of which were increased at both time points. The findings indicate that impaired social cognition and emotional disturbances which develop as a result of PPA treatment, are accompanied by significant nanoscale changes in the synaptic architecture of brain region involved in social communications and emotional activities.

Disclosures: M. Zhvania: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.08/B26

Topic: B.05. Synaptic Plasticity

Support: 2020/37/B/NZ7/03499
2023/49/B/NZ7/02978

Title: The mGluR2/3 antagonists boost antidepressant-like effects of psilocybin and scopolamine at the behavioural, molecular and cellular level.

Authors: B. CHRUSCICKA-SMAGA¹, J. TUREK¹, B. POCHWAT¹, Z. BEDROOD², B. SZEWCZYK¹, *A. PILC³;

¹Neurobio., Maj Inst. of Pharmacol. Polish Acad. of Sci., Kraków, Poland; ²Nencki Inst. of Exptl. Biol., Warsaw, Poland; ³Neurobio., Maj Inst. of Pharmacology, PAS, Krakow, Poland

Abstract: Hallucinogens such as ketamine, scopolamine, and psilocybin affecting different neurotransmitter systems including glutamatergic, muscarinic, and serotonergic, have been all shown to exert rapid antidepressant (AD) effects both in preclinical and clinical studies. Although they demonstrate significant therapeutic effectiveness, the adverse effects they cause are often difficult for patients to accept, and limit their clinical use. Notably, our previous studies have shown that mGluR2/3 antagonist, LY341495 is able to enhance AD-like action of ketamine along with the significant reduction of their adverse effects. Accordingly, our goal was to investigate the behavioural, molecular, and cellular effects of psilocybin and scopolamine co-administered with mGluR2/3 antagonists as a potentially more effective therapeutic strategy. Our results demonstrate that single, subeffective dose of LY341495 enhances significantly AD-like effects of psilocybin in tail suspension test in naive mice. The AD-like effect is rapid (1h) and long-lasting (3 and 7 days). Co-administration of LY341495 affects also psilocybin induced head twitch response that refers to hallucinogenic-like behaviour and may indicate a potential

reduction of side effects. Similarly, subchronic co-treatment with scopolamine and mGluR2 NAM, VU6001966 at subeffective doses alleviates the CUMS-induced depressive-like behaviours such as decreased sucrose consumption, without affecting cognitive effects in novel object recognition test. Behavioural outcomes of psilocybin and LY341495 co-administration are further correlated with time-dependent (at 10min, 1h, 24h, and 3 days) changes in phosphorylation of AMPA receptors (GluA1 subunit at serine 831) and ERK1/2 protein in the prefrontal cortex of naïve mice. A significant increase in the activity of both signaling molecules coincides with changes in dendritic spines morphology 3 days after co-administration of psilocybin and LY341495. Taken together, our behavioural outcomes are associated with enhanced synaptic strength, a “fingerprint” of AD-like activity. Targeting two distinct neurotransmission systems with two substances administered at lower doses may reduce the likelihood of adverse effects while enhancing therapeutic efficacy, thereby achieving a more optimal balance between safety and effectiveness. Our co-administration approach seems to address better the multifaceted nature of depression, potentially improving treatment outcomes while minimizing undesired effects.

Disclosures: **B. Chruscicka-Smaga:** None. **J. Turek:** None. **B. Pochwat:** None. **Z. Bedrood:** None. **B. Szewczyk:** None. **A. Pilc:** None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.09/B27

Topic: B.05. Synaptic Plasticity

Title: Immunohistochemical morphometric analysis of synaptic reorganization in the hippocampus of rats during global ischemia

Authors: ***V. AKULININ**¹, **S. STEPANOV**¹, **D. AVDEEV**¹, **A. SHORONOVA**¹, **I. TSUSKMAN**¹, **D. AKULININ**², **V. SERGEEV**¹;

¹Omsk State Med. Univ., Omsk, Russian Federation; ²Plekhanov Rus. Univ. Econ., Moscow, Russian Federation

Abstract: Modern tasks involving segmentation of complex tissue architectures increasingly rely on machine learning technologies. In this study, we sought optimal methods for segmenting and classifying synaptic structures in the hippocampus during ischemic injury. Transient global ischemia was modeled in Wistar rats via 20 min occlusion of common carotid arteries (OCCA, n=36). Synapses in the CA1 and CA3 regions of the hippocampus were analyzed using light microscopy (hematoxylin-eosin and thionine staining, immunohistochemical reaction for p38) at 6 h, 1, 3, 7, 14, and 30 days post-ischemia. Intact animals served as controls (n=6). Morphometric analysis of synaptic terminals was performed, and statistical hypotheses were tested using nonparametric methods in the R environment. In immunohistochemical imaging of

synapses, color images of the hippocampus showed overlapping structures that needed to be differentiated by color, shape, size, and brightness. Using the Ilastik software, we segmented relevant objects (terminals, dendrites, perikarya, cell nuclei) and trained classification trees to recognize them. The classified objects were separated into different channels and stored in a multilayer container file. Subsequent segmentation of the previously identified objects was performed with StarDist. The combined use of Ilastik and StarDist enabled quantification of relative area, numerical density of terminals (NDT), size, shape, texture, and brightness. In stratum lucidum, NDT decreased by 44.3% at 6 h during OCCA, then gradually recovered to control levels by day 7, exceeded control values at day 14, and returned to baseline by day 30. The average terminal area was 16.7% larger than control at 6 hours and 1 day post-ischemia, normalized by days 3, 7, and 30, and was lower than control at 14 days. Pixel brightness was inversely proportional to chromogen content: initially (6 h, 1 day) it increased to 120-190 units, followed by a return to control levels (75-115 units) by 3, 7, 14, and 30 days. This likely reflects ischemia-induced neuropil swelling and hydroptic type of terminal degeneration. Supporting this hypothesis, significant correlations between independent variables were revealed across time points. The strongest correlation was observed between terminal area and brightness ($\rho = 0.78$) at 6 h post-OCCA, which logically corresponds to synaptic swelling and breakdown of p38-positive material. Swelling of terminals was accompanied by reduced NDT and increased terminal area — a negative correlation ($\rho = 0.64$). Statistically significant differences were also found between the CA1 and CA3 hippocampal layers.

Disclosures: V. Akulinin: None. S. Stepanov: None. D. Avdeev: None. A. Shoronova: None. I. Tsuskman: None. D. Akulinin: None. V. Sergeev: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.10/B28

Topic: B.05. Synaptic Plasticity

Title: Role of rho guanine nucleotide factor 4 in the brain

Authors: *H. KIM¹, J. KIM¹, K. LEE¹, K. YOO¹, C.-S. LIM², H. KIM^{1,3};

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²Dept. of Pharmacol., Wonkwang Univ., Jeonbuk, Korea, Republic of; ³Biomed. Res. Institute, Chungbuk Natl. Univ. Hosp., Cheongju-si, Korea, Republic of

Abstract: Rho guanine nucleotide exchange factor 4 (Arhgef4) is highly expressed in various brain regions; however, its role remains unclear. Our previous study demonstrated that Arhgef4 acts as a negative regulator of excitatory postsynaptic activity. In this study, we generated forebrain-specific Arhgef4 conditional knockout mice to investigate the role of Arhgef4 in synaptic development, neuronal signaling, and behavior. In these mice, Arhgef4 protein levels

were significantly reduced in the forebrain, while levels of pre- and postsynaptic proteins remained unchanged. However, in cultured hippocampal neurons from cKO mice, PSD-95 levels in the postsynaptic regions were elevated, and dendritic protrusion density was decreased. Consistently, miniature excitatory postsynaptic currents (mEPSCs) recorded from hippocampal neurons of cKO mice were significantly increased. Behaviorally, Arhgef4 cKO mice exhibited enhanced long-term memory and showed reduced anxiety-like behaviors. Taken together, these findings suggest that Arhgef4 is a critical modulator of synaptic architecture and function, contributing to the regulation of learning, memory, and anxiety in the brain.

Disclosures: H. Kim: None. J. Kim: None. K. Lee: None. K. Yoo: None. C. Lim: None. H. Kim: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

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Program #/Poster #: PSTR152.11/B29

Topic: B.05. Synaptic Plasticity

Support: NIH/NINDS R01-NS115400
NIH/NINDS T32-NS105602

Title: Selective Blockade of Microtubule Invasion into Dendritic Spines Illuminates Cytoskeletal Roles in Synaptic Plasticity

Authors: *H. L. MILLER, E. D. HOLLAND, E. W. DENT;
Neurosci., Univ. of Wisconsin - Madison, Madison, WI

Abstract: Dendritic spines are small actin-rich protrusions that serve as the primary sites of excitatory synaptic input. Their formation, maintenance, and plasticity are critical for synaptic function and fundamental cognitive processes, such as learning and memory. Microtubules (MTs), dynamic cytoskeletal polymers, routinely polymerize into dendritic spines in an activity-dependent manner, influencing spine shape and function. However, the precise role of these MT spine invasions remains unclear, in part due to the lack of tools that can selectively disrupt MT entry into spines without affecting global MT dynamics. To address this, we developed a novel construct termed LifeAct-MTED, which couples the MT elimination domain (MTED) from the *Drosophila* Efa6 protein with LifeAct, an actin-binding peptide that localizes to f-actin-rich dendritic spines. Expression of LifeAct-MTED in cultured hippocampal neurons specifically inhibits MT entry into spines while preserving normal MT dynamics in the dendritic shaft. We are using this construct to investigate how MT invasions of dendritic spines contribute to postsynaptic structure and function under both basal and potentiated conditions. Current analyses include quantifying changes in dendritic spine density, morphology, and postsynaptic protein expression (e.g., PSD-95), as well as measuring global neuronal activity through culturing

neurons on microelectrode arrays (MEAs). Together, these studies aim to clarify the role of MT dynamics in synaptic plasticity and provide insights into cytoskeletal mechanisms underlying learning and memory.

Disclosures: H.L. Miller: None. E.D. Holland: None. E.W. Dent: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.12/B30

Topic: B.05. Synaptic Plasticity

Support: Korea Ginseng Corporation
Colorado State University

Title: Ketamine reverses chronic stress-induced mental disorders via the expression of Ca^{2+} -permeable AMPA receptors in mice

Authors: *S. ROH¹, J. FLOWERS⁴, P. VETTER², M. WILES², E. BLACK², E. BOUCKOVA³, M. WUSTRAU², A. ZAYTSEVA², R. LEE¹, S.-H. LEE¹, S. KIM¹;

¹Biomed. Sci., ³Neurosci., ²Colorado State Univ., Fort Collins, CO; ⁴Colorado State Univ. Molecular, Cell. & Integrative Neurosciences, Fort Collins, CO

Abstract: One mechanism postulated for ketamine's actions involves the enhancement of excitatory synaptic drive. However, ketamine is a noncompetitive NMDA receptor (NMDAR) antagonist that inhibits excitatory synaptic transmission. This contradictory question of how ketamine enhances excitatory activity while blocking NMDARs can be explained by an increase in AMPA receptor (AMPA)-mediated synaptic activity, but the mechanisms are unknown. There are two general types of AMPARs formed through combination of their subunits: GluA2-containing Ca^{2+} -impermeable and GluA2-lacking, GluA1-containing Ca^{2+} -Permeable AMPARs (CP-AMPARs). We revealed that low-dose ketamine (1 μM , a concentration that blocks approximately 50% of NMDAR-induced currents⁶¹) rapidly induced the expression of CP-AMPARs in cultured hippocampal neurons one-hour post-treatment. This ketamine-induced CP-AMPA expression enhanced glutamatergic synaptic strength in cultured hippocampal neurons. When a sub-anesthetic dose of ketamine is given to mice, it rapidly increases synaptic GluA1 levels, but not GluA2, in the hippocampus. Furthermore, electrophysiological recordings from CA1 pyramidal neurons in hippocampal slices revealed that a single low-dose of ketamine induced CP-AMPA expression. Additionally, a single subanesthetic low-dose of ketamine (5-10 mg/kg) decreased anxiety- and depression-like behaviors in naïve animals and reversed depression-like behavior, fear memory loss, and social dysfunction caused by chronic restraint stress (CRS) in mice. Finally, these ketamine's rapid antidepressant effects in both naïve and

chronically stressed mice required CP-AMPA expression. These findings demonstrate that CP-AMPA expression is important for the ketamine's rapid antidepressant onset.

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Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.13/B31

Topic: B.05. Synaptic Plasticity

Support: ETH Zürich
Swiss National Science Foundation (SNSF)

Title: In silico biophysical modelling approach integrated with an in vitro platform for studying synaptic transmission and plasticity

Authors: *V. VASILIAUSKAITE¹, G. AMOS², K. VULIC¹;
¹ETH Zurich, Zurich, Switzerland; ²ETH Zurich, Lab. of Biosensors and Bioelectronics, Zurich, Switzerland

Abstract: Advances in microelectrode arrays (MEAs) and in human induced pluripotent stem cell (hiPSC) technology have enabled the collection of data with high spatiotemporal resolution. Integrating MEAs with microstructured platforms presents a powerful approach that offers high-throughput and long-term recordings of neuronal networks with precise connectivity, which can be used to study fundamental neural processes. In this work, we couple an in vitro platform with a biophysical Hodgkin-Huxley model and simulation-based inference to extract mechanistic parameters from electrophysiological data, allowing us to study human synaptic function and plasticity.¹

In biological experiments, we use single-cell PDMS microstructures with structural motifs that enforce axonal directionality thereby ensuring well-defined pre- and postsynaptic neurons and their locations. The experimental platform allows maintaining hundreds of parallel neuronal pairs on a single MEA unit for over 100 days, demonstrating functional synapses through pharmacological validation and long-term potentiation studies.

The well-characterized *in vitro* system allows for direct experimental validation of the model. To optimally navigate the multidimensional parameter space of each experiment and perform *in silico* hypotheses testing, we developed a computational model of a network of two synaptically connected multicompartmental neurons. We considered ion channel dynamics suitable for hiPSC-derived cells. Neurons are connected by an excitatory synapse with AMPA and NMDA components. We fitted the model using simulation-based inference, targeting key summary

statistics such as latency delay, conduction speed, and spontaneous firing rates. Coupled with an experimental platform, capable of isolating and recording from single neuronal pairs, this approach enables quantification of AMPA and NMDA receptor-specific alterations following long-term potentiation stimulation. This integrated approach represents the first system combining isolated synaptic pairs, long-term stability, and mechanistic modeling, offering unprecedented opportunities for studying human synaptic function and plasticity.

¹An integrated in vitro platform and biophysical modeling approach for studying synaptic transmission in isolated neuronal pairs; G. Amos et al.; *Neuron*, submitted, 2025.

Disclosures: V. Vasiliauskaite: None. G. Amos: None. K. Vulic: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

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Program #/Poster #: PSTR152.14/B32

Topic: B.05. Synaptic Plasticity

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Title: Predictive value of retinal UCHL1 for cognitive decline in Alzheimer's disease

Authors: *D.-T. FUCHS¹, A. RENTSENDORJ¹, A. HUTTON¹, J.-P. S. VIT¹, E. ROBINSON¹, S. SHAHIN¹, M. DAVIS¹, B. GAIRE¹, S. L. GRAHAM², L. SCHNEIDER³, M. MIRZAEI², V. K. GUPTA², K. BLACK¹, J. G. MEYER¹, Y. KORONYO¹, M. KORONYO-HAMAOU¹;

¹Cedars Sinai Med. Ctr., Los Angeles, CA; ²Macquarie Univ., Sydney, Australia; ³USC, Los Angeles, CA

Abstract: Ubiquitin carboxyl-terminal hydrolase L1 (UCHL1), a key enzyme in the ubiquitin-proteasome system, is critical for synaptic maintenance. Its deficiency has been linked to cerebral amyloid- β (A β) accumulation in Alzheimer's disease (AD). However, its role in the retina, particularly in relation to synaptic integrity and cognitive decline, remains uncharacterized. We investigated retinal UCHL1 expression and its association with synaptic protein levels and cognitive performance in 65 postmortem retinas from individuals with mild cognitive impairment (MCI) due to AD and AD dementia, compared to age- and sex-matched cognitively normal controls (NC). Membrane-bound UCHL1 and pre-/post-synaptic proteins (VGLUT1, synaptophysin, PSD95, NMDAR2A) were assessed using immunohistochemistry,

western blotting, and mass spectrometry. Synaptic ultrastructure was examined using transmission electron microscopy. Associations between retinal protein levels, AD pathology (Braak, ABC scores), and cognitive status (MMSE, CDR) were analyzed using Pearson's or Spearman's correlation tests. Additionally, AI-based multivariable Random Forest modeling identified key retinal predictors of disease staging and cognitive impairment.

We observed early and substantial loss of pre- and post-synaptic proteins in both the inner and outer plexiform layers of MCI and AD retinas, with reductions in VGLUT1 (50-59%) and synaptophysin (57-77%), as well as PSD95 (48-66%) and NMDAR2A (58-72%) versus NC controls. UCHL1 levels were decreased by 54-70% across retinal layers in MCI/AD groups. UCHL1 deficiency showed strong inverse correlations with phosphorylated tau pS396 ($r = -0.70$, $p < 0.0001$) and very strong correlations with retinal A β_{42} burden ($r = -0.88$, $p < 0.0001$). Synaptic and UCHL1 reductions were closely linked to A β -induced p75 neurotrophin receptor-mediated cell death in the retina. Importantly, among dysregulated retinal proteins, UCHL1 emerged as a top predictor of cerebral tauopathy, Braak stage, and cognitive decline in Random Forest analysis. Overall, these findings reveal a robust relationship between retinal UCHL1 loss, synaptic dysfunction, and AD pathology, positioning retinal UCHL1 as a promising non-invasive biomarker for cognitive impairment and a potential therapeutic target for AD.

Disclosures: D. Fuchs: None. A. Rentsendorj: None. A. Hutton: None. J.S. Vit: None. E. Robinson: None. S. Shahin: None. M. Davis: None. B. Gaire: None. S.L. Graham: None. L. Schneider: None. M. Mirzaei: None. V.K. Gupta: None. K. Black: None. J.G. Meyer: None. Y. Koronyo: None. M. Koronyo-Hamaoui: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.15/B33

Topic: B.05. Synaptic Plasticity

Support: Fundacion La Caixa Grant LCF/BQ/PI23/11970039
Joachim Herz Foundation
ERC grant 945700

Title: Spatial coordination of synaptic plasticity revealed by SpyDen, a novel open-source dendritic analysis toolkit

Authors: *M. F. EGGL¹, S. WAGLE², J. FILLING³, T. CHATER⁴, Y. GODA⁵, T. TCHUMATCHENKO⁶;

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Abstract: Quantifying synaptic number, strength, and their temporal changes is essential for understanding neuronal activity and plasticity. Precise analysis of dendritic spine dynamics and dendritic molecular composition critically depends on accurately identifying labeled proteins and mRNAs within microscopy images. Typically, such image analyses are done manually, requiring multiple software platforms to identify dendritic spines, track dendrites, and detect mRNA puncta. Current automated tools often address only partial analysis steps, are optimized for specific resolutions, or lack flexible customization. To overcome these limitations, we developed **SpyDen**, an open-source Python package emphasizing: (i) multi-task ease-of-use, (ii) data export in common open formats, and (iii) full user-editability of software-generated annotations. Featuring an intuitive graphical user interface and comprehensive tutorials, SpyDen empowers users to perform dendrite, synapse, and mRNA/protein analyses without programming skills. We tested SpyDen in a study employing organotypic hippocampal slices from postnatal day 6-7 Wistar rats. Slices were perfused with artificial cerebrospinal fluid containing MNI-glutamate, allowing precise photolytic glutamate uncaging at targeted dendritic spines (either 1 or 3, 7 and 15 simultaneously). SpyDen facilitated efficient analysis of hundreds of synapses stimulated in various spatial configurations on shared dendritic branches, enabling development of a protein diffusion-based model. This model elucidates how spatial arrangements of synapses influence synaptic strength changes, synapse head volume dynamics, and coordinated plasticity within dendritic segments. Second, SpyDen was applied to cell slice images to investigate synaptic size stability at the population level, despite marked individual fluctuations. Inspired by SpyDen-derived data, we formulated a stochastic model demonstrating how local plasticity events can coexist with global mechanisms maintaining synaptic stability, thus contributing to memory encoding. In summary, SpyDen provides a robust, reproducible platform for synaptic imaging analysis, offering insights into synapse dynamics related to spatially correlated plasticity events. This interdisciplinary approach facilitates deeper understanding of synaptic plasticity mechanisms relevant across diverse neuroscience studies.

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Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.16/B34

Topic: B.05. Synaptic Plasticity

Title: Toluene neurotoxicity alters morphology of rat brain motor cortex

Authors: *T. BIKASHVILI, M. MIKADZE;
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Abstract: Toluene, a common inhalant, affects the motor cortex by disrupting its normal function, potentially leading to impaired motor control. Prolonged or high-level toluene exposure can result in neurological symptoms like tremors, muscle weakness, and reduced coordination, all of which are controlled by the motor cortex. Effects of toluene exposure on the motor cortex may vary depending on several factors including the level and duration of exposure, the age of the individual exposed, individual susceptibility. The effects of toluene on the morphology of neurons in the motor cortex were studied in adolescent (P28-30) and adult (P110-120) male rats of different ages. Experimental rats were exposed to toluene vapor at a concentration of 2000 ppm for 3-4 minutes per day for 40 days. The number of pyramidal neurons in the motor cortex and their fine structure were studied. The results showed that in adults there are fewer changes in the fine structure of neurons, mainly affecting the mitochondria, where individual cristae are damaged. Toluene exposure can impact mitochondrial function in pyramidal neurons as toluene metabolism in the body can lead to the formation of reactive intermediates such as reactive oxygen species. Increased production of reactive oxygen species (ROS) contributes to oxidative stress and mitochondrial DNA damage. The changes were much more pronounced in rats that inhaled toluene at the age of one month. The cause of irreversible damage to neurons and their gradual degeneration, along with damage to mitochondria, must also be destructive changes in other organelles, when neither the structures involved in energy supply nor synthetic processes can provide even the minimum necessary for the functioning of the cell. In such cells, as a rule, there is an accumulation of large heterogeneous lysosomes and their absorption of damaged organelles. The accumulation of autophagosomes, other secondary lysosomes, and residual bodies, together with the damage to organelles, leaves no doubt that the destruction of such cells is progressing and their eventual complete degeneration awaits them. Thus, the changes described in the fine structure are clearly those that ultimately lead to neuronal death, which is manifested in a decrease in the number of neurons. Toluene exposure leads to changes in astrocyte morphology and function. Since astrocytes create a specific environment for neurons, changes in them affect neuronal function.

Disclosures: T. Bikashvili: None. M. Mikadze: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.17/B35

Topic: B.05. Synaptic Plasticity

Title: Neuroplastogen activity of ketamine and serotonergic psychedelics in postnatal cortical neurons: morphometric, cytoskeletal and BDNF release analysis

Authors: *J. PINTO, C. MALTBY, M. BIANCHI;
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Abstract: Clinical depression represents a challenge to the field of psychiatry, with ~50% of patients experiencing little to no relief from current antidepressant drugs. The recent emergence of ketamine as a rapid and lasting antidepressant has paved the way for other compounds with novel mechanisms of action such as serotonergic psychedelics (psilocybin, DMT, LSD) as potential therapeutics. Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist dissociative anaesthetic widely used in human and veterinarian medicine as well as recreationally for its psychedelic-like effects. Ketamine's S-enantiomer induces rapid and lasting antidepressant effects, and has received regulatory approval for use in clinician-guided treatment of depression. Ketamine has been shown to induce synaptogenesis and dendritic growth in experimental models, suggesting plastogenic mechanisms underlying its antidepressant effects. This study aimed to investigate the neuroplastogen activity of ketamine by examining morphological and biomolecular changes induced in postnatal rodent neurons. Cortical neurons were isolated from P0-P1 rat pups and cultured in vitro for 10 days (Sholl Analysis) or 13 days (PSD-95 and molecular analyses) before 24 h exposure to 10 μ M ketamine. Neurons were fixed with 4% paraformaldehyde at DIV11 for Sholl analysis of dendritic arborisation, or at DIV14 for analysis of dendritic spines by counting PSD95-positive puncta along MAP2-positive dendrites. Morphometric and spine analyses were conducted by immunocytochemistry for MAP2/PSD95. Cell culture media and lysates were collected at DIV14 for analysis of BDNF expression (Mesoscale Discovery U-Plex ELISA) and acetylated α -Tubulin expression (Infrared Western Blot) respectively.

24 h exposure to 10 μ M ketamine induced a significant increase in dendritic branching compared to vehicle-treated controls and a significant increase in dendritic spine density, with ~25% more PSD-95 positive puncta detected along the initial 30 μ m segment of secondary dendrites. A significant increase in culture media BDNF was also observed. Serotonergic psychedelics showed neuroplastogen activity similar to that of ketamine. These data provide valuable insight into ketamine's ability to induce structural changes in neurons, which may underlie its rapid antidepressant effects. The results confirm ketamine's neuroplastogen activity at both presynaptic and synaptic levels, and importantly, our work establishes a platform for testing novel compounds with potential to mimic or exceed ketamine's neuroplastogen effects—especially useful in early screening of psychedelic or psychedelic-derivative drugs.

Disclosures: **J. pinto:** A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited. **C. Maltby:** A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited. **M. Bianchi:** A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.18/B36

Topic: B.05. Synaptic Plasticity

Title: Psilocybins effects on behaviour, 5-HT_{2A} receptor occupancy, and neuroplastogen activity in mice

Authors: *D. SELLERI¹, C. GAVIN¹, C. MALTBY¹, E. PASCHEN¹, J. PINTO¹, A. KLEIN², Z. A. HUGHES³, M. BIANCHI¹;

¹Ulysses Neurosci. Ltd, Dublin, Ireland; ²Gilgamesh Pharmaceuticals, Burbank, CA; ³Gilgamesh Pharmaceuticals, NY, NY

Abstract: Psilocybin has shown rapid and sustained antidepressant effects in patients with major depressive disorder (MDD), yet the neurobiological mechanisms underlying these outcomes remain unclear. This study aimed to investigate the relationships between 5-HT_{2A} receptor occupancy (RO) achieved by psilocybin and the head twitch response (HTR), the effects of psilocybin on anxiety- and depression-like symptoms and on downstream markers of synaptic plasticity and microtubule dynamics in key brain regions in mice. Microtubules are critical for the formation and maintenance of the neuronal cytoskeletal architecture and promote structural synaptic plasticity. Post-translational modifications (PTMs) of α -tubulin, such as N-terminal acetylation and C-terminal tyrosination/detyrosination, dynamically regulate microtubule stability and function, influencing processes ranging from axonal transport to dendritic and synaptic remodelling. Altered brain microtubule dynamics are implicated in psychiatric diseases including depression and therefore may be involved in the molecular pathways targeted by psilocybin.

In vivo 5-HT_{2A} RO was determined via displacement of [3H]MDL100,907 in the prefrontal cortex. To relate RO with behavioural outcomes, we analysed the HTR, and behaviour in the elevated zero maze (EZM) and forced swim test (FST). Subsequently, we measured PTMs of alpha-tubulin and expression of key synaptic proteins in the prefrontal cortex and amygdala. Psilocybin produced dose-dependent 5-HT_{2A} RO (RO₅₀=0.5 mg/kg) and an inverted-U dose-response in HTR, with peak effects aligning with RO of 57-73%. Behaviourally, a 1.5 mg/kg dose increased time in the open in the EZM, while 3 mg/kg reduced immobility in the FST, 20 h and 24 h after dosing, respectively. Both dose levels shifted α -tubulin PTMs toward a more dynamic microtubule state in both brain regions. Synaptic marker expression of PSD-95, SV2A and synaptophysin were selectively increased in the prefrontal cortex, suggesting an increase in synaptic plasticity in the prefrontal cortex, not the amygdala.

These findings suggest that the therapeutic effects of psilocybin could involve a dose- and region-specific enhancement of neuronal plasticity, with distinct molecular signatures underlying its anxiolytic and antidepressant properties.

Disclosures: D. Selleri: A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited. C. Gavin: A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited. C. Maltby: A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited. E. Paschen: A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited. J. pinto: A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited. A. Klein: A. Employment/Salary (full or part-time): Gilgamesh Pharmaceuticals. Z.A. Hughes: A. Employment/Salary (full or part-time): Gilgamesh Pharmaceuticals. M. Bianchi: A. Employment/Salary (full or part-time): Ulysses Neuroscience Limited.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.19/B37

Topic: B.05. Synaptic Plasticity

Support: AARG-NTF-23-1150820 (Alzheimer's Association)
OIA 2242771 (NSF)
20GM109098 (NIH/NIGMS)

Title: Ab mediated reorganization of synaptic nano-architecture underlies vulnerability and compensatory plasticity at diverse spines

Authors: *A. SKEENS¹, J. SCRIPTER², M. HRUSKA³;

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Abstract: The loss of excitatory synapses that form on dendritic spines underlies cognitive decline in Alzheimer's disease (AD). By binding to spines, pathological hallmarks of AD - A β and Tau - perturb synaptic function and plasticity, yet how diverse synapses succumb to AD pathology remains unknown. In this study we utilized Stimulated Emission Depletion (STED) nanoscopy in fixed and living cultured cortical neurons to monitor how A β disrupts nano-organization of endogenous proteins in spines synapses. Prior work demonstrated that aligned nanomodules of pre-synaptic and post-synaptic proteins (e.g., Bassoon, SYT1, VGluT1, PSD-95) form building blocks of dendritic spine synapses, and the formation of new aligned nanocluster units underlies spine structural plasticity. A β disrupted this nano-organization in unexpected ways. Rather than leading to uniform loss of nanomodules in all spines in an LTD-like manner, A β selectively destabilized PSD-95 in the smallest spines, which typically contain only one nanomodule. In contrast, larger spines with multiple PSD-95 nanomodules were structurally preserved, and some even increased in size—suggesting a compensatory response at these more stable synapses. These findings show that spines with different nano-architectures respond differently to A β : small spines are particularly vulnerable, while larger, more complex spines may adapt to preserve synaptic integrity. Our imaging provides unique nanoscale insight into how A β may shift the balance between LTP and LTD in AD. Understanding this interplay of synaptic vulnerability and local compensation could open new avenues for restoring synaptic function in Alzheimer's disease.

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Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.20/B38

Topic: B.05. Synaptic Plasticity

Support: RTG2550/1736 project ID 411422114

Title: Gephyrin filaments represent the structural basis of inhibitory postsynaptic densities

Authors: *A. MACHA;

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Abstract: The multifunctional protein gephyrin clusters glycine and GABA type A receptors at the postsynaptic membrane in the CNS. Gephyrin has been proposed to form the inhibitory postsynaptic density by liquid-liquid phase separation, involving a complex interplay between receptor binding and oligomerization via its conserved G- and E-domains. Our single particle cryo-EM analyses uncovered that dimerization of E-domain allowed the formation of filaments in which several E-domains are linked by Z-shaped interfaces formed by subdomain two (SDII) of adjacent dimers. Deletion of SDII abolished the formation of filaments, liquid-liquid phase separation and synaptic receptor clustering. Additional structural data rationalizes two mutations previously identified in human patients with epileptic encephalopathy, thus underscoring the functional importance of the newly discovered filaments and underlying molecular mechanism for postsynaptic density formation by gephyrin.

Disclosures: A. Macha: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.21/B39

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01MH136381A1

Title: Characterization of synapse dynamics in the α CamKII-F89G knock-in mouse line

Authors: *E. KOGAN¹, J. LU², R. YASUDA³, Y. ZUO¹;

¹Univ. of California-Santa Cruz, Santa Cruz, CA; ²Biol. Sci., Lehigh Univ., Bethlehem, PA;

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Abstract: The α -isoform of Ca²⁺/calmodulin-dependent kinase II (α CaMKII) is a central regulator of postsynaptic signaling and synaptic plasticity, and is essential for learning and memory. Although α CaMKII has been implicated in multiple forms of synaptic plasticity, its role

in regulating the structural dynamics of synapses in vivo remains poorly understood. To address this, we utilized a newly developed α CaMKII-F89G knock-in (KI) mouse line, which carries a phenylalanine-to-glycine substitution at position 89. This mutation allows for rapid and reversible inhibition of α CaMKII activity by the small molecule 1-Naphthylmethyl-PP1 (1NM-PP1), without disrupting baseline kinase function. Unlike previous transgenic models, this KI line avoids confounds from α CaMKII overexpression, enabling precise temporal control of α CaMKII function in the adult brain. We crossed α CaMKII-F89G KI mice with Thy1-GFP-M mice to sparsely label apical dendrites of layer 5 pyramidal neurons and conducted chronic in vivo two-photon imaging to monitor dendritic spine dynamics over time. At baseline, dendritic spine turnover in the KI mice was comparable to wild-type controls. However, following 1NM-PP1 administration, spine formation rates remained unchanged, but newly formed spines exhibited more immature morphology and were more likely to be eliminated. These findings suggest that acute inhibition of α CaMKII impairs the stabilization and maturation of new synapses, highlighting a critical role for α CaMKII in the consolidation of structural plasticity in the adult cortex.

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Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.22/B40

Topic: B.05. Synaptic Plasticity

Title: Connectomic traces of Hebbian plasticity in the entorhinal-hippocampal system

Authors: *E. GRASSO^{1,3}, M. CORTEZE^{2,4}, H. SCHMIDT³;

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Abstract: The key model of how we learn and memorize is Hebbian learning in the hippocampus, via long-term potentiation of synapses, allowing the storage of associations, linkage to places, and their consolidation into imprinted episodes. Learning is therefore expected to change synaptic weights. With the notion of hippocampal circuits being the primary site of learning in the mammalian brain, it has been assumed that all synapses in these circuits are constantly exposed to synaptic plasticity, and possibly in a learned state. However, a testing of these hypotheses is so far missing. In particular, the systematic mapping of synaptic weight distributions, and their relation to Hebbian preconditions has not been achieved yet in the hippocampal-entorhinal system. Here, we report such a systematic connectomic mapping of synaptic weight distributions and their relation to same-axon same-dendrite paired synaptic configurations across the hippocampal-entorhinal system. By analyzing millions of synapses and

tens of thousands of paired synaptic configurations from 3D EM-based automated circuit reconstructions in hippocampal areas CA3, CA1, and layers 2 and 3 of the medial entorhinal cortex (MEC), we found systematic and unique synaptic weight distributions, with almost 50% (but not 100%) of synaptic weights in CA1 being in a Hebbian-consistent state, CA3 uniquely exhibiting small synaptic weights with indications of learned states, and MEC resembling previous data from other isocortices, with only up to 20% learned synaptic configurations. We further analyzed the sublayer-specificity of these weight distributions, finding the molecular layer of CA1 and the lower layers of CA3 being the most unique site of potential learning. Together, this data provides a first systematic synaptic weight analysis of the key neuronal system involved in memory formation in mammalian brains.

Disclosures: E. Grasso: None. M. Corteze: None. H. Schmidt: None.

Poster

PSTR152: Synaptic Plasticity and Structural Remodeling: Mechanisms Shaping Brain Function and Dysfunction

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.23/B41

Topic: B.05. Synaptic Plasticity

Support: R01MH136381A1

Title: Dissociating the hallucinogenic and neuroplastic effects of psilocybin

Authors: *J. BAKER¹, J. LU², E. KOGAN³, Y. ZUO⁴;

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Abstract: Psychedelics such as psilocybin induce both acute hallucinogenic experiences and long-lasting synaptic changes, raising the question of whether these effects are mediated by shared or distinct neural mechanisms. Recent research suggests that both psilocybin's hallucinogenic and neuroplastic effects require serotonin 2A receptor activation (5HT2AR), a receptor most densely expressed in cortical layer 5 pyramidal neurons (L5 PyrNs). Yet, much remains unknown regarding the role of 5HT2ARs expressed by L5 PyrNs in psilocybin-induced hallucinations and neural plasticity. To address this, we used chronic in vivo two-photon imaging to track dendritic spine dynamics of L5 PyrNs in the cortex and quantified the head twitch response (HTR), a validated rodent proxy for psychedelic-induced hallucinations. Leveraging cell-type-specific conditional knockout and rescue models targeting the 5HT2AR in L5 PyrNs, we found that these two effects are dissociable. Deletion of 5HT2ARs in L5 PyrNs abolished psilocybin-induced dendritic spine formation but did not affect the HTR. Conversely, restoring 5HT2AR expression in L5 PyrNs partially rescued structural plasticity without reinstating the HTR. These findings demonstrate that psilocybin engages distinct neuronal circuits to promote

its neuroplastic and hallucinogenic effects, and support the development of targeted psychedelic-based therapies that harness neural remodeling without perceptual disruption.

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Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.01/B42

Topic: B.05. Synaptic Plasticity

Support: NIH Grant R01DA014133
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NIH Grant K01DA060334

Title: Sex- and Withdrawal-Dependent Remodeling of the Synaptic Proteome in the Nucleus Accumbens and Prefrontal Cortex After Cocaine Exposure

Authors: ***Y. YIM**¹, A. LABANCA⁴, T. MARKOVIC⁵, R. FUTAMURA², A. GODINO³, L. HOLT⁷, C. AZIZIAN⁸, B. T. KIPP¹, V. KONDEV¹, E. KAHN⁶, A. M. MINIER-TORIBIO³, T. M. GYLES⁹, E. J. NESTLER¹⁰;

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Abstract: Substance use disorders (SUDs) remain a major public health issue in the United States, with effective treatment hindered by their complex neurobiological underpinnings. Dysregulated signaling within reward-related brain regions, such as the nucleus accumbens (NAc) and prefrontal cortex (PFC), plays a central role in driving drug-seeking behavior and relapse. While the transcriptional responses to drugs of abuse have been relatively well-studied, our understanding of proteomic changes at synapses remains limited. Gaining insights into these changes could reveal more effective therapeutic targets for SUD treatment. In this study, we build on previous research investigating cocaine-induced proteomic adaptations by examining the effects of sex and withdrawal (WD) on the synaptic proteome in the NAc and PFC. We used adult male and female C57BL/6J mice (12 weeks old), administered daily intraperitoneal (I.P.) injections of cocaine (20 mg/kg) or saline (vehicle) for 7 days, followed by either 24 hours or 30 days of forced abstinence (WD). The NAc and PFC were extracted and synaptosomes were

isolated for analysis using liquid chromatography-tandem mass spectrometry (LC-MS/MS), followed by label-free quantification at the Yale/NIDA neuroproteomics core facility. Our analysis identified several synapse-enriched proteins, including ephexin1, that were differentially regulated depending on brain region, sex, and WD duration. Although most cocaine-regulated proteins are neuron-derived, a significant subset was enriched in astrocytes or microglia, highlighting a potential role for these non-neuronal proteins in synaptic function. A key finding was that, after 30 days of WD, female mice exhibited ~2.5 times more significant proteomic changes in the NAc than male mice. Conversely, in the PFC after 24 hours of WD, male mice showed ~2.5 times more significant proteomic changes, predominantly downregulation, compared to females. We are currently exploring the role of ephexin1 in drug-seeking behavior, focusing on its NAc- and sex-specific effects. Overexpression of ephexin1 in males increases conditioned place preference scores compared to females. Moreover, male mice overexpressing ephexin1 show altered cocaine-seeking behavior, while natural reward-seeking behavior remains unchanged. We are now investigating the effects of ephexin1 knockdown. This research aims to shed light on the molecular reorganization of synapses within the reward circuitry, which may ultimately influence an individual's susceptibility to relapse. By deepening our understanding of these mechanisms, we expect to inform the development of targeted therapies for SUD.

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Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.02/B43

Topic: B.05. Synaptic Plasticity

Title: Understanding the link between cellular homeostasis and neuronal slow wave activity through synaptic plasticity

Authors: *S. NOMURA^{1,2}, H. YAMASAKI², K. YOSHIDA^{3,2}, C. SHIMIZU², M. YANAGISAWA², Y. IINO², S. SHI²;

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Abstract: Accumulating evidence suggests that cortical synaptic strength increases during wakefulness and decreases during sleep, reflecting sleep pressure. We previously demonstrated a causal link between synaptic strength in the prefrontal cortex (PFC) and both the amount and depth of sleep. However, the mechanisms underlying synaptic upregulation during wakefulness remain unclear. In this study, we addressed this question by combining bioinformatic analyses of public omics datasets, in vitro live-cell imaging of murine cortical neurons, and in vivo sleep phenotyping. First, we investigated interactions between synaptic plasticity and cellular

homeostasis homeostasis, as several studies have reported that prolonged wakefulness leads to intracellular imbalances such as DNA damage and oxidative stress. To explore this at the transcriptional level, we performed comparative analyses of single cell RNA-seq datasets obtained under conditions associated with synaptic plasticity and disrupted homeostasis: sleep deprivation (SD), learning, hypoxia, and traumatic brain injury. We found that the transcriptomic signature in SD decomposes into gene modules shared with these other states. These modules are associated with synaptic plasticity tightly linked to processes maintaining cellular homeostasis—specifically, cytoskeleton organization, chromatin remodeling, and DNA repair. Based on these findings, we hypothesized that synaptic plasticity encodes intracellular imbalances as a molecular signature of “cellular sleep need”, which in turn drives organismal sleep to restore homeostasis. To test the effect of cellular homeostatic imbalance on synaptic strength, we performed live-cell imaging on primary cortical neurons subjected to two treatments: (1) a wake-related neurotransmitter cocktail mimicking prolonged wakefulness, and (2) a stress cocktail inducing intracellular homeostatic imbalance. In both conditions, dendritic spine head size increased, supporting our working hypothesis. Further experiments revealed a relationship between these stress-induced spine dynamics and both long-term potentiation pathways and sleep-regulatory kinases. Finally, we discuss how perturbations of these genes alter sleep phenotypes in mice. Together, our findings suggest that neural activity during wakefulness imposes a cost to cellular homeostasis, a fundamental trade-off for neurons, and that PFC synaptic strength may encode the level of intracellular imbalance as a proxy for sleep need.

Disclosures: S. Nomura: None. H. Yamasaki: None. K. Yoshida: None. C. Shimizu: None. M. Yanagisawa: None. Y. Iino: None. S. Shi: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.03/B44

Topic: B.05. Synaptic Plasticity

Support: R00AG065645

Title: Integrated Multi-Omics Analyses of Synaptosomes Revealed Synapse-Associated Novel Targets in Alzheimer's Disease

Authors: *S. KUMAR;
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Abstract: Synapse dysfunction is an early event in Alzheimer's disease (AD) caused by various factors, including amyloid beta, p-tau, inflammation, and aging. However, the precise molecular mechanism underlying synapse dysfunction in AD remains largely unknown. To understand this, we comprehensively analyzed the synaptosomes fraction in post-mortem brain samples from AD patients and cognitively normal individuals. We conducted high-throughput transcriptomic

analyses to identify changes in microRNA (miRNA) and mRNA levels in synaptosomes extracted from the brains of unaffected individuals and those with AD. Additionally, we performed mass spectrometry analysis of synaptosomal proteins in the same sample group. These analyses revealed significant differences in the levels of miRNAs, mRNAs, and proteins between the two groups. To gain further insights into the pathways or molecules involved, we employed an integrated omics approach to study the molecular interactions of deregulated synapse miRNAs, mRNAs, and proteins in samples from individuals with AD and the control group, demonstrating the impact of deregulated miRNAs on their target mRNAs and proteins. Furthermore, the DIABLO analysis revealed complex relationships among mRNAs, miRNAs, and proteins that could be key in understanding the pathophysiology of AD. Our study identified novel synapse-associated candidates that could be critical in restoring synapse dysfunction in AD.

Disclosures: S. Kumar: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.04/B45

Topic: B.05. Synaptic Plasticity

Support: NSFC/RGC/JRS (N_HKU735/21)
RCG/GRF (17102120, 17108821, 17103922)
RGC/CRF (C1024-22GF, C7074-21G)
HMRF (09200966)

Title: The role of KIF5B in localization of RNA-binding proteins and specific synaptic modifications in living mouse brain

Authors: *C. LAM¹, C. S. LAI²;

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Abstract: Dendritic spines play a significant role in facilitating localized signal transduction, with changes in their morphology, accompanied by formation and elimination, underlie the experience-dependent restructuring of neural connections. This structural plasticity relies on the precise delivery of molecular cargo within dendrites. However, the mechanisms underlying such targeted transport remain poorly understood. In this study, we aim to investigate the role of the kinesin motor protein KIF5B in transporting RNA binding proteins (RBPs) within the mouse brain. Through *in utero* electroporation and awake two-photon imaging, we seek to visualize the subcellular localization and dynamics of selected RBPs in both wild-type and KIF5B-deficient mouse brains during and after learning. This approach will provide insights into how KIF5B contributes to the spatial regulation of protein metabolism during learning and memory

consolidation. Current efforts are focused on optimizing plasmid constructs for *in vivo* imaging of RBP transport.

Disclosures: C. Lam: A. Employment/Salary (full or part-time): The University of Hong Kong.
C.S. Lai: A. Employment/Salary (full or part-time): The University of Hong Kong.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.05/B46

Topic: B.05. Synaptic Plasticity

Support: CONAHCYT Ciencia de Frontera CF-2023-I-796
UNAM-DGAPA-PAPIIT IA208524
UNAM-DGAPA-PAPIIT IA203421
Alzheimer's Association AARF-21-722869

Title: Unveiling epigenetic-driven synaptic remodeling by parallel analysis of nuclei and synapses using NucleuSynapse-Tag

Authors: Y. MORENO LOPEZ¹, *G. PRIETO²;

¹Inst. De Neurobiología, Juriquilla, Querétaro, Mexico; ²Inst. De Neurobiología, UNAM, Juriquilla, Mexico

Abstract: Neuronal functions rely on coordinated molecular mechanisms across cell compartments, with communication between the nucleus and synapses. However, a multiplex and quantitative analysis of nuclear and synaptic content in parallel remains a significant technical challenge. To fill this gap, we tagged neurons with EGFP by stereotaxic injection of AAV-EGFP viral particles into mice's dorsal dentate gyrus (DG). This was followed by dorsal hippocampal dissection, homogenization, and differential centrifugation to obtain the nuclear (P1) and synaptosomal crude fractions (P2); both P1 and P2 were obtained from the same hippocampal homogenate. After filtration, fractions were immunolabeled and analyzed by flow cytometry. Our data show that, in EGFP⁺ events, NeuN and PROX1 identified nuclei from DG neurons, while synaptosomes were identified by size, FM4-64, and VGluT1. Bright-field, confocal, and electron microscopy confirmed the identity and integrity of EGFP⁺ nuclei and EGFP⁺ synaptosomes isolated from DG neurons tagged with EGFP. Through parallel analyses of synaptosomes and nuclei tagged with EGFP using AAV-EGFP-shRNA-SUV39H1 particles, our novel approach, named NucleuSynapse-Tag, provided the first direct evidence supporting the idea that epigenetic mechanisms modulate BDNF protein levels at the synapse. Notably, unlike current methods that focus either on nuclei or on synapses, the NucleuSynapse-Tag protocol offers a quantitative approach for studying synaptic and nuclear molecular markers in parallel from a single brain sample, by tracking genetically fluorescent-tagged specific populations of neurons. Hence, combined with tools like AAV, Cre mice, and tracers, our approach enables a

comprehensive analysis of molecular remodeling in two interdependent subcellular compartments that control neuronal function and plasticity.

Disclosures: Y. Moreno Lopez: None. G. Prieto: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.06/B47

Topic: B.05. Synaptic Plasticity

Support: NIA R00AG064042

Title: Eliciting age-induced changes in neuronal activity-dependent transcription and DNA damage

Authors: *J. UM;

Developmental, Regenerative, Stem Cell Biol. (DRSCB), Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Environmental stimuli trigger changes in neuronal activity that induce adaptive modifications to morphology and connectivity in post-mitotic neurons which are some of the longest-lived cells. Unfortunately, neuronal activity poses an inherent risk to genome integrity as activity-induced transcription of vital genes is associated with the formation of DNA double-strand breaks (DSBs) at select gene regulatory elements. Strikingly, our lab recently discovered that the neuronal-specific immediate early gene (IEG) NPAS4 plays a critical dual role in both specifying cell-type specific transcription for synaptic plasticity and promoting repair of neuronal activity-induced DSBs. However, vital IEGs including c-Fos, c-Jun and Npas4 are downregulated with aging. Moreover, NPAS4 declines in cellular and murine models of aging and age-related neurodegeneration, with total knock-out (KO) drastically reducing the median life span in mice. Hence, it's vital to uncover other vital activity regulated genes (ARGs) and how aging affects them. However, age-induced changes in the transcriptome of ARGs and neuronal activity induced DSBs remain unknown. To uncover ARGs that are vulnerable to aging, we are utilizing our in-house enriched environment (EE) paradigm to induce physiological activation of neurons. We find that that in-house EE paradigm is able to successfully induce significant activation of known IEGs such as Fos and Npas4. Furthermore, using chemogenetic neuronal activation through designer receptors exclusively activated by designer ligands (DREADDs), we find that both our non-Cre and Cre-dependent nuclear-tagged activating DREADD constructs elicit highly specific expression of Fos and Npas4 in the hippocampus in the presence of a designer ligand, agonist 21 (C21). With these tools alongside next-generation sequencing such as single-cell RNA sequencing (scRNA-seq), we are beginning to identify vulnerable IEGs and related pathways in varying cell-types that get altered with physiological aging. Our preliminary data suggests that key IEGs including Fos and Npas4 are significantly

downregulated and that multiple key pathways in synaptic plasticity are altered with physiological aging. Together, these findings identify the vital IEGs at a single-cell resolution that are vulnerable to the process of physiological aging which will be instrumental in discovering key candidates to halt or otherwise reverse the process of brain aging.

Disclosures: J. Um: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.07/B48

Topic: B.05. Synaptic Plasticity

Title: Rad52 and R-loops facilitate DNA double-stranded break repair in hippocampal neurons

Authors: *E. HASELJIC;

Washington Univ. in St.Louis, Saint Louis, MO

Abstract: Neuronal activity plays a crucial role in shaping brain circuits during development and maintaining connectivity with age. It induces the de novo transcription of thousands of genes that mediate long-term neuronal adaptation. However, activity also triggers DNA double-strand breaks (DSBs) and their repair at promoters of rapidly induced genes. Recent work in mice identified a neuronal-specific chromatin modifier NPAS4:NuA4, a neuronal-specific chromatin modifier, as a key regulator of cell-type-specific transcription and DSB repair. Genome-wide, NPAS4:NuA4 binds regulatory elements undergoing repeated activity-induced DSBs and facilitates their repair. NPAS4 deletion increases DNA breaks and reduces the recruitment of repair factors like MRE11 and RAD50, suggesting NPAS4:NuA4 provides an on-demand protective mechanism in active neurons. However, the mechanisms underlying this repair and its functional significance remain unclear. In non-neuronal cells, the NuA4 complex promotes homologous recombination (HR) and suppresses non-homologous end-joining (cNHEJ). To assess HR and cNHEJ factor expression in active neurons, we injected wildtype mice with low-dose kainic acid (KA), a glutamate receptor agonist that synchronously activates hippocampal neurons. We found that RAD52, an HR factor, is highly induced at both RNA and protein levels in activated hippocampal tissue. In situ hybridization and analysis of public human and mouse single-cell RNA-seq confirmed RAD52 expression in hippocampal neuronal layers. Genome-wide binding experiments suggest RAD52 localizes to NPAS4 sites undergoing DSBs. Interestingly, NPAS4 deletion reduces Rad52 expression, indicating RAD52 may be a direct NPAS4 target. RAD52 is well-studied in proliferating cells, but its role in non-dividing cells remains unclear. In neurons, RAD52 might promote DNA repair at actively transcribed genes by a mechanism dependent on R-loops, nucleic acid structures where nascent RNA hybridizes to the template DNA strand. Preliminary genome-wide mapping reveals that R-loops form at NPAS4-bound DSB sites and co-localize with RAD52. These preliminary data led us to the hypothesis that NPAS4:NuA4 complex promotes an error-free repair pathway facilitated by RAD52 and R-

loops. These studies will test an exciting possibility that neurons utilize RNA to ensure error-free repair at sites prone to damage. Identifying an RAD52- and RNA-mediated repair mechanism in neurons will provide insights into how postmitotic cells maintain genome integrity throughout their lifespan.

Disclosures: E. Haseljić: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.08/B49

Topic: B.05. Synaptic Plasticity

Support: National Brain Research Centre core fund

Title: Early-life stress -induced rna-methylation regulates spatial memory

Authors: D. BANERJEE¹, S. SULTANA¹, S. SAMADDAR¹, T. W. BREDY², *S. BANERJEE¹;

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Abstract: Memory mechanism known so far attributes to experience dependent changes in adult brain. However, little is known about how developmental abnormalities contribute to memory impairments. Among the various factors influencing memory, RNA-based mechanisms have recently drawn considerable interest for their role in experience-driven memory regulation. We propose that developmental changes could modulate RNA function, potentially leading to significant effects on memory in adulthood. In this study, we used an early life stress (ES) paradigm to investigate the impact of the N6-methyladenosine (m6A) modification of RNA in memory. The ES paradigm includes the separation of pups from the mother for 3 hours daily from postnatal day 2 to 14 (P2-P14). We assessed the m6A profile from the hippocampus of P21 mice using RNA-immunoprecipitation coupled with sequencing (RNA-IP Seq). The RNA IP-Seq data revealed ~291 hypermethylated transcripts. ES-induced hypermethylation was preferentially observed in the untranslated regions of coding transcripts. Further, 89 hypermethylated long non-coding RNAs (lncRNAs) were also detected. The hypermethylation is attributed by ES-dependent reduction of demethylase FTO (Fat mass and Obesity-associated). We observed that mice pups exposed to the ES paradigm showed deficits in spatial memory and increased anxiety in adulthood. The overexpression of FTO in the hippocampus of ES-exposed mice reversed the spatial memory deficit but not anxiety. Further, the knockdown of FTO reduced protein synthesis, suggesting a direct role of m6A RNA modification and translation of plasticity proteins. We are measuring the correlation between m6A RNA modification and neural activity pattern using genetic labelling of activated neurons using Npas4 driven fluorescent

tagging following exposure to ES. Comprehensively, our study highlights a molecular approach to reverse ES-induced memory loss via manipulation of the epitranscriptome.

Disclosures: D. Banerjee: None. S. Sultana: None. S. Samaddar: None. T.W. Bredy: None. S. Banerjee: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.09/B50

Topic: B.05. Synaptic Plasticity

Support: Seed of Independence Grant, Department of Developmental Biology, WashU
W. M. Keck Foundation Fellowship, WashU

Title: Npas4 regulation of transcription and DNA repair in the aging brain

Authors: *S. PADMANABAN;
Developmental Biol., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Neurons adapt to stimuli by inducing gene transcription in response to activity, enabling learning and memory. While essential for plasticity, this process also risks generating DNA double-strand breaks (DSBs) at enhancers and promoters of activity-inducible genes. How neurons protect their genomes during heightened synaptic activity remains unclear, with implications for cognitive aging and neurodegeneration. The neuron-specific transcription factor NPAS4 is a master regulator of activity-inducible gene expression and essential for maintaining excitation-inhibition balance in neuronal circuits. Our lab recently found that NPAS4 couples with NuA4, a chromatin remodeler complex, in active hippocampal neurons. Impaired NPAS4-NuA4 function causes dysregulated activity-dependent transcription, reduced inhibitory neurotransmission, and increased DSBs across the genome, and reduced organismal longevity. These findings suggest that failure of NPAS4-NuA4-mediated genome protection may drive age-related neuronal decline. However, how NPAS4-NuA4 regulates transcription and DSB repair remains unknown. Using Mass Spectrometry, we identified acetylated histone H2AZ as a major target for NPAS4-NuA4 in activated mouse hippocampal tissues. Using CUT&RUN, a chromatin profiling technique, we found that acute deletion of NPAS4 and Tip60 (histone acetyl transferase component of NuA4) in hippocampal neurons results in reduced acetylated H2AZ deposition at NPAS4-bound regulatory elements. H2AZ has been implicated in DSB repair and RNA Polymerase II (RNAPII) transcriptional regulation. In preliminary results, CUT&RUN in activated hippocampal neurons shows that the acute deletion of NPAS4 reduces RNAPII promoter proximal pausing, an important regulatory step. Additionally, using intronic read analysis from bulk RNA-Seq, we observe increased RNAPII elongation speed with loss of NPAS4. While these results provide insights into NPAS4-mediated transcription, it is unclear

how NPAS4-NuA4 facilitates high-fidelity DSB repair at these sites. To identify repair factors, I will use APEX2-mediated proximity labeling to identify proteins recruited by NPAS4-NuA4. Using CRISPR-Cas9, we have engineered an NPAS4-APEX2 mouse to determine the proteomic profile surrounding NPAS4, at different time points after neuronal activation. This unbiased approach will reveal key repair factors involved in protecting active neuronal genomes. Future studies will focus on how NPAS4-NuA4 function changes with age and across neuronal subtypes. This work aims to define the molecular mechanisms that preserve genome integrity during neuronal activity with age.

Disclosures: S. Padmanaban: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.10/B51

Topic: B.05. Synaptic Plasticity

Support: W. M. Keck Foundation grant KF-05617242

Title: Initial steps toward developing platform to track timing of learning-related gene expression in living animals in real time using bioluminescent reporters

Authors: *M. TOLEDANO¹, A. LUPTAK², J. PRESCHER³, P. F. WORLEY⁴, O. STEWARD⁵;

¹Anat. and Neurobio., Univ. of California, Irvine, Anaheim, CA; ²Pharmaceut. Sci., ³Chem., Univ. of California, Irvine, Irvine, CA; ⁴Dept Neurosci/Neurol, Johns Hopkins Sch. Med., Baltimore, MD; ⁵Reeve-Irvine Res. Ctr., Univ. of California Irvine, Irvine, CA

Abstract: Synaptic plasticity during learning involves activation of expression of key genes. Recent technological advances allow tracking of gene expression in living neurons using fluorescent reporters, but deploying these technologies in living animals remains challenging due to cumbersome camera systems, and complexity of recording gene expression by neuronal ensembles in real time in living mice. Here, we report initial steps toward developing platforms to achieve this goal using bioluminescent reporter systems for non-invasive, real-time monitoring of synthesis of gene products in living animals. Our platform uses the luciferase from the marine copepod *Gaussia princeps* (Gluc). Unique properties include rapid maturation of the enzyme and "flash kinetics" in which interaction with the substrate rapidly inactivates the luciferase enzyme. Previous studies used these unique properties to track the synthesis of the plasticity-related gene *Arc* in neurons in culture in real time (Na et al 2016, Neuron, 91:3, 561-573). Here, we report initial steps toward adapting the platform for living mice. We engineered lentivirus to express the Arc/Gluc fusion protein previously used by Na et al, and injected the virus into the CA1 region of male and female mice. After allowing time for expression (7-12 days), we prepared living brain for live imaging with the *in vivo* imaging system (IVIS). The key preliminary step to

benchmark the system is demonstration of flash kinetics after addition of the luciferin substrate coelenterazine (CTZ). For this, brain slices were imaged by IVIS before and after bath delivery of CTZ. Robust luminescence was produced from the area of the lentivirus injection in the CA1 region of hippocampal slices with a mean peak bioluminescent signal of $1.8 \times 10^5 \pm 5.9 \times 10^4$ photons per second during the first 60 seconds, followed by two-phase decay in signal (mean r^2 0.991 ± 0.005) to a plateau of $< 20\%$ peak signal (mean plateau $18\% \pm 13\%$) within 7 minutes. These data document canonical flash kinetics for the *Gaussia* luciferase, demonstrating the integrity of the enzyme and the utility of the Arc/Gluc system for assessing synthesis of new proteins in response to synaptic activation. Using data from our previous studies that estimate attenuation of luminescence by depth in brain, skull and scalp, the intensity of luminescence generated in slices is sufficient to be detected by IVIS in intact mice. These results set the stage for studies of dynamics of Arc/Gluc protein synthesis in response to patterns of activation in hippocampal slices and in intact mice.

Disclosures: **M. Toledano:** None. **A. Luptak:** None. **J. Prescher:** None. **P.F. Worley:** 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

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.11/B52

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 5R00MH118423-05
NIH/NIGMS T32 GM144834

Title: Activation of the integrated stress response enhances excitability in hippocampal CA1 cell populations

Authors: *G. YANG¹, S. A. MCKENZIE²;

¹Neurosciences, Univ. of New Mexico, Albuquerque, NM; ²Neurosciences, UNM HSC, Albuquerque, NM

Abstract: Protein synthesis is essential for long-term memory formation and synaptic plasticity. Translation typically proceeds via the cap-dependent pathway, which recruits the eIF4F complex to the 5' mRNA cap, but under cellular stress, cap-independent translation of specific proteins may occur through the integrated stress response (ISR). Most plasticity-related proteins are produced via the cap-dependent pathway and downregulation of this translational mechanism - which may occur with ISR activation - impairs late phase long-term potentiation (L-LTP). Here, we investigated how ISR activation affects hippocampal neural dynamics during learning. Using

iPKR mice (Shrestha et al., 2020), we used a chemogenetic strategy to upregulate the ISR and downregulate the cap-dependent translation in CA1 pyramidal cells. Chemogenetic ISR activation led to a robust increase in firing rates of both pyramidal cells and interneurons around 2 hours after infusion of the chemogenetic agent, with elevated excitability persisting for days. No such changes occurred in saline-treated animals or in control mice lacking iPKR expression. Neuronal firing rates were decreased with anisomycin infusion which inhibits both cap-dependent and cap-independent translation. These findings suggest that proteins produced through the ISR activation induce sustained changes in hippocampal network excitability. ISR induced changes in neuronal excitability may underlie memory impairments and cognitive dysfunctions associated with stress, injury, or disease-related ISR activation.

Disclosures: G. Yang: None. S.A. McKenzie: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.12/B53

Topic: B.05. Synaptic Plasticity

Support: NIH R01NS13344103

Title: Temporal-specific increase in neuronal membrane proteasome activity induced by enhanced visual experience in the optic tectum of *Xenopus laevis* tadpoles

Authors: B. BAAH KONADU¹, J. LIN², *H. HE²;

¹Biol., ²Georgetown Univ., Washington, DC

Abstract: Proteasomes are multi-unit enzymes that degrade aggregated, unwanted, or dysfunctional proteins and are crucial for normal neuronal function. They are either composed of 20S core particles capped with 19S regulatory subunits that form the 26S/30S proteasomes, or remain uncapped as stand-alone 20S proteasomes. Neuronal membrane proteasomes (NMPs) are stand-alone 20S proteasomes found in the neuronal plasma membrane. Recent studies from our lab and others suggest that NMPs are involved in timely degradation of activity-induced nascent proteins in neurons, and may play a critical role in regulating neuronal activity in both central and peripheral nervous system. Intriguingly, NMP inhibition during visual training abolished learning-induced behavioral plasticity and resulted in a deterioration of baseline visual avoidance behavior in tadpoles. By contrast, without the visual training, NMP inhibition did not interfere with the behavior, suggesting that NMP function is specifically required in experience-dependent plasticity mechanisms. Preliminary data from our lab showed that a brief period of enhanced visual experience (VE, similar to that used for the visual training) induced three distinct transcriptional-independent and dependent phases of *de novo* protein synthesis in the visual processing center of the tadpole brain and NMPs actively degrade nascent proteins in the early and middle phases of the VE-induced protein synthesis. To further elucidate how NMP activity

is regulated by plasticity-inducing sensory experience in the brain, here, we quantitatively probed the proteasome activity of NMPs in tadpole brain at different time points following VE. By combining pre-injection of the NMP-specific inhibitor in live brain and fluorogenic substrate-based proteasome activity assay in tissue lysate, we evaluated the proportion of NMP contribution in the overall proteasome activity level. Our result showed that NMP-specific proteasome activity significantly increased during the early and middle phase of protein synthesis following VE onset, consistent with bouts of NMP-mediated nascent protein degradation. These results provide a fine-scale delineation of the temporal dynamics of activity-induced protein synthesis and NMP-mediated degradation of nascent proteins in response to physiologically relevant sensory experience. It also shed light on cellular mechanisms underlying the temporal-specific proteostatic regulation of activity-induced nascent proteome that may be critical for maintaining circuit stability in experience-dependent plasticity.

Disclosures: B. Baah Konadu: None. J. Lin: None. H. He: None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.13/B54

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

Support: NIH R56MH125895
Transformative Research Falk Award

Title: Single-nuclei transcriptomic maps identified a mitochondrial pathway for epigenetic programming of rapid antidepressant action

Authors: *Y. SAGI¹, B. BIGIO^{2,1}, M. AZAM¹, O. BARNHILL⁴, A. A. MATHE⁵, C. NASCA^{2,1,3};

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⁵Karolinska Institutet, Stockholm, Sweden

Abstract: Histone acetylation regulates every physiological function and is dysregulated in multiple human diseases. Here we show a link between a key mitochondrial marker, previously known for its role in metabolic function, and the acetylation of specific histone tails with corresponding changes in neuronal activity and coordinated behavior. Using Cre-dependent loss of function and calcium imaging approaches, we found that suppression of this mitochondrial marker led to a decrease in acetylation of the histone K27H3 mark in glutamatergic neurons of the mouse ventral dentate gyrus and neuronal activity in these neurons during social interaction bouts. These effects were specific to the socialization bouts. Similarly to the genetic down-regulation, chronic stress, a primary risk factor for multiple human diseases, disrupted this mitochondrial pathway. Pharmacological upregulation of this key mitochondrial marker in

glutamatergic neurons of ventral dentate gyrus boosted neuronal activity during socialization. Ongoing work using single-nuclei RNA sequencing assays and bioinformatic approaches further showed that this mechanism is a key target for rapid antidepressant response to ketamine. Together, our findings reveal a novel role of mitochondria in the regulation of epigenetic processes for plasticity of the brain.

Disclosures: **Y. Sagi:** None. **B. Bigio:** None. **M. Azam:** None. **O. Barnhill:** None. **A.A. Mathe:** None. **C. Nasca:** None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.14/B55

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

Support: NIH R01MH128311

Title: Neuronal exosomes identified a brain mitochondrial pathway of epigenetic programming in treatment resistant depression

Authors: ***B. BIGIO**^{1,3}, J. DOBBIN⁵, O. BARNHILL⁶, Y. SAGI⁴, J. MURROUGH⁷, N. WILLIAMS⁸, C. NASCA^{2,3};

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Abstract: Treatment resistant depression (TRD) is a leading cause of disability worldwide; there is a dearth of new mechanistic models for the development of better therapeutic strategies. Our and other groups showed that boosting mitochondrial metabolism of acetyl-L-carnitine (LAC) leads to a rapid and long-lasting antidepressant response in multiple rodent models by activating epigenetic processes of histone acetylation. In recent years, we also showed decreased levels of this pivotal mitochondrial metabolite LAC in patients with depression including severe clinical phenotypes of TRD linked to childhood trauma. These LAC-deficient phenotypes were also characterized by brain insulin resistance. Unlike the role of systemic mitochondrial metabolism, the understanding of molecular mechanisms of brain mitochondrial metabolism and the related epigenetic pathways in TRD has been limited to postmortem brain measures. Here, we used the exosome technology to isolate neuronal exosomes and characterize key molecular markers of mitochondrial metabolism and the related pathways in subjects with TRD before and after transcranial magnetic brain stimulation (TMS) using an accelerated theta burst protocol. Our ongoing analyses showed for the first time a link between a key mitochondrial marker assayed in neuronal exosomes and a treatment resistant course of illness. These phenotypes are also

characterized by corresponding changes in the levels of activity of an epigenetic marker important for histone acetylation. Further work is ongoing to determine the role of this pathway of mitochondrial-related epigenetic regulation in the responses to TMS. In all, these findings suggest that mitochondrial metabolism has important effects on epigenetic processes in patients with treatment resistant depression and point to this model of mitochondrial-related epigenetic regulation as a mechanistic pathway for the regulation of plasticity.

Disclosures: **B. Bigio:** None. **J. Dobbin:** None. **O. Barnhill:** None. **Y. Sagi:** None. **J. Murrough:** None. **N. Williams:** None. **C. Nasca:** None.

Poster

PSTR153: Brain Plasticity: Transcription and Translation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.15/B56

Topic: B.05. Synaptic Plasticity

Support: NIH Grant 5R35GM119831-04
UC Davis HGFG

Title: Transcriptomic and Epigenetic Mechanisms of Psychoplastogens Identify Cellular and Molecular Mechanisms of Action and Response Competency

Authors: ***E. FENTON**^{1,4}, I. K. AARRESTAD^{5,4}, N. R. SEBAN^{6,4}, S. A. LOZANO^{7,4}, D. E. OLSON^{2,4}, A. S. NORD^{3,4};
²Chem., ³Genomics Div., ¹Univ. of California, Davis, Davis, CA; ⁴Inst. for Psychedelics, Davis, CA; ⁵Neurosci., UC Davis, Davis, CA; ⁶Neurosci., ⁷Ctr. for Neurosci., Univ. Of California Davis Neurosci. Grad. Program, Davis, CA

Abstract: Roughly 15% and 8% of adults in the United States experience a substance use disorder or major depressive disorder, respectively. The psychedelic class of medicines with agonism at the serotonin 2A receptor has shown promise for treatment of each of these; however, the often concomitant hallucinatory effects diminish their clinical utility, regulatory approval, and widespread adoption. A major question in the psychedelic field is whether the hallucinations can be separated from the antidepressant effects, or if they themselves confer therapeutic effects. While current clinical trials of these drugs demonstrate strong efficacy, the full mechanisms of action are not fully understood. Here we compare the transcriptomic (snRNAseq) and epigenetic (snATACseq) differences between a hallucinogenic drug 5-MeO-DMT and a non-hallucinogenic analog, Tabernanthalog. Both of these drugs show preclinical promise in treating MDD and SUD and induce cellular phenotypes such as spine growth. Psychedelic compounds have been shown to induce immediate early gene (IEG) expression, but the extent to which this drives the therapeutic effects are unknown. We demonstrate that while 5-MeO-DMT shows transcriptomic strong activation of immediate early genes 1 hour after administration, this is not seen in the TBG group. Furthermore, this activation is strongest in Layer 4/5 Glutamatergic neurons in the

mouse mPFC, and further pronounced in cells expressing the serotonin 2A receptor. We identify both overall IEG activation and specific genes such as Fos and Arc that have been implicated in this response previously, but also others such as Tiparp and Nr4a3 that are thus far unassociated with the psychedelic response. Additionally, we show that elements of epigenetic competency are linked with the ability of a cell type to respond.

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Poster

PSTR153: Brain Plasticity: Transcription and Translation

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Topic: B.05. Synaptic Plasticity

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Title: Dynamic nBAF Chromatin Remodeling Complex Regulates RNA Polymerase II Elongation During Activity Induced Gene Transcription

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Abstract: Signal-dependent RNA Polymerase II (Pol2) productive elongation is an integral component of gene transcription, including those of immediate early genes (IEGs) induced by neuronal activity. However, it remains unclear how productively elongating Pol2 overcome nucleosomal barriers. Using RNAi, three degraders, and several small molecule inhibitors, we show that the neuronal BAF (nBAF or mammalian SWI/SNF) complex is required for activity-induced transcription of neuronal IEGs, including *Arc*. Among other things, the nBAF complex facilitates productive elongation in the gene body via interaction with the elongation complex and elongation-competent Pol2. Mechanistically, Pol2 elongation is mediated by activity-induced nBAF assembly (especially, ARID1A recruitment), and its ATPase activity. The intrinsically disordered region at the C-terminus of SMARCC2 -a core nBAF subunit- plays an important role in the process. Together, our data suggest that the nBAF complex regulates several aspects of Pol2 transcription and reveal mechanisms underlying activity-induced Pol2 elongation. These findings may offer insights into human maladies etiologically associated with mutational interdiction of BAF functions.

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Poster

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Topic: B.05. Synaptic Plasticity

Support: State of Arizona, DHS
Barrett, The Honors College at Arizona State University

Title: Psilocybin reduces depressive-like behavior and improves cognition in healthy aging mice via epigenetic regulation of plasticity-related genes

Authors: T. HANSON¹, M. G. SEMPLE¹, D. LIFSHITZ¹, B. A. FLORES¹, J. BALDUCCI¹, S. A. HARKER², C. R. LEWIS³, *S. E. MENNENGA¹;
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Abstract: Psilocybin is a serotonergic psychedelic compound that shows promise for reducing symptoms of mood disorders and enhancing cognitive function. Emerging evidence suggests these effects may involve long-lasting epigenetic regulation of neuroplastic mechanisms, but little is known about how these changes relate to functional improvements, particularly in aging populations. Here, we investigated whether psilocybin produces behavioral and epigenetic effects in a mouse model of healthy aging. Eleven-month-old male and female C57BL/6 mice received two intraperitoneal injections of either psilocybin (1 mg/kg) or saline, one week apart. Behavioral testing began three days after the final injection and included assessments of learning and memory (Y-Maze, Novelty and Location Recognition) and affective behavior (Open Field, Novelty-Suppressed Feeding, Marble Burying). Brain tissue was collected from the ventromedial prefrontal cortex (vmPFC) and bilateral dorsal hippocampus, and DNA was extracted for epigenome-wide methylation analysis using the Illumina Mouse Methylation BeadChip array. We show, for the first time, that psilocybin enhances cognition in aging females, and reduces depressive-like behavior in both sexes during aging, without negative side-effects. Moreover, psilocybin treatment affected epigenetic regulation at thousands of CpG sites, representing hundreds of genes. We also found striking sex differences in more than half of the genes affected by psilocybin treatment. These results support our hypothesis; that psilocybin safely and effectively ameliorates age-related cognitive decline and emergence of mood symptoms. This study represents a novel effort to investigate the behavioral and epigenetic effects of psilocybin in aging mice and implicates psilocybin as an effective therapeutic for age-related cognitive and affective symptoms.

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Poster

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Program #/Poster #: PSTR153.18/B59

Topic: B.05. Synaptic Plasticity

Title: Epigenomic signatures of psychedelic treatment: A brain-targeted epigenome wide association study (BEWAS) of ketamine and MDMA

Authors: *C. LEWIS¹, M. SEMPLE¹, B. B. YAZAR-KLOSINSKI², S. E. MENNENGA³;
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Abstract: Ketamine and MDMA are two emerging psychedelic therapies showing promise for treating mood and trauma-related disorders. However, the molecular mechanisms underlying their therapeutic effects remain largely unknown. Here, we present the first Brain-Enriched Epigenome-Wide Association Study (BEWAS) to assess DNA methylation changes in genes highly expressed in brain tissue following psychedelic treatment. Participants were recruited from clinical trials of ketamine (N=20, MDD/PTSD) and MDMA-assisted therapy (N=16, PTSD). Pre- and post-treatment DNA was extracted from blood (ketamine) or saliva (MDMA) and assayed using the Infinium MethylationEPIC array. BEWAS analyses targeted 2,197 brain-enriched genes. Mixed models controlling for age, sex, and cell composition and FDR-corrected Stouffer-Lipták-Kechris gene-level analyses revealed significant methylation changes at 788 genes following ketamine and 1,027 genes following MDMA ($q_s < 0.01$). Both psychedelics exhibited overlapping epigenetic effects on genes such as *PTPRN2*, *SHANK2*, and *ABR*, implicating shared effects across synaptic remodeling and vesicle dynamics. Functional enrichment analysis ($q < 0.05$) revealed that both psychedelics alter DNA methylation of genes related to immune regulation (e.g., cytokine signaling) and mental processes (e.g., cognition, emotion). These findings suggest that ketamine and MDMA induce unique and convergent lasting epigenetic modifications in genes relevant to brain plasticity, immune function, and psychiatric health. This study offers novel insights into the molecular mechanisms of ketamine and MDMA and supports the utility of peripheral epigenomic markers for monitoring psychedelic effects.

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Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.19/B60

Topic: E.06. Vision

Title: Dysregulation of neuronal activity-dependent immediate early genes in a mouse model of Angelman syndrome

Authors: *B. GIRI¹, S. DAS^{2,3}, S. JANA^{2,4}, N. JANA^{2,5};
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Abstract: Angelman syndrome is a neurodevelopmental disorder characterized by impaired motor and cognitive development, speech impairment (Williams CA et al., 2010). Ube3a a novel protein of the HECT family of E3 ubiquitin ligase which also has transcriptional co activator function identified as a major molecular player behind Angelman syndrome (Ramamoorthy S et al., 2008, Huang L et al., 1999). Paternally inherited copy of the *UBE3A* gene is silenced due to imprinting in neuronal cell (Mabb AM et al., 2011). Transgenic mice model with maternal deficient copy of Ube3a mimic behavioural and molecular characteristics of Angelman syndrome making it a very potent tool to investigate the molecular mechanism behind Angelman syndrome. (Jiang YH et al., 1998). Main obstacle in cracking the molecular underpinnings of Angelman syndrome is that the targets of the Ube3a is not well characterized . Very few targets of the Ube3a is identified so far most of them are associated with the ligase activity of the Ube3a . However the co -activator function of Ube3a and its relation to disease pathology is very less explored field. Therefore identifying the genes which are regulated by the co-activator function of Ube3a is very crucial to understand the disease . We used the mouse synaptic plasticity , RT2 Profiler PCR Array to identify synaptic plasticity-associated genes altered by Ube3a deficiency in the visual cortex of P25 mice, a model supported by Yashiro et al. (2010). Comparing control and Ube3a maternal-deficient mice, we found significant changes in immediate early genes (IEGs), with prominent downregulation of Arc and Egr1-4 in Angelman Syndrome (AS) mice. qRT-PCR and immunoblotting, immunofluorescence studies confirmed reduced mRNA and protein levels of these IEGs. Dark rearing experiments indicated that IEG downregulation is visual stimulus-dependent, as both control and Ube3a-deficient mice showed similar IEG levels in the absence of visual input. Parallel experiments in the hippocampus revealed a similar trend, suggesting a global effect. Further investigation showed increased histone deacetylase 2 (HDAC2) activity in Ube3a maternal deficient mice, implicating epigenetic regulation in the downregulation of IEGs.

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Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

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Topic: B.07. Network Interactions

Support: The project is supported by a Ramalingaswami fellowship from the Department of Biotechnology, India (BT/HRD/35/02/2006) and a startup grant from IIT Kanpur awarded to DD (Senior Author)
This research utilized the High Performance Cluster (Param Sanganak) facilities at the Computer Centre, IIT Kanpur.

Title: Understanding odor frequency encoding by a biophysically relevant computational model of the piriform cortex

Authors: *A. KUMAR¹, O. CHAUDHARI², M. JINDAL³, A. MODI², D. DASGUPTA¹;
¹Biol. Sci. and Bioengineering, ²CSE, ³Electrical engineering, Indian Inst. of Technol. Kanpur, India, Kanpur, India

Abstract: The mammalian olfactory system possesses the remarkable ability to encode rapid temporal features present in natural odor stimuli, generated by the natural turbulent airflow. Furthermore, mitral and tufted cells (M/Ts) of the mouse olfactory bulb can couple their activities to specific odor frequencies [1]. However, little is known how this information gets encoded in higher downstream cortical areas like the piriform cortex (PCx), which has already been known for its role in odor identity encoding. To study this, we simulated a patch of biophysically relevant PCx network model (500 pyramidal cells (PYRs), 50 feedback (FBs), & 50 feedforward (FFs)) using the NEURON simulation environment. We used previously recorded *in vivo* activities of M/Ts in response to two odor frequencies (2Hz and 20Hz) and three odor mixtures (A, B, & Mix) [1] as input to simulate the network model. We conducted 336 trials by randomly shuffling the OB inputs to the PCx network while maintaining the same interconnections within PCx. To investigate the frequency encoding at the cellular level, we used the spiking data obtained from each of the 500 excitatory pyramidal cells (PYRs) in response to 2 Hz and 20 Hz frequencies of an odor to perform statistical comparison using a two-tailed T-test. Whereas to study how odor frequency is encoded within the population activity of PCx and their individual contribution to encoding, we have used a 1D Convolutional Neural Network (CNN) and cross-entropy loss function, respectively. We find that 4.4-11.8 % of PYRs in the PCx could significantly discriminate between odor frequencies (2 vs 20 Hz) in the initial 500 ms of odor stimulation. 1D CNN model trained on 60% and tested on 40% of trials could achieve a frequency discrimination accuracy of 95.3±1.6%, 87.4±3.2%, 73±4.3% (odor A, B, and Mix respectively) compared to the shuffled controls (~50%). Furthermore, to elucidate the role of different synaptic connections on odor frequency encoding, we simulated various virtual knockout models of PCx and analyzed their responses in the same manner. Knockout of FF-PYR & FB-PYR connections improved accuracies across all conditions. Conversely, knocking out PYR-PYR connections decreased accuracies across all conditions. The classifier performance remained similar to the control network during FF-FF and FB-FB knockout networks. Trial-averaged (n=300) cross-entropy loss function plots indicated that the contribution for frequency encoding is indeed similar for the majority of neuronal populations, a signature of a distributed population code.

1. Dasgupta, D., et al., *Coupling of mouse olfactory bulb projection neurons to fluctuating odour pulses*. J Neurosci, 2022.

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Poster

PSTR154: Computational Modeling of Synaptic Networks

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Topic: B.07. Network Interactions

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National Research Foundation of Korea(NRF) Grant RS-2024-00358070
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Title: Higher-order connectivity, jointly determined by inter-soma distance, net synaptic inputs and net synaptic outputs, influences recurrent dynamics in mouse V1 layer 2/3

Authors: *D. KANG, H. SHIN;
Sch. of Biol. Sci., Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Understanding the logic of recurrent connectivity in neocortex and linking it to neural activity has been a long-standing goal of neuroscience. The functional connectomics data spanning multiple areas of mouse visual cortex provides an unprecedented opportunity to address these questions (The MICrONS Consortium, 2025 *Nature*). Using this dataset, we sought to determine the rules underlying higher-order connectivity in primary visual cortex (V1) layer 2/3. Connection probability between a pair of neurons depends on the inter-soma distance. While this ‘distance rule’ is widely accepted for first-order connectivity, it is not sufficient to recapitulate higher-order connectivity. We found that scaling the distance-based connection probability by the total number of input and output synapses for each neuron succeeded in recapitulating second-order connectivity with remarkable accuracy. Next, we sought to identify neural activity metrics that are indicative of connectivity measures. Prior literature suggested that population coupling, defined as correlation between a neuron’s activity and the population net activity, is indicative of net synaptic inputs (Okun et al., 2015 *Nature*). We verified this relationship among proofread V1 layer 2/3 neurons in the MICrONS data, and in the in-silico simulation of this network. The correlation between population coupling and net synaptic input was non-existent in random networks drawn from uniform connection probability (Erdős-Rényi network). Factoring in distance, net synaptic output, and net synaptic input progressively increased this correlation, in that order of importance. In sum, higher-order connectivity is determined by net synaptic inputs and outputs in addition to inter-soma distance, and higher-order connectivity influences the relationship between population coupling and net synaptic inputs.

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Poster

PSTR154: Computational Modeling of Synaptic Networks

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ERDF-Project Brain dynamics, No. CZ.02.01.01/ 00/22_008/0004643
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Title: Intrinsic ion dynamics underlies the temporal nature of resting-state functional connectivity

Authors: O. C. GONZALEZ¹, *P. SANDA², M. V. BAZHENOV³, J. HLINKA², G. P. KRISHNAN⁴;

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Abstract: The neural mechanisms underlying the emergence of functional connectivity in resting-state fMRI activity remain poorly understood. Recent studies have proposed that resting-state activity may be marked by brief periods of strong co-fluctuations among brain regions, which is reflective of overall functional connectivity, while others have noted a continuum in co-fluctuations over time with varying level of correlation to the functional connectivity. These findings raise the critical question about the neural mechanisms that underpin the temporal nature of resting-state activity. In this study, we investigated the temporal nature of resting-state activity and functional correlation using a biophysically realistic whole-brain computational model. The resting-state activity in the model arose from the temporal variations in ion concentrations of potassium (K⁺) and sodium (Na⁺), intracellular chloride (Cl⁻) ions, and the activity of the Na⁺/K⁺ ATPase pump. The emergent resting-state activity was marked by transient periods of high co-fluctuations, and the functional connectivity during different levels of co-fluctuations had varying levels of correlation to the functional connectivity measured for the entire simulated period of the time, similar to experimental observations. The periods of high co-fluctuations were aligned with large changes in extracellular ion concentrations. Furthermore, critical parameters controlling ion dynamics profoundly influence both the temporal patterns of these high co-fluctuation periods, and the spatial organization of resulting functional connectivity. Additionally, we observed that the balance between excitatory and inhibitory (EI) neuronal activity modulates the frequency and magnitude of these transient events. Collectively, these results suggest that intrinsic fluctuations in ion dynamics could serve as a plausible mechanism for the temporal nature of co-fluctuations, offering a potential neural basis of resting-state functional connectivity.

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Poster

PSTR154: Computational Modeling of Synaptic Networks

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Topic: B.07. Network Interactions

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Title: Decoupled surrogate networks for efficient background input optimization in biophysical circuit models

Authors: *N. NOVIKOV¹, S. MCELROY³, J. CHEN⁴, C. E. SCHROEDER², S. BICKEL⁵, M. N. O'CONNELL⁶, S. DURA-BERNAL⁷, S. A. NEYMOTIN⁶;

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Abstract: Brain circuits operate in distinct regimes depending on various conditions, including the behavioral state and ongoing task demands. Accordingly, biophysical circuit models require a systematic approach for tuning them for various operating regimes. A natural target for adjustment is the background inputs that mimic the influence of brain areas and modulatory systems not explicitly included in the model. Since biophysical models are highly nonlinear, mapping background inputs to population firing rates requires computationally expensive simulations. With many populations involved, exhaustively exploring a high-dimensional input space is impractical. A common approach is to break the optimization into simpler, low-dimensional problems.

We propose a method that creates, for each original population P, a surrogate population P' composed of random spike generators firing at the target rate for P. In the surrogate network, every original connection $P1 \rightarrow P2$ is replaced by $P1' \rightarrow P2$, preserving synaptic properties. The result is a set of independent subnetworks: each original population receives surrogate recurrent inputs matching the desired firing rates, but the populations are no longer dynamically coupled. This decoupling allows us to treat each population separately: we sweep through multiple background intensities and choose the one that yields the population firing rate best matching the target value.

We tested the method on our existing biophysical model of the auditory thalamocortical circuit (A1) which includes 43 neural populations. We added AMPA-mediated background noise to each neuron, whose conductance follows an independent Ornstein-Uhlenbeck (OU) process. Each population was parametrized by a mean OU value, and the standard deviation of OU was derived linearly from the mean. With downscaled synaptic weights, our method successfully predicted the background parameters that produce population firing rates close to the target

values. With stronger weights, the error increased due to inter-population activity correlations not captured by our method. We suggest that it could be compensated by other optimization algorithms, using our prediction as the initial guess. Our approach to background regime tuning paves the way for reproducing attentional modulation in the A1 model and offers a general framework for exploring state-dependent activity in other biophysical models.

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Poster

PSTR154: Computational Modeling of Synaptic Networks

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Program #/Poster #: PSTR154.05/C5

Topic: B.07. Network Interactions

Title: Presynaptic homeostatic plasticity mediated by multi-synaptic boutons induces maladaptive effects in neuronal network models of the hippocampus

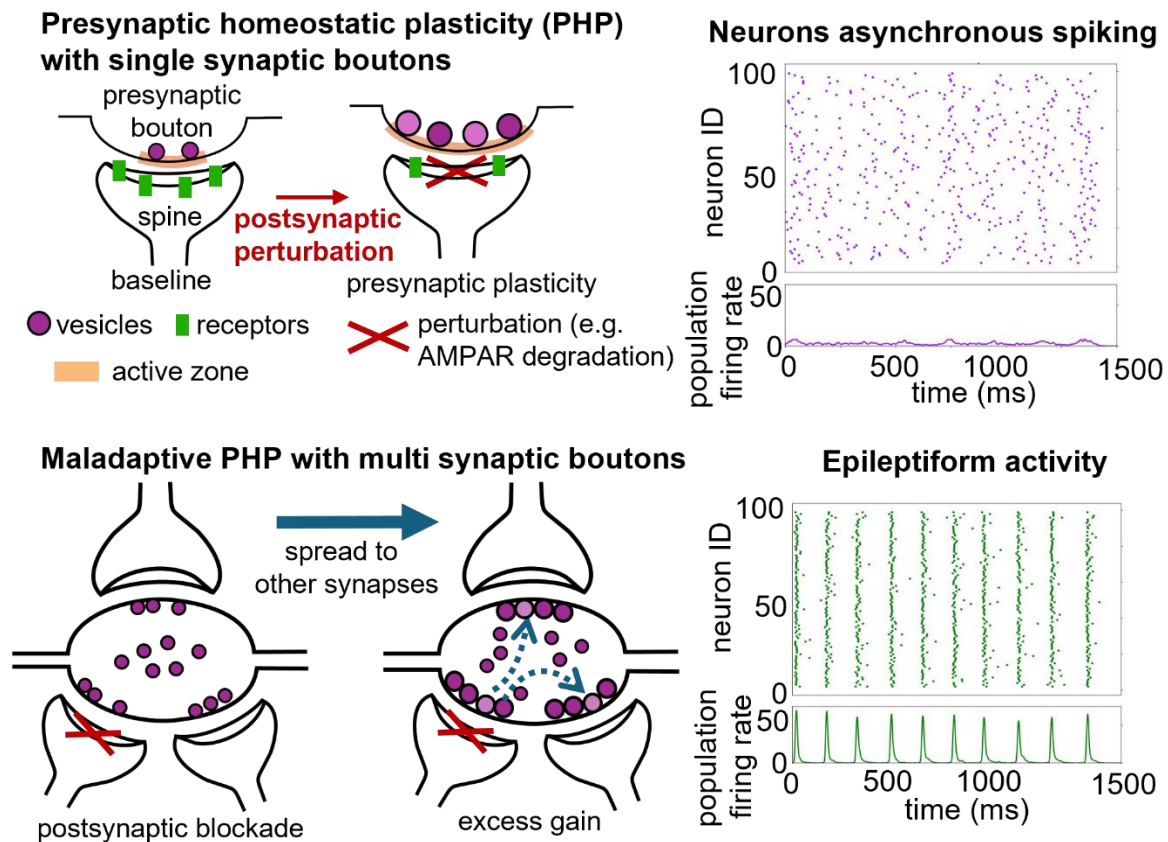
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Abstract: Homeostatic plasticity (HP) stabilizes the function of individual neurons and neural circuits in response to diverse perturbations including toxins, disease and infection. HP can be expressed postsynaptically via the well-established ‘quantal scaling’, an adjustment of neurotransmitter receptor abundance. HP can also be expressed presynaptically, as recently documented in hippocampus and cerebellum. Presynaptic homeostatic plasticity (PHP) is induced by partial disruption of postsynaptic AMPA receptor function or number. This perturbation elicits a compensatory increase in presynaptic vesicle release that precisely preserves synaptic gain at the perturbed synapse.

We here employ computational modeling to identify novel maladaptive effects of PHP in a setting of neural degeneration. We hypothesize that PHP spreads through a widespread anatomical feature of synapse organization in hippocampus: multi-spine boutons (MSBs). It has been demonstrated that 40% of spine synapses in hippocampus Stratum oriens and Stratum radiatum are contacted by MSBs, each with 2-7 independent postsynaptic targets. In our model, we induce PHP at single spines via stochastic AMPA receptor losses as observed during neurodegeneration. Due to the spatial proximity of active zones in MSBs, we incorporate a hypothetical spread of PHP induced in one synapse to all the synapses within an MSB, thereby potentiating healthy synapses above baseline, a potentially maladaptive effect. Indeed, in simulations of hippocampal neuronal network dynamics, we uncover pathological states including synchronous spiking similar to low-frequency oscillatory patterns reported during epileptic seizures. We go on to test the intersection of pre- and post-synaptic HP, revealing anomalies in synaptic weight distributions, also facilitating pathological synchronous activity.

Our computational approach makes testable predictions regarding the hypothetical spread of homeostatic plasticity through MSBs with potential relevance to the etiology of neurological and psychiatric diseases of synaptic origin.



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Poster

PSTR154: Computational Modeling of Synaptic Networks

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Title: Computational Modelling of Cortical Biomarkers of Parkinson's Disease

Authors: *J. JUNG^{1,2}, A. NEWTON^{3,2}, D. W. DOHERTY^{4,2}, L. CHEN^{5,2,7}, H.-Y. CHU^{6,2,8}, T. WICHMANN^{9,2}, Y. SMITH^{10,2}, S. A. NEYMOTIN¹¹, W. W. LYTTON^{12,2,3,13},

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Abstract: Parkinson's disease (PD) disrupts the dynamics of the motor cortex (M1), the major output pathway to the spinal cord. However, the role of different motor areas—including the cortical circuit itself—in producing PD symptomatology and serving as therapeutic targets remains underexplored. To assess the cortex as a site of pathology, we developed a computational model of M1 incorporating pyramidal tract (PT) neuron dysfunction and declined thalamocortical (TC) synaptic strength observed in MitoPark mice—a genetic model of progressive parkinsonism. PT excitability parameters were derived from frequency-current curves obtained from slice recordings at early (16-18 weeks) and late (25-28 weeks) stages of disease. TC synaptic strength was reduced by 25% and 50% in early- and late-stage models, respectively, based on optogenetic data. A movement-activated state was simulated by enhancing adrenergic drive to mimic neuromodulatory engagement during behavior. At rest, early-stage networks exhibited mildly increased beta oscillations in layer 5 intratelencephalic (IT5) neurons. In contrast, late-stage networks showed suppressed PT activity, interneuronal desynchronization, and elevated beta oscillations in IT5. Local field potential analysis revealed a 7-fold increase in delta-beta phase-amplitude coupling (PAC) and a 3-fold increase in delta-low gamma PAC relative to wild-type controls. During simulated movement, late-stage networks exhibited a 2.5-fold increase in beta-gamma PAC (rather than delta-beta or delta-low gamma PAC), along with elevated IT5 firing, excitatory-inhibitory imbalance, and disrupted IT5-PT coordination. To reverse pathological PAC patterns, we tested simulated optogenetic stimulation of various neuronal populations at different frequencies. The most effective approach involved theta-band stimulation of layer 5 somatostatin and parvalbumin inhibitory interneurons, which restored inhibitory synchrony, reduced IT5 activity, and normalized PAC. These *in silico* results highlight local cortical dysfunction as a key driver of impaired network dynamics in PD, potentially mirroring broader basal ganglia and thalamic disruption. Abnormal PAC patterns may serve as sensitive biomarkers of disease progression, informing targeted neuromodulatory therapies.

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Poster

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Program #/Poster #: PSTR154.07/C7

Topic: B.07. Network Interactions

Title: How inhibition shapes spiking and bursting activity in stochastic recurrent networks

Authors: *A. TEASLEY;
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Abstract: Pyramidal neurons in mammalian cortical layer 5 (L5) send long-range projections to other cortical areas and subcortical structures. Understanding the outputs of the cortex thus requires understanding the activity of these neurons. Thick-tufted L5 pyramidal neurons (TPNs) generate two types of action potentials: 1) the classic sodium-potassium action potentials (Na-K APs) generated at the axon hillock, which propagate down the axon to trigger neurotransmitter release and backpropagate across the soma and dendritic tree, and 2) slow calcium spikes in the apical dendrite, triggered by the coincidence of a back-propagating Na-K AP and dendritic depolarization (Larkum et al., 1999). These calcium spikes can then trigger a burst of Na-K APs. Parvalbumin positive (PV+) and Somatostatin-positive (SOM+) interneurons specialize in inhibiting TPNs' somata and apical dendrites respectively, suggesting a role for regulating the bursting vs non-bursting regime of pyramidal activity (Campagnola et al., 2023; Urban-Ciecko et al., 2016; Hu et al., 2014; Murayama et al., 2009). Dendrite-dependent bursting has been proposed as a mechanism for coincidence detection (Larkum, 2013), multiplexed spike-burst sensory coding (Naud and Sprekeler, 2018), and provide a substrate for powerful and biologically plausible learning algorithms (Greedy et al., 2022; Payeur et al., 2021). Understanding these theoretically requires a theory for the joint spiking and bursting activity in cortical networks. Here, we study a simple stochastic model of dendrite-dependent bursting. Using tools from statistical field theory, we develop the joint probability density functional of spikes and bursts in recurrent networks of pyramidal and inhibitory cells. This allows the prediction of the TPNs' mean spike and burst rates, as well as pairwise and higher-order correlations between spikes and bursts. We show how somatic vs dendritic-targeting inhibition shapes the population activity. Our analysis predicts, for example, regions in parameter space of bistability between bursting and non-bursting regimes. Networks with PV+ vs SOM+ interneurons can exhibit different dynamics and undergo different bifurcations for identical parameters. Simulations confirm our theoretical predictions. Our approach opens new avenues to investigating how dendritic nonlinearities interact with network structure to shape population activity.

Disclosures: A. Teasley: None.

Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.08/C8

Topic: B.07. Network Interactions

Title: Efficient image encoding via biologically plausible networks and brain-inspired learning rules

Authors: *H. C. B. BASNAYAKE¹, G. POGONCHEFF², M. BEYELER³;

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Abstract: A fundamental challenge of the visual system is to encode complex sensory information within the activation of comparatively few neurons. Recent research has shown that nonnegative matrix factorization (NMF) and related dimensionality reduction techniques yield parts-based representations that mirror those observed in the visual system. Neurobiologically, spike-timing dependent plasticity (STDP) combined with homeostatic mechanisms has been proposed as a biologically plausible alternative capable of producing similar codes. Here, we systematically compared the representational outcomes of different learning rules - including NMF, principal component analysis (PCA), STDP, and backpropagation - using a single-layer spiking neural network trained on Fashion MNIST. We evaluated each method's ability to produce sparse, parts-based receptive fields and reconstruct input images. Our findings show that STDP-based learning, when paired with strict winner-take-all inhibition, reliably produces interpretable parts-based representations akin to NMF, outperforming PCA and conventional backpropagation in representational sparsity. Notably, the emergence of these representations depends on both input complexity and competitive network dynamics. This work highlights key conditions under which biologically inspired learning rules approximate efficient visual coding and offers a computational framework for probing the emergence of structured representations in spiking systems.

Disclosures: H.C.B. Basnayake: None. G. Pogoncheff: None. M. Beyeler: None.

Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.09/C9

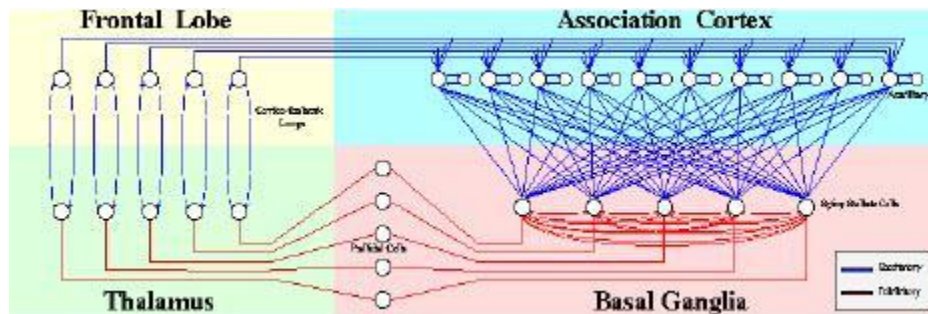
Topic: B.07. Network Interactions

Title: Encoding of salient information without gating in a spiking cortico-thalamo-striatal model of working memory

Authors: *J. K. KROGER;

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Abstract: Thalamus and basal ganglia have been implicated in working memory (WM, Houk & Wise, 1993; Graybiel & Kimura, 1995). We created a realistic, spiking model of association cortex (AC, e.g., parietal lobe), spiny stellate cells (SS) in basal ganglia (BG), substantia nigra, pallidal cells, thalamus (Th), and frontal lobe (Fl). What signals the loading of perceived information into working memory? Previously, a signal from some other source, called a gating signal, to open the gates into working memory. In our model, there is no gating. Instead, valence signals from substantia nigra, through spiny stellate cells, initiate the perceived stimulus information be loaded into WM. When a novel pattern co-occurs with a valence signal from substantia nigra, A sparse input signal activates 1-4 stellate cells. If >1 , "slow winner-take-all" prunes the set to 1 during subsequent learning presentations. This is permitted by mutual stellate inhibition and the training function. Subsequent recognition of the learned pattern is accomplished via cortico-striatal connection weights. Stellate cells reaching threshold produce a burst of 10 spikes at 10msec/spike. Spike inhibits tonically active inhibitory pallidal cells, which cease inhibition of thalamic cells. Thalamus cells in turn approach an active state, inducing sustained activity in the thalamo-cortical loop. As a frontal cell becomes active, it induces retention of the input pattern only if the pattern is still present in association cortex. Pattern presentation duration in AC must be on the order of 50-100 msec for retention to occur (for the parieto-fronto-parietal circuit to complete). Similar effects have been observed in human studies. Frontal and association cells demonstrate sustained activity densities similar to those found in monkey cortical cells (Bodner, Kroger, & Fuster, 1996). Percepts loaded into WM become "learned" and will be retained in WM at subsequent presentations without a valence signal. We provide a series of executions of the model working with inputs to show the actions of the network.



Disclosures: J.K. Kroger: None.

Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.10/C10

Topic: B.07. Network Interactions

Title: An ensemble modeling framework to make structural connectivity predictions from whole brain neuronal activity relevant for a given behavioral function

Authors: *T. BISWAS¹, T. LI³, S. CHALYSHKAN¹, F. KUBO⁴, J. E. FITZGERALD²;
²Neurobio., ¹Northwestern Univ., Evanston, IL; ³Harvard Univ., Cambridge, MA; ⁴RIKEN Ctr. for Brain Sci., Saitama, Japan

Abstract: Theoretical neuroscientists have often tried to understand how the structure of a neural network relates to its function using two different approaches: The first idea hypothesizes that biology is optimized through natural selection and learning to find structures that optimize relevant biological considerations, such as task performance and energetics. The second idea is that biological structures need not be optimal, just good enough, leaving an ensemble of viable structural possibilities which nevertheless may possess key conserved structural features. Both optimization theories and ensemble modeling approaches have repeatedly proven their worth, and it would simplify theory building considerably if predictions from both theory types could be derived and tested simultaneously. Specifically, to utilize advancements in whole-brain imaging techniques for small organisms like *C. elegans*, larval zebrafish, and larval *Drosophila*, we've developed such a unified formalism that can be applied to both optimization and ensemble modeling approaches to make inferences about network connectivity (structure) from network activity (function). We focus on analyzing the solution space of synaptic weights that allow a threshold-linear neural network to respond in a prescribed way to a limited number of input conditions. For ensemble modeling, if we have access to all the relevant neuronal responses, we can identify common synaptic weight features (such as existence of an excitatory or inhibitory synapse) that occur across all solutions bounded by an arbitrary ellipsoid or a maximal biological cost. For optimization purposes, we compute the synaptic weight vectors that minimize quadratic loss functions representing familiar biological costs, such as the sum of squares of all the network weights. We derive a common solution to this suite of nonlinear problems by showing how each of them reduces to an equivalent linear problem that can be solved analytically. Identifying the equivalent linear problem is challenging, however we show how tensor formalism from theoretical physics provides an elegant geometrical perspective that allows us to solve the problem approximately in an analytical way or exactly using numeric methods. In a concurrent submission we show how we can apply our ensemble modeling framework to whole-brain recordings of larval zebrafish in the context the optokinetic behavioral response.

Disclosures: T. Biswas: None. T. Li: None. S. Chalyshkan: None. F. Kubo: None. J.E. Fitzgerald: None.

Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.11/C11

Topic: B.07. Network Interactions

Title: An Ensemble Modeling Approach To Predicting Synaptic Connections And Neural Activity From Pretectal Responses To Optokinetic Stimuli

Authors: *S. CHALYSHKAN¹, T. BISWAS¹, F. KUBO², H. BAIER³, J. E. FITZGERALD¹;

¹Neurobio., Northwestern Univ., Evanston, IL; ²RIKEN Ctr. for Brain Sci., Saitama, Japan;

³Genes - Circuits - Behavior, Max Planck Inst. of Neurobio., Planegg, Germany

Abstract: The optokinetic response (OKR), a gaze-stabilizing reflex in larval zebrafish, is thought to be mediated by the pretectum, a retinorecipient brain region that processes motion-related visual input. Here we combined an ensemble modeling framework and a function-linked (FuL) connectomics dataset, which combined electron microscopy-based synaptic connectivity with calcium imaging of pretectal neurons during visual motion stimuli, to predict circuit function from structure. Pretectal neurons were grouped into functional response types using several classification schemes. We then constructed a response matrix incorporating fluorescence responses of the response types, modeled retinal input, and a stimulus-independent bias term. The retina-pretectum circuit was modeled as a recurrent network with feedforward retinal input that accounts for this response matrix. We explored several methods for predicting synaptic connections and resulting activity. Most simply, we optimized synaptic weights using L2-norm minimization (W -min). To evaluate the robustness of individual synaptic predictions, we also computed the critical weight norm (W -crit), which quantifies the consistency of each synapse's weight sign across the ensemble of solutions by finding the smallest weight norm permitting synapse sign ambiguity. Similar activity predictions ranked by W -crit consistently identified accurate synaptic contributions among the top three to five candidates across all response types, outperforming W -min-based predictions. This predictive power was assessed by withholding individual stimulus conditions and reconstructing neuronal responses based on the remaining stimulus conditions. Finally, we enhanced model performance by optimizing retinal input magnitudes and bias terms for prediction accuracy. Our approach yielded robust functional predictions and generated connectivity hypotheses that can be tested with the FuL connectomics dataset. These findings demonstrate the utility of ensemble modeling for linking structure to function in neural circuits and establish a framework for future structural validations.

Disclosures: S. Chalyshkan: None. T. Biswas: None. F. Kubo: None. H. Baier: None. J.E. Fitzgerald: None.

Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

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Program #/Poster #: PSTR154.12/C12

Topic: B.07. Network Interactions

Support: Zuckerman STEM leadership program

Title: Sex-based network connectivity shapes cognitive function in XX and XY neuronal models

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Abstract: Sex differences in cognitive function are well documented, but their network-level biological origins remain unclear due to confounding hormonal and environmental factors. To isolate genetic contributions, we used isogenic iPSC-derived cortical neurons from a rare mosaic Klinefelter donor (XX/XY), where XX iPSCs and XY iPSCs were separated to form a female and a male iPSC lines with the same genetic background. Using calcium imaging, we identified a temporal divergence in network development: XY networks showed early enhanced connectivity, whereas XX networks matured to exhibit greater connectivity later. XY networks also developed increasing synchronization over time. These dynamic features were sufficient to classify independent XX and XY networks with high accuracy from additional iPSC-derived cortical neurons recordings, revealing robust chromosomal influences on network architecture. Simulated information flow analyses showed faster and broader propagation in early XX networks, which later reversed in mature XY networks. In cognitive modeling tasks, XX networks favored parallel processing, while XY networks showed more focused responses. These results suggest that sex chromosome composition shapes network topology in ways that may underlie cognitive differences. Our findings uncover fundamental, chromosome-driven differences in cortical wiring that link network topology to emergent function, paving the way for sex-informed neuroscience and personalized interventions.

Disclosures: S. Stern: None.

Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.13/C13

Topic: B.07. Network Interactions

Title: Modelling the propagation of optogenetic stimulation in the C. elegans connectome

Authors: *C. SEGUIN¹, S. DVALI², R. BETZEL⁴, A. LEIFER³, A. ZALESKY⁵;
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Abstract: Understanding how information is communicated in complex brain networks—connectomes—remains a major challenge in modern neuroscience. Here, we investigate this question using optogenetic stimulation of single neurons in the C. elegans model organism. We show that network communication models (Seguin et al., 2023) computed on the C. elegans structural connectome can parsimoniously predict causal, polysynaptic signalling elicited by targeted neuronal perturbations.

Randi et al., 2023 performed systematic optogenetic stimulation of single neurons in the C.

C. elegans head while recording organism-wide neural activity using calcium imaging. The authors combined stimulation experiments from a total of 113 worms into a neuron-by-neuron matrix of signal propagation.

We used an established map of the entire synaptic wiring of the *C. elegans* nervous systems—the worm's structural connectome—as the anatomical substrate for models of neural communication. We employed graph-theoretical models to compute the structural capacity for polysynaptic signalling between every pair of neurons in the organism and found that this measure correlates with the strength of causal responses to single-neuron optogenetic perturbations.

In particular, the communicability model—predicated on propagation via diffusive broadcasting—provided the most accurate explanations of signalling strength ($r = 0.53$, $p < 10^{-12}$; 160 neuron pairs), outperforming alternative models as well as structural connectivity (SC) weights alone. Importantly, communicability was predictive of polysynaptic signalling between neuron pairs that did not share a synaptic contact ($r = 0.35$, $p < 10^{-12}$; 112 neuron pairs), indicating that this model can explain indirect transmission via multi-hop signalling pathways. Our findings indicate that simple network communication models—in particular communicability—can predict the propagation of causal neuronal signalling through complex synaptic connectivity. These results add to recent work in the human connectome, which reported that communicability could predict the cortex-wide propagation of direct electrical stimulation. Together, these studies suggest simple principles of signal propagation in complex brain networks conserved across drastically different species and spatial scales.

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Poster

PSTR154: Computational Modeling of Synaptic Networks

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.14/C14

Topic: B.07. Network Interactions

Title: Large-scale biophysical model of human cortex predicts the effects of TMS at the cellular and circuit level in Alzheimer's Disease

Authors: *T. KHASHAN¹, F. D. BORGES², J. TAJCHMAN³, E. URDAPILLETA⁴, E. SANTARNECCHI^{5,6}, S. DURA-BERNAL^{7,8};

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⁵Cognitive Neurol., Harvard Med. Sch., Boston, MA; ⁶Dept. of Neurol., Massachusetts Gen. Hospital, Harvard Med. Sch., Boston, MA; ⁷Physiol. and Pharmacol., SUNY Downstate Hlth. Sci. Univ., Brooklyn, NY; ⁸Ctr. for Biomed. Imaging & Neuromodulation, The Nathan S. Kline Inst. for Psychiatric Res., Orangetown, NY

Abstract: Transcranial magnetic stimulation (TMS) is a non-invasive technique that modulates neuronal excitability and circuit activity with high regional precision. While highly promising results have been reported for TMS as a therapeutic approach for Alzheimer's disease (AD), its underlying mechanisms remain unclear, and stimulation protocols require personalized optimization to fully harness its potential. Multiscale mechanistic biophysical models provide a powerful framework to integrate experimental data and simulate brain dynamics across molecular, cellular and circuit scales.

We simulated TMS effects in a detailed biophysical model of human cortical circuitry, featuring 15,567 neurons across six layers, based on electron microscopy data from the human temporal cortex (h01). The model includes realistic axons, distance-dependent connectivity, synaptic background activity, and short-term plasticity to replicate in vivo-like firing. It was implemented using the NEURON simulator and NetPyNE modeling tool.

We simulated neuronal membrane voltages, spiking activity, LFPs and EEG signals during baseline and repetitive 1 ms biphasic TMS pulses at different E-field intensities. The cells exhibited heterogeneity in action potential thresholds and robust neuronal entrainment at 40 V/m and 60 V/m, whereas isolated neurons showed minimal response for these E-fields. These results demonstrate that in vivo-like background synaptic activity significantly lowers AP threshold and amplifies entrainment, thus suggesting that circuit dynamics shape TMS-induced responses by modulating neuronal excitability.

To simulate AD-specific effects in our model we integrated reduced inhibitory input, loss in AMPA/NMDA conductance, and alterations in ion channel conductivity (e.g., Kv3.1, SK, Ih). As a next step, we will apply TMS stimulation to the AD model to evaluate how disease-related changes impact stimulation response. We expect to observe enhanced excitability, reduced action potential thresholds, and altered LFP signatures compared to the healthy circuit, reflecting a shift in network activity.

Future directions will include validating against human TMS-EEG clinical data, simulating AD EEG biomarkers, and optimizing TMS parameters to restore healthy dynamics.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.01/C15

Topic: B.09. Glial Mechanisms

Support: PROSNII 2025

Title: Exploration of Mesenchymal Stem Cells and Schwann-Like Cells in Modulating Glial Scar Formation in the Retrosplenial Cortex of CD1 Mice

Authors: *T. CAMPOS ORDONEZ, L. S. VÁZQUEZ MURO, N. J. CARRILLO-GONZÁLEZ, A. G. CASTILLO-GALINDO, G. ESCOBAR CAMBEROS, G. GUDIÑO-CABRERA;

Univ. de Guadalajara, Zapopan, Mexico

Abstract: The retrosplenial cortex plays a crucial role in memory formation and is particularly vulnerable to damage caused by strokes, brain tumors, and traumatic brain injuries. Following brain injury, astrocytes contribute to damage control by forming glial scars—astrocytic accumulations that act as protective barriers. However, these scars can also hinder neuronal reconnection and delay tissue regeneration. Bone marrow-derived mesenchymal stem cells (BM-MSCs) and Schwann-like cells differentiated from MSCs have demonstrated neuroregenerative potential, particularly in spinal cord injuries and peripheral nerve repair. Their ability to modulate inflammation and support axonal recovery suggests they may be relevant in addressing gliosis within the retrosplenial cortex. While MSC-derived Schwann-like cells have been studied for nerve regeneration, their specific role in glial scar modulation within the retrosplenial cortex of CD1 mice remains largely unexplored. This study evaluated the effect of transplanting BM-MSCs and Schwann-like cells into the retrosplenial cortex on glial reactivity in adult mice. Sixty-day-old CD1 mice served as marrow donors, and their tissues were processed through primary cell culture to isolate BM-MSCs and Schwann-like cells. Adult recipient mice were subdivided into three groups for stereotaxic surgery: BM-MSCs, Schwann-like cells, and a sham control group (vehicle). Twenty-one days post-surgery, immunohistochemistry was performed to assess glial fibrillary acidic protein (GFAP) expression, providing insight into astrocytic reactivity. The findings indicated that treatment with BM-MSCs and Schwann-like cells did not alter GFAP expression in the retrosplenial cortex among the groups. This suggests that these cell types may require further investigation to elucidate their therapeutic potential. Future studies should explore additional markers of astrocytic reactivity (e.g., vimentin, S100 β), neuronal plasticity, and functional recovery to assess their impact on gliosis in the retrosplenial cortex.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.02/C16

Topic: B.09. Glial Mechanisms

Support: German Research Foundation (DFG) Grant AL 2956/1-1
German Research Foundation (DFG) RU 2795 ‘Synapses under Stress’
(Ro2327/13-1, 13-2)

Title: Role of TRPV4 channels in cellular volume and ion dysregulation in hippocampal astrocytes during energy deprivation

Authors: *I. ÁLVAREZ-MERZ, N. PAPE, W. K. KAFITZ, C. R. ROSE;
Inst. of Neurobiology, Heinrich-Heine-University Düsseldorf, Düsseldorf, Germany

Abstract: During brain ischemia, Transient Receptor Potential Vanilloid 4 (TRPV4) channels contribute to neuronal swelling and calcium overload. However, their role in astrocytes remains controversial. Some results point to TRPV4-mediated ion influx and cell swelling, while contrasting evidence suggests a potential protective role of this channel, acting as an osmosensor and ameliorating astrocytic volume changes. In this study, we conducted immunohistochemical analysis on mouse hippocampal tissue sections, which revealed a label for TRPV4 in a subpopulation of astrocytes. Dynamic confocal imaging was performed in acute brain slices from both male and female adult mice to study changes in cellular volume. Astroglial swelling induced by hypoosmolar stress was unaltered by pharmacological inhibition of TRPV4 using HC-067047, indicating that it does not involve TRPV4 activation. Transient energy deprivation was induced by perfusing brain slices with a glucose-free artificial cerebrospinal fluid containing the glucose analogue 2-deoxyglucose and the cytochrome C antagonist sodium azide (“chemical ischemia”; c.i.) for 2 (mild c.i.) or 5 minutes (moderate c.i.). Nonetheless, the inhibition of TRPV4 did not reduce astrocytic swelling upon moderate metabolic inhibition. In contrast, live-cell confocal fluorescent microscopy using the membrane-permeable calcium indicator Fluo-4 AM showed that HC-067047 diminished mild c.i.-induced calcium signals, suggesting that TRPV4 promotes astrocytic calcium loading during metabolic stress. Finally, the use of the genetically-encoded nanosensor ATeam1.03^{YEMK} in organotypic tissue slices revealed that HC-067047 also attenuated the ATP loss in astrocytes upon c.i., demonstrating the contribution of TRPV4 to the energy depletion of astrocytes during metabolic inhibition. Taken together, these findings indicate that during periods of compromised energy metabolism, TRPV4 promotes astroglial pathology by aggravating ion dysregulation and cellular energy loss, without contributing to astroglial swelling. However, further research is required to clarify whether the calcium influx is a direct or indirect effect of astrocytic TRPV4 activation. Better understanding of its molecular mechanisms may reveal a novel therapeutic target to ameliorate ischemic brain injury.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

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Topic: B.09. Glial Mechanisms

Support: NIH R01 EY028284
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Research to Prevent Blindness
EyeSight Foundation of Alabama
Heidelberg Engineering

Title: Spatially distinct macroglial responses to acute intraocular pressure elevation in the living human macula

Authors: ***R. G. STRICKLAND**¹, M. M. SOMERVILLE¹, S. LIN¹, M. GARNER¹, A. S. BLAKE², G. H. GROSSMAN², C. A. GIRKIN³, A. K. GROSS¹;

¹Univ. of Alabama at Birmingham, Birmingham, AL; ²Advancing Sight Network, Birmingham, AL; ³UCSD, San Diego, CA

Abstract: Glaucomatous optic neuropathy is characterized by progressive retinal ganglion cell loss with elevated intraocular pressure (IOP) as the only modifiable risk factor. In animal models, acute IOP elevation induces macroglial reactivity, including astrocytes and Müller glia, that may sensitize the retina to further IOP related injury. Since the macula demonstrates regional vulnerabilities in glaucoma, this study investigates spatial patterns of macroglial reactivity following acute IOP elevation to define these acute responses in the living human macula. Three research-consented brain-dead organ donors underwent screening for inclusion criteria and one eye was randomly selected to undergo IOP elevation via viscoelastic gel injection into the anterior chamber (mean IOP: 41 mmHg for 8-9 hours) while the contralateral eye was maintained at physiological levels. Eyes were dissected, formalin-fixed and maculas were paraffin embedded and sectioned at 5 μm for immunohistochemistry, RNA *in-situ* hybridization, and spatial transcriptomics. Mean RNA expression and surface area of macroglial intermediate filaments were compared between treated and control eyes in 6 parafoveal regions and in the fovea. In our initial two donors, there was greater RNA expression (represented as puncta per nuclei) in the outer nuclear layer for *TGFB1*, a regulator of macroglial reactivity, ($\Delta=1.16\pm0.58$) within the inferior nasal macula, and increased vimentin, a marker for Müller glia gliosis, ($\Delta=182.57\pm150.19 \mu\text{m}^2$) in the superior fovea of treated eyes. In the inner nuclear layer, we found an increase in RNA expression for *GJAI* (connexin 43, a key gap junction between macroglia) ($\Delta=1.79\pm0.38$) in the superior fovea and a decrease in GFAP (glial fibrillary acidic protein, an macroglial gliosis marker) surface area ($\Delta=-206.99\pm93.65 \mu\text{m}^2$) in the superior temporal macula. In the ganglion cell layer, there was an increase in *GFAP* expression ($\Delta=2.75\pm0.41$) in the inferior nasal macula, and in one donor a relative decrease of Piezo1 puncta (a mechanosensitive ion channel expressed in macroglia, $\Delta=-8.57\pm5.55$) in the inferior temporal macula. Additionally, preliminary spatial transcriptomics from one donor implicate transcripts involved in glial neurotransmitter uptake and metabolism as well as TGF- β signaling. These results support macroglial reactivity to acute IOP elevation in superior and inferior regions of the macula. This is expected since these regions project to respective regions of the optic nerve head which are known to be susceptible to strain. Further understanding the mechanisms of gliosis in response to elevated IOP could have therapeutic implications for glaucoma.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.04/C18

Topic: B.09. Glial Mechanisms

Support: T32DA053558
K01DA062014
P01DA047233
R01DA040620
R01DA007359

Title: Astrocytic CREB in Nucleus Accumbens Modulates Transcriptomic, Neuronal, and Behavioral Responses to Cocaine

Authors: ***L. M. HOLT**¹, A. M. MINIER-TORIBIO², R. FUTAMURA², C. J. BROWNE², F. J. MARTINEZ-RIVERA², T. MARKOVIC², T. M. GYLES², E. M. PARISE³, C. AZIZIAN⁴, Y. YIM², V. KONDEV², M. ESTILL², A. LABANCA², G. ROJAS², Y. DONG⁵, L. SHEN², E. J. NESTLER²;

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Abstract: Drug addiction is characterized by neuronal adaptations that support a shift from goal-directed behaviors to habitual, compulsive drug-seeking with persistent effects on cognition and decision-making. With an aim of better understanding the underlying biology of addiction, investigations of the transcriptional response to drugs of abuse have revealed potential therapeutic targets. However, these studies have largely overlooked nonneuronal cells. We therefore performed RNA-sequencing on whole-cell sorted astrocytes from the nucleus accumbens (NAc) and bioinformatically characterized the astrocyte transcriptome following cocaine self-administration in male mice. We found that astrocytes exhibit robust and contextually-specific transcriptional signatures that implicate CREB as a cocaine-induced transcriptional regulator in astrocytes. CUT&RUN-sequencing revealed increased astrocytic CREB DNA binding in this brain region in response to cocaine as well as putative gene targets of astrocytic CREB. Viral-mediated manipulation of NAc astrocytic CREB activity in combination with behavioral procedures revealed that NAc astrocytic CREB increases the rewarding and reinforcing responses to cocaine. We also found that astrocytic CREB dampens astrocytic calcium dynamics and thereby selectively increases D1-type medium spiny neuronal activity to promote cocaine reward. Furthermore, we found a sex-specific effect wherein female astrocytic CREB activity in NAc is not sensitive to cocaine. Our results demonstrate, for the first time, that transcriptional mechanisms in astrocytes regulate addiction-related neuronal and behavioral plasticity.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.05/C19

Topic: B.09. Glial Mechanisms

Support: ANR ADORASTRAU
ANR JANUS
FONDATION Alzheimer (ADOMEMOTAU)
ANR-11-INBS-0011—NeurATRIS
LabEx DISTALZ
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Vaincre Alzheimer (FR-24054T)

Title: Upregulation of adenosine A_{2A} receptor in astrocytes is sufficient to trigger hippocampal multicellular dysfunctions and memory deficits.

Authors: ***D. BLUM**¹, A. LAUNAY¹, L. BUEE², M. ORR³, E. AUDINAT⁴, A.-L. BOUTILLIER⁵, G. BONVENTO⁶, K. CAMBON⁷, E. FAIVRE⁸;

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Abstract: Adenosine is an ubiquitous neuromodulator that ensures cerebral homeostasis. It exerts numerous functions through the activation of G-protein-coupled adenosine receptors (ARs), in particular A₁ (A₁R) and A_{2A} (A_{2A}R) receptors. Interestingly, A_{2A}R levels are upregulated in cortical and hippocampal regions in several pathological conditions such as Alzheimer's disease, tauopathies or epilepsy. Such abnormal upregulations have been particularly reported in astrocytes, glial cells that play a key role in regulating synaptic plasticity. However, the overall impact and the underlying mechanisms associated with increased A_{2A}R in astrocytes remain poorly understood. In the present study, we induced the upregulation of A_{2A}R in hippocampal astrocytes using dedicated AAVs and comprehensively evaluated the functional consequences in 4 months-old C57Bl6/J mice. Our results show that A_{2A}R upregulation primarily promotes alterations of astrocyte reactivity, morphology and transcriptome, with a link to aging-like phenotype as well as secondary impairments of neuronal excitability and microglial phenotype. These changes driven by a restricted A_{2A}R upregulation in hippocampal astrocytes were sufficient to induce impairments of short-term spatial memory and spatial learning. This study highlights the impact of astrocytic A_{2A}R upregulation, as seen in various neurological conditions, on the development of a detrimental multicellular response associated with memory

alterations and provides an additional proof-of-concept for the value of targeting this receptor in different neurodegenerative conditions.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.06/C20

Topic: B.09. Glial Mechanisms

Title: The impact of altered PINK1 enzymatic activity on glial health and neuronal resilience

Authors: *G. FIORINO¹, X. HOU¹, F. C. FIESEL², W. SPRINGER³;

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Abstract: Background: Loss-of-function (LOF) mutations to the PINK1-PRKN mitochondrial quality control pathway comprise the most common genetic causes of early onset Parkinson's disease (PD), characterized by loss of nigrostriatal dopaminergic (DA) neurons. In addition to DA neuron death, neuroinflammation is another PD hallmark known to contribute to neurodegeneration. There remains a gap-in-knowledge surrounding the underlying mechanisms through which loss of PINK1-PRKN function impacts glial health and neuroinflammatory signaling, and whether this may thereby contribute to neurodegeneration. There is also increasing evidence that enhancing mitochondrial autophagy (mitophagy) activation is neuroprotective. Our lab has discovered a PINK1 gain-of-function (GOF) variant that endogenously enhances mitophagy activation and will serve as a genetic proof of concept to broadly determine the therapeutic potential of mitophagy activation in PD. In this study, we aim to uncover the impact of PINK1 LOF on glial health and inflammatory signaling, and the therapeutic potential of PINK1 GOF. **Results:** Using different isogenic PINK1 mutant iPSC lines, we thoroughly examined the impact of PINK1 LOF to glial health and inflammatory signaling. We measured inflammatory factors present in the conditioned media of PINK1 LOF and isogenic wild-type (WT) control glia. Interestingly, we observed that PINK1 mutant glia increasingly secreted certain factors related to pro-inflammatory signaling and senescence. We further identified reduced health in PINK1 mutant glia, suggesting that glia, and not only DA neurons, may also be vulnerable in PD. To determine the contribution of the mutant glial secretome to neurodegeneration, we utilized a transwell system and found that the PINK1 LOF glia damaged neuronal health. To investigate the therapeutic potential of PINK1 GOF, we generated NGN2-inducible i3Neurons and found that PINK1 GOF enhanced mitochondrial respiration, reduced ROS production, and increased resilience of neurons against PD-relevant stressors compared to WT controls. **Conclusions:** These results suggest that PINK1 LOF increases vulnerability of glia, which in turn contributes to neurodegeneration. These results highlight the importance of the PINK1-PRKN pathway to glial health and function and the role of glia-neuron crosstalk in

the pathogenesis of PD. Lastly, we found that the PINK1 GOF variant enhances neuronal resilience, which will be further investigated in the context of preventing toxic neuroinflammation.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.07/C21

Topic: B.09. Glial Mechanisms

Support: De Préfargier Foundation

Title: Striatal Myelin Vulnerability in a Mouse Model of Glucose Transporter 1 Deficiency Syndrome

Authors: S. BURLET-GODINOT¹, D. VORBURGER¹, H. FIUMELLI², A. HERTANU³, I. JELESCU³, D. C. DE VIVO⁴, U. MONANI⁴, *J.-L. MARTIN¹, **P. J. MAGISTRETTI**²;
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Abstract: Glucose transporter type 1 deficiency syndrome (Glut1DS), also called De Vivo disease, is a rare pediatric neurometabolic disorder caused by mutations in *SLC2A1*, the gene that encodes the Glut1 transporter. These mutations hinder glucose passage across the blood-brain barrier, and affected children typically present with drug-resistant epileptic seizures, developmental delay, and locomotor deficits. Using a multimodal approach—diffusion MRI, quantitative PCR (qPCR), and immunohistochemistry—in a murine Glut1DS model (Glut1^{+/-} mice), we examined how chronic cerebral energy deprivation alters brain structure, focusing on motor-control regions such as the cerebral motor cortex and striatum. Diffusion tensor imaging (DTI) and diffusion kurtosis imaging (DKI) revealed microstructural abnormalities particularly in the striatum of Glut1^{+/-} mice. In this region, DTI diffusivities were significantly higher while kurtosis values were lower compared to controls, suggesting reduced barriers to diffusion and tissue complexity, which is consistent with compromised myelin integrity. Consistent with these findings, qPCR analysis showed significant down-regulation of key myelin-associated genes (Mbp, Plp1, Mog, Mag, Mobp) and of genes involved in lipid metabolism (Etnppl, Ugt8a) in the striatum of Glut1^{+/-} mice, pointing to impaired myelin synthesis or maintenance. Finally, immunohistochemical analysis revealed marked astrocytic changes in Glut1^{+/-} mice, with a notable increase in GFAP-positive cells—especially in the dorsal striatum—suggesting heightened astrocytic reactivity. However, the number of Olig2-positive cells was not affected in this forebrain region. Together, these data identify the striatum as a primary site of vulnerability to glucose transport deficiency in Glut1DS, characterized by reduced myelin integrity and

increased astrocytic reactivity in motor-critical regions. Targeting striatal myelination pathways may therefore offer a promising therapeutic avenue to mitigate the locomotor deficits seen in Glut1DS patients.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.08/C22

Topic: B.09. Glial Mechanisms

Title: Leveraging iPSC-derived astrocytes to accelerate the discovery of novel drugs targeting neuroinflammation

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¹Concept Life Sci., Edinburgh, United Kingdom; ²Fios Genomics, Edinburgh, United Kingdom

Abstract: Astrocytes, the main glial cell type in the human central nervous system, normally play critical roles in neuroprotection, immunity, and homeostasis. However, upon exposure to specific neuroinflammatory cues, they become pro-inflammatory and neurotoxic. Neurotoxic astrocytes promote chronic neuroinflammation, directly contributing to neurodegeneration. Evidence suggests that astrocytes become dysfunctional at the pre-symptomatic stage of neurodegenerative diseases. Therefore, targeting neurotoxic astrocytes can provide a novel therapeutic approach to prevent neurodegeneration. To accelerate the preclinical development of new drugs targeting neurotoxic astrocytes we (i) Assessed the validity of commercially available human iPSC-derived astrocytes exposed to neuroinflammatory stimuli as a representative model of reactive neurotoxic astrocytes and (ii) Developed an *in vitro* astrocyte polarization assay of high reproducibility and translational value. Human iPSC-derived astrocytes (at least two different lots of cells) were exposed to the proinflammatory “TIC” cytokine cocktail (30 ng/mL TNF α , 3ng/mL IL-1 α , and 400 ng/mL C1q) for 24 hours, in the presence or absence of selected positive controls, including dexamethasone, and compared to resting astrocytes. RNA-seq libraries were generated using the Roche KAPPA mRNA HyperPrep. Gene-level counts were quantified by Salmon and normalized by TMM. Differential expression was performed using Limma, followed by Reactome pathway and GO term GSEA. Expression of key polarization markers and effectors was confirmed by RTqPCR. In addition, cell culture supernatants were collected and used for cytokine secretion profiling by Luminex Multiplex. Astrocytes expressed key maturity markers and displayed a consistent transcriptomic profile at baseline. TIC stimulation consistently induced a strong inflammatory response at both the transcriptional and protein levels, including the upregulation of markers of neurotoxic astrocytes. This response

significantly overlapped with that observed in independently generated iPSC-derived astrocytes exposed to TIC. Dexamethasone and other small molecules reproducibly inhibited the TIC-induced polarization of astrocytes. In conclusion, we validated commercially available human iPSC-derived astrocytes exposed to TIC as an accurate model of the neurotoxic reactive phenotype, featuring minimal turnaround time and consistent responses across lots. We additionally validated reference compounds that strongly and reproducibly inhibit TIC-induced astrocyte polarization, providing a fully validated assay for drug discovery applications.

Disclosures: **T. Modebadze:** A. Employment/Salary (full or part-time): Concept Life Sciences. **M. Gurney:** A. Employment/Salary (full or part-time): Concept Life Sciences. **H. Scott:** A. Employment/Salary (full or part-time): Concept Life Sciences. **S.J. McCafferty:** A. Employment/Salary (full or part-time): Concept Life Sciences. **J. Sleight:** A. Employment/Salary (full or part-time): Fios Genomics. **D. Pearce:** A. Employment/Salary (full or part-time): Fios Genomics. **E. Malavasi:** A. Employment/Salary (full or part-time): Concept Life Sciences.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: PSTR155.09/C23

Topic: B.09. Glial Mechanisms

Support: NIH intramural research program 1ZIAN003137

Title: Distribution and trafficking of fatty acid binding proteins in brain development and injury

Authors: ***J. TABET**^{1,2}, J. YIN³, Q. YUAN⁴;

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Abstract: Fatty acid trafficking has a major influence on brain lipid profile and is strongly implicated in neurological disease. Using genetic and imaging studies in the *Drosophila* model, we evaluate fatty acid binding proteins (FABPs) and their roles in neural development and injury responses. Our previous studies have revealed that Odorant Binding Protein 44a (Obp44a), a highly abundant secreted protein produced by the CNS glia, is a non-canonical FABP that binds to long-chain fatty acids, facilitating their trafficking between neuron and glia, as well as their efflux into the hemolymph. Notably, an axonal injury model that ablates Olfactory Receptor Neuron (ORN) and Johnston's Organ (JO) in the fly antennae has demonstrated the recruitment of Obp44a to the degenerating axons, suggesting a role for FABPs as lipid scavengers to clear axonal debris. To understand the mechanism of FABP recruitments in axon injury and degeneration, we examined the cellular distribution and trafficking of GFP-tagged FABPs in the *Drosophila* brain. Among the FABPs we evaluated, our preliminary results indicate that human FABP5 and FABP7 preserve their expected intracellular localization, similar to *Drosophila*

FABP (dFabp), demonstrating their role in trafficking fatty acids to cellular compartments. *Drosophila* Glial Lazarillo (GLaz) has both cytoplasmic localizations as well secretions into the neuropil. Evaluating GLaz in our axon injury models reveals it has a recruitment to injured sites that, similarly to its human homologue apolipoprotein D (ApoD), is sex-specific, with male GLaz being highly expressed in antennal lobe regions. Together, our work demonstrates the *Drosophila* brain to be a fit model to study the role of FABPs in neural development and injury, guiding our investigations in understanding the importance of fatty acid recruitment to human health and disease.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

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Program #/Poster #: PSTR155.10/C24

Topic: B.09. Glial Mechanisms

Title: Glutamate transporter modulator cefepime prevents lipopolysaccharide-induced chronic pain and depressive-like behaviors by reducing glutamate mediated excitotoxicity in mice

Authors: *A. KHAN¹, P. J. RONAN², S. RAHMAN¹;

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Abstract: Evidence indicates that brain astroglial glutamate transporter 1 (GLT-1, a human homologue of excitatory amino acid transporter 2), plays an important role in the reuptake of excess glutamate, which helps prevent damage due to excitotoxicity induced by inflammation. We have previously shown that acute GLT-1 modulator cefepime, a fourth-generation beta-lactam cephalosporin antibiotic reduces lipopolysaccharide (LPS)-induced depressive-like behaviors and cognitive impairment in mice, an LPS-induced inflammatory model. Here we aimed to determine the effects of repeated administration of cefepime on tactile allodynia, thermal hyperalgesia, depressive-like, anxiety-like and cognitive deficit-like behaviors in a mouse model of chronic pain and depressive-like behaviors induced by LPS. In addition, we have examined the effects of repeated administration of cefepime on astroglial expression of GLT-1 and microglial expression of ionized calcium-binding adaptor molecule 1 (Iba-1) in the hippocampus (HC) and prefrontal cortex (PFC) of male and female mice using Western blot analysis. We also determined the effects of repeated administration of cefepime on TNF- α and IL-1 β in the HC and PFC of male and female mice using ELISA. Experiments were conducted in C57BL/6J male and female mice (7-9 weeks old). The chronic inflammatory response was induced by an intraperitoneal injection of LPS (0.75 mg/kg/day) for 7 consecutive days. Cefepime (200 mg/kg) was administered intraperitoneally 1 h prior to LPS administration for 7 consecutive days. Two-way ANOVA revealed that chronic treatment with cefepime significantly increased the paw withdrawal threshold ($p < 0.0001$) and latency time ($p < 0.0001$) in a sex-specific manner. Repeated administration of cefepime sex-dependently decreased the immobility

time during forced swim test ($p < 0.0001$) and tail suspension test ($p < 0.0001$). Moreover, chronic treatment with cefepime sex-dependently increased the open arm time ($p < 0.0001$) during elevated plus maze test and spontaneous alternation between arms ($p < 0.0001$) during Y-maze test. Western blot analysis indicated that repeated administration of cefepime sex-dependently reversed the downregulation of astroglial GLT-1 expression ($p < 0.0001$) and reduced the microglial expression of Iba-1 ($p < 0.0001$) in the HC and PFC. Furthermore, chronic treatment with cefepime sex-dependently reversed the LPS-induced increased TNF- α ($p < 0.0001$) and IL-1 β ($p < 0.0001$) levels in the HC and PFC. Overall, these results suggest that positive glutamate transporter modulator cefepime could be developed as potential therapeutic utility for comorbid chronic pain and depression.

Disclosures: A. Khan: None. P.J. Ronan: None. S. Rahman: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

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Program #/Poster #: PSTR155.11/C25

Topic: B.09. Glial Mechanisms

Support: Clinical Neuroscience “First in man” award # 20182601
State of California Brain Injury Research Center
NIH SBIR:# 1R43NS106972-01

Title: Proteomic identification of novel GFAP fragments in traumatic brain injury link biofluid profiles to human astrocyte proteinopathy and patient outcomes

Authors: *I. B. WANNER¹, Y. CHEN², J. R. LOPEZ³, J. GORNBEIN⁴, G. SHAW⁵, T. VAN METER⁶, P. VESPA⁷;

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Abstract: Monitoring traumatic brain injury (TBI) patients is essential for alleviating secondary complications and improving outcome. TBI triggers secondary injury, deranging proteostasis with protein degradation and proteinopathy. Pathological protein aggregation in post-mortem TBI brains impels a need for early detection by noninvasive biomarkers. GFAP, as promising TBI biomarker need to have TBI proteoforms and post-translational modifications (PTMs) defined. Addressing these gaps, our translational study identified the human GFAP degradome post-TBI linking fragments and PTMs in patient cerebrospinal fluid (CSF) and in human cerebral traumatized astrocytes. High confidence mass spectrometry of immunoprecipitated GFAP fragments from 6 TBI CSF samples identified a novel GFAP trauma-cleavage site. Immunoblotting with epitope-defined antibodies confirmed GFAP fragments, with coil1

fragments preferentially fluid release, and coil2 fragments selectively cell-retained. MS2 spectral ion signatures validated fragment citrullination and acetylation sites. Antibodies specific to citrullinated GFAP revealed individual TBI patient signatures and unique non-cytoskeletal aggregates in reactive, wounded and dystrophic astrocytes after stretch injury. Calpain and caspase GFAP proteolysis was analyzed using selective inhibitors and fluorescent reporters. Sequential GFAP breakdown products (BDPs) and their release was measured in cultured human astrocytes (5-48 hours post-injury, 3 donors). GFAP BDPs were also measured over ten post-TBI days in CSF (24 patients, 102 samples) by rigorous replicate-based scaled immunoblotting densitometry. Longitudinal analysis determined significant covariate effects of age and body temperature. Full-length (50kDa) and long GFAP BDPs (45-49kDa) decreased over time, while calpain-generated GFAP BDPs (37-39kDa) remained elevated with strongest covariance to full-size GFAP ($r=0.82$; FDR Logworth=24). Caspase-generated GFAP BDPs (<37kDa) had secondary rises and 15-19kDa BDPs showed missingness, consistent with cellular retention of coil2 BDPs. Calpain-generated GFAP (37-39kDa) predicted good (7+8) versus poor (1-6) patient recovery on the extended Glasgow Outcome scale (Cohen's $d=1.85$; $p=0.014$). In the culture trauma model, the release profile of calpain GFAP BDP (37kDa) distinguished mild (3psi, $n=4$ donors) from severe (5psi, $n=5$) injury at 5 hours post-stretch ($p<0.03$). Collectively, the GFAP degradome dynamics and PTMs provide novel biomarker longitudinal profiling to support patient monitoring and stratification and a potential for future tracking of astroglial proteinopathy after TBI.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.12/C26

Topic: B.09. Glial Mechanisms

Support: KAUST baseline to PJM

Title: Corticosterone Reprograms Astrocyte Metabolism Toward a Pentose Phosphate Pathway-Driven Antioxidant State

Authors: X. LIN, P. J. MAGISTRETTI, *H. FIUMELLI;
KAUST, Thuwal, Saudi Arabia

Abstract: Astrocytes are central regulators of brain energy metabolism and redox homeostasis. Chronic exposure to corticosterone (CORT), a stress hormone and the principal rodent glucocorticoid, disrupts cerebral glucose utilization and promotes neuropsychiatric vulnerability. Yet, the metabolic adaptations that astrocytes deploy under prolonged CORT exposure remain poorly understood. Here, we show that chronic CORT treatment induces a morphological shift in

astrocytes from a protoplasmic to a fibrous reactive-like phenotype. Integrated transcriptomic and metabolomic analyses reveal a profound metabolic reprogramming characterized by increased glucose uptake, suppression of glycolytic flux, and redirection of glucose metabolism toward the pentose phosphate pathway (PPP). CORT treatment upregulates the expression of G6PD, the rate-limiting enzyme of the PPP, elevates NADPH levels, and lowers the GSH/GSSG ratio, indicating heightened oxidative stress and engagement of antioxidant defense pathways. Glucose uptake assays confirm enhanced import, while extracellular flux analysis (Seahorse) reveals a marked reduction in ATP production from both glycolytic and mitochondrial sources. Consistent with this metabolic shift, glycogen stores were depleted, and lactate release into the extracellular medium was elevated. The latter likely reflects impaired mitochondrial pyruvate oxidation, as supported by increased expression of Pdk2 and Pdk4, which inhibit pyruvate dehydrogenase and thereby promote the diversion of pyruvate toward lactate production. Interestingly, CORT downregulates Glut1 expression while upregulating Glut3, Glut4, and Glut8, suggesting a compensatory remodeling of glucose transporter expression to maintain glucose influx under chronic stress. Together, these findings highlight a glucocorticoid-induced metabolic switch that favors antioxidant capacity over energy production. This adaptive shift may enhance astrocyte resilience under stress and unveil novel potential metabolic targets for therapeutic intervention in stress-related neuropsychiatric disorders.

Disclosures: X. Lin: None. P.J. Magistretti: None. H. Fiumelli: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

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Program #/Poster #: PSTR155.13/C27

Topic: B.09. Glial Mechanisms

Support: NIH/NINDS 1R01NS134887

Title: Integrated Single-Cell Analysis Reveals Disease-associated Glial Subtypes and Regulatory Factors in Neuroinflammatory Diseases

Authors: *H. KIM^{1,2}, M. ZHU², J. PARK³, H. CHEN⁴, F. GUO⁵;

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Abstract: This study conducted an integrated analysis of publicly available human single-cell and single-nucleus RNA-sequencing (sc/snRNA-seq) datasets to characterize cellular states and regulatory mechanisms in neuroinflammatory disorders, including normal aging, Alzheimer's disease (AD), multiple sclerosis (MS), and traumatic brain injury (TBI). Using the Harmony algorithm, we profiled ~1.1 million cells from human brain samples and uncovered both shared

and disease-specific glial heterogeneity across six major central nervous system (CNS) lineages. A key finding was an age-dependent escalation of immune-cell infiltration in CNS, most pronounced in TBI and MS, marked by increased lymphoid and myeloid populations and higher T- and B-cell fractions. Microglial heterogeneity was greater in TBI and MS than in aging or AD, with MS microglia showing strong up-regulation of endoplasmic-reticulum (ER) stress, inflammatory, and complement pathways. Oligodendrocytes and astrocytes also displayed distinct disease-associated transcriptional signatures. A disease-specific oligodendrocyte subtype exhibited heightened ER and oxidative-stress signatures, indicating compromised myelination and robust inflammatory gene expression. Likewise, a disease-specific astrocyte subtype showed ER stress, complement activation, and A1-like neurotoxic features. Across aging, AD, MS, and TBI brains compared with young controls, shifts in the abundance and phenotypic states of these glial clusters correlated significantly with disease stage, neuronal stress, cell death, and CNS immune infiltration. Transcription-factor profiling of disease-specific glial subtypes identified SOX2 as a pivotal regulator of disease-associated astrocytes; diminished SOX2 activity coincided with elevated complement expression and neurotoxic polarization. In vivo validation using Aldh1l1-Cre mice confirmed that astrocyte-specific SOX2 loss exacerbates neurotoxic phenotypes. These findings suggest that transcription regulators of inflammatory or neurotoxic glia cell subtypes may serve as universal and promising therapeutic targets for modulating central nervous system inflammation and maintaining tissue homeostasis.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

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Program #/Poster #: PSTR155.14/C28

Topic: B.09. Glial Mechanisms

Support: NSF Cooperative Agreement No. OIA-2242771

Title: Leveraging early life neurotoxic insult to elucidate tripartite synaptic development and maturation in the prefrontal cortex

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Abstract: Astrocytes, the primary glial cell type in the central nervous system (CNS), play a central role in promoting synaptic development and regulating brain homeostasis. A growing body of evidence supports the idea that astrocyte dysfunction at the “tripartite synapse” contributes to pathology in psychiatric and neurological disease, but the long-term consequences of disruptions in tripartite synaptic development during early life are still largely unknown. One

such neurotoxic insult that significantly impacts early development is prenatal opioid exposure (POE), which has steadily increased in the United States since the early 2000s. However, most studies to date have focused on the acute effects of POE during the perinatal period, resulting in a crucial gap in understanding of the long-term effects of POE on brain development.

Preliminary findings in our lab using single-cell RNA sequencing (scRNA-seq) of astrocyte-enriched samples from postnatal day 10 (P10) mouse cortex revealed around 600 differentially expressed genes (DEGs) with POE compared to vehicle exposure. Prominent regulators of astrocyte structure, such as Ntrk2 and Hepacam, along with functional genes like Aqp4, Gja1, and Kcnj10, were significantly downregulated in the POE groups. By contrast, many of the upregulated DEGs were associated with mitochondrial function, lipid metabolism, and oxidative stress. These results suggest that POE elicits a shift in astrocytic transcriptomes away from typical maturation milestones and support of synapses toward a maladaptive state of increased ROS, disrupted lipid metabolism, and impaired cellular energetics. Here, we used our POE model of early life neurotoxic insult to study tripartite synaptic development in the prefrontal cortex, a hallmark region for higher-order brain function. Pregnant C57Bl/6J mouse dams were orally dosed the opioid buprenorphine or vehicle control daily from gestational day 7 until P11. On P0-2, pups received retroorbital injections of systemic PHP.eB adeno-associated viruses (AAVs) carrying fluorescent reporters specific for either neurons (i.e. CaMKII-mCherry) or astrocytes (GFAP-IckGFP or GFAP-mKate2.5) to visualize tripartite synaptic cellular morphology. Following sacrifice between days P30-P35 (equivalent to mouse adolescence), brains were fixed-frozen, and 10 micron thick sections containing PFC were processed for either spatial transcriptomics (Visium HD, 10x Genomics) or fluorescence immunohistochemistry; the latter of which was followed by imaging via either standard confocal or super-resolution stimulated emission depletion (STED) microscopy.

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Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.15/C29

Topic: B.09. Glial Mechanisms

Support: NSF Grant 2235079

Title: Investigating the role of mitochondrial transcellular transfer between glia and neurons in CNS injury

Authors: *K. J. BACHTLE¹, G. I. LUNA AHUMADA¹, A. GHOSH¹, S. L. SHARPE², M. R. C. BHATTACHARYA¹;

¹Neurosci., ²Univ. of Arizona, Tucson, AZ

Abstract: Mitochondria make up a significant portion of neuronal volume due to high energetic demands. Neurons are especially susceptible to stress and injury and therefore rely heavily on glial cells for proper circuit maintenance. One newly emerging method of intercellular communication within the CNS is known as mitochondrial transcellular transfer (mitoTCT), defined as the active exchange of mitochondria between cells. Prior in vitro studies have observed that under stress conditions, neurons can uptake released glial mitochondria, improving overall neuronal survival and function. Just as transferred healthy intact mitochondria can aid in neuroprotection, transferred dysfunctional mitochondria can contribute to CNS disease progression. However, the major regulators and mechanisms of this process in vivo in the brain remain unknown. We developed an in vivo model of mitoTCT in *Drosophila melanogaster* in which we can quantify mitoTCT using confocal microscopy and imaging flow cytometry. Following nerve injury, more glial mitochondria are found within injured larval neurons than in uninjured controls. In contrast, adult neurons in the thoracic ganglion take up comparably fewer mitochondria after injury to incoming nerves. Currently we are evaluating how dTRPA1-induced excessive neuronal activity impacts the magnitude and frequency of mitoTCT in the adult CNS to identify additional triggers of transfer. Together, our work introduces a robust in vivo genetic platform to further investigate the mechanisms regulating mitochondrial transfer between glia and neurons, which could offer new insights to enhance neuronal survival in neurodegenerative diseases.

Disclosures: K.J. Bachtle: None. G.I. Luna Ahumada: None. A. Ghosh: None. S.L. Sharpe: None. M.R.C. Bhattacharya: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.16/C30

Topic: B.09. Glial Mechanisms

Support: NIH R41AG084421
NIH R41AG085831

Title: Serum-free ipsc derived astrocyte differentiation to model neuroinflammation and reactive astrocytes

Authors: *N. BUTELET, W. W. POON, A. DUONG, P. ZHOU, C. HOWARD, B. MONTGOMERY;
NeuCyte, Inc., Mountain View, CA

Abstract: Emerging studies highlight the transcriptomic diversity of regionally specified human astrocytes and the contribution of reactive astrocytes to neurological disease. Thus, there is a growing need for human astrocytes to model human disease and to be utilized in drug discovery efforts. While human primary sources of astrocytes are difficult to obtain, induced pluripotent

stem cell (iPSC)-based technologies have enabled the development of protocols to generate hiPSC astrocytes. Many current methods for iPSC-derived astrocytes employ the use of serum, which leads to reactive astrocytes, limiting their use to study the role of astrocytes contributing to neuroinflammatory mechanisms of disease. We have previously developed robust and rapid, serum-free protocol for the generation of cryopreserved iPSC-derived astrocytes from different disease backgrounds. Here we provide an in-depth molecular and functional characterization of our serum-free iPSC derived astrocytes. Activation of iPSC derived astrocytes via external stressors enabled the study of neuroinflammatory mechanisms of immunoreactive astrocytes cell autonomously or in the context of the brain environment when co-cultured with iPSC derived neurons, microglia and brain microvascular endothelial cells in 3D isogenic microphysiological systems. Incorporation of iPSC-derived astrocytes in different in vitro contexts provide potential drug screening platforms for identification of drugs targeting neurodegenerative and neuropsychiatric conditions.

Disclosures: **N. Butelet:** A. Employment/Salary (full or part-time): NeuCyte. **W.W. Poon:** A. Employment/Salary (full or part-time): NeuCyte. **A. Duong:** A. Employment/Salary (full or part-time): NeuCyte. **P. Zhou:** A. Employment/Salary (full or part-time): NeuCyte. **C. Howard:** A. Employment/Salary (full or part-time): NeuCyte. **B. Montgomery:** A. Employment/Salary (full or part-time): NeuCyte.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.17/C31

Topic: B.09. Glial Mechanisms

Support: R01DK134650

Title: Contribution of TrkB.T to astrogliosis in 5xFAD mice

Authors: ***R. BASS, III**^{1,2};

¹UF Scripps Biomed. Res., Palm Beach Gardens, FL; ²Scripps Res., Jupiter, FL

Abstract: Astrogliosis is an inflammatory phenotype present in traumatic brain injury and in diseases such as Parkinson's disease and Alzheimer's disease. Astrocytes undergoing this process exhibit several changes: increased morphological complexity, increased number of astrocytes, and altered expression of genes such as Gfap. Unpublished data from our lab shows that performing an astrocyte-specific deletion of the Ntrk2 gene, which encodes the neurotrophin receptor TrkB, blocks the formation of reactive astrocytes in the hypothalamus and prevents diet-induced obesity when mice are fed a high-fat diet. Interestingly, TrkB is only expressed as two truncated isoforms (TrkB.T1 and TrkB.T2) in astrocytes. These isoforms do not have the tyrosine kinase domain found in the full-length isoform, TrkB.FL, which is expressed in neurons. Here, I study the role of astrocytic TrkB.T in 5xFAD mice, a model of Alzheimer's disease that

exhibits astrogliosis beginning at 2 months of age. I perform an astrocyte-specific *Ntrk2*-cKO and examine the impact of this deletion on the formation of astrogliosis and other 5xFAD-associated phenotypes. I predict that phenotypes such as increased morphological complexity exhibited by reactive astrocytes in 5xFAD mice will be decreased in 5xFAD mice with astrocytes lacking *TrkB*.

Disclosures: R. Bass: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.18/C32

Topic: B.09. Glial Mechanisms

Support: R01AG082362
T32GM008541
K01AG062683

Title: Apoe e4 astrocytes disrupt neuronal lipid homeostasis and proteostasis in human ipsc co-culture model

Authors: *J.-G. S. ROSA¹, L. QIAN², A. PELLETIER³, R. HUANG³, T. TCW³, A. SCRIVO⁴, A. CUERVO⁴, J. TCW³;

¹Grad. Program for Neurosci., ²Pharmacology, Physiol. and Biophysics, ³Boston Univ., Boston, MA; ⁴Albert Einstein Col. of Med., Bronx, NY

Abstract: Polymorphisms in the *APOE* gene have strong associations to late-onset Alzheimer's disease (AD) risk, with the *APOE E4* variant (*APOE4*) increasing AD risk up to 15-fold in homozygotes compared to carriers of the neutral allele *APOE E3* (*APOE3*). While the past three decades of research have identified several A β - and tau-associated pathologies exacerbated by *APOE4*, our understanding of the cell type-specific effects of *APOE4* remains incomplete. As astrocytes are the primary expressors of *APOE* in the brain, we investigated the cell-autonomous effects of *APOE4* on astrocyte biology as well as the non-cell-autonomous effects of astrocytic *APOE4* on neurons. To study human astrocytes, we differentiated astrocyte monocultures from isogenic *APOE 3/3* and *APOE 4/4* human induced pluripotent stem cells (hiPSC) from AD *APOE 4/4* patients (N=3). RNA-seq analysis revealed that the lysosome KEGG pathway was among the most significantly downregulated pathways in *APOE 4/4* astrocytes across all hiPSC lines. Using snRNA-seq data from the Seattle Alzheimer's Disease Brain Cell Atlas, we validated that astrocytes from postmortem AD *APOE4*-carriers (N=84 donors) exhibit significant downregulation of lysosome pathways. As the lysosome is a key site for regulation of growth and catabolism, we hypothesized that lysosomal dysfunction may underlie toxic lipid accumulation in *APOE 4/4* astrocytes. We determined that *APOE 4/4* astrocytes exhibit increased intracellular lipids and cytokine secretion (n=3-6), as well as reduced lysosomal

acidification, proteolytic activity, and lipid catabolism (n=3-6). Macroautophagy, a process by which intracellular cargo is trafficked to the lysosome for degradation, was significantly reduced in *APOE* 4/4 astrocytes (n=3). To determine the impact of astrocytic *APOE4* on neurons, we developed a mixed genotype co-culture model in which *APOE* 3/3 *NGN2*-induced neurons (70%) were cultured with either *APOE* 3/3 or 4/4 isogenic astrocytes (30%). After two weeks co-culture, neurons increased TUBB3 and MAP2 marker expression and increased neurite extension relative neurons cultured alone (n=3). *APOE* 4/4 co-cultures had significantly reduced lipid catabolism, lysosomal activity, and macroautophagy as well as increased cell stress relative to *APOE* 3/3 co-cultures (n=6). These results suggest astrocytic *APOE4* expression is sufficient to impair lipid homeostasis and proteostasis in astrocytes and in neurons. Future investigation is required to understand the mechanisms of *APOE4* astrocyte-mediated lipid and proteostasis impairment.

Disclosures: J.S. Rosa: None. L. Qian: None. A. Pelletier: None. R. Huang: None. T. Tcw: None. A. Scrivo: None. A. Cuervo: None. J. Tcw: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.19/C33

Topic: B.09. Glial Mechanisms

Support: Templeton Medical Research Foundation
Ohio Lions Eye Research Foundation

Title: Changes in Glia at the Nodes of Ranvier in Glaucoma

Authors: *M. TERZIC¹, C. M. DENGLER-CRISH², M. A. SMITH¹, S. D. CRISH³;
²Pharmaceut. Sci., ¹Northeast Ohio Med. Univ., Rootstown, OH; ³Pharmaceut. Sci., NEOMED, Rootstown, OH

Abstract: Glaucoma, the leading cause of irreversible blindness worldwide, is characterized by early dysfunctions in retinal ganglion cell (RGC) axons, including deficits in axonal transport and impaired neuronal signaling. In the DBA/2J mouse model, which develops age-related glaucomatous neurodegeneration, optic nerve (ON) pathology includes disruptions at the nodes of Ranvier, specialized locations essential for action potential propagation. Healthy nodes exhibit a dense concentration of the voltage-gated ion channel Nav1.6 subtending the entire node ("normal"). Intriguingly, although glaucoma is not classified as a myelinopathy, DBA/2J mice display nodal abnormalities reminiscent of multiple sclerosis, including increased nodal width and either disrupted Nav1.6 distribution ("split" nodes) or complete absence of Nav1.6 ("absent" nodes). To investigate potential mechanisms driving this pathology, we examined glial contact at nodes. In healthy optic nerves, over 95% of nodes are contacted by astrocytes, which maintain ionic homeostasis, clears extrasynaptic glutamate, and provides metabolic support. Surprisingly,

in DBA/2J mice, nearly half of the *normal* nodes lacked astrocytic contact even at pre-pathological ages, and 10-15% exhibited microglial contact. Strikingly, 90-95% of pathological nodes (split or absent) lacked *both* astrocytic and microglial contact at all ages examined. These findings suggest that loss of glial support at nodes of Ranvier precedes and potentially drives nodal pathology and impaired axonal signaling in glaucoma. In particular, astrocyte detachment may undermine local ionic balance and metabolic supply, fostering a microenvironment conducive to axonal dysfunction and eventual degeneration. The early onset of these changes, before overt neurodegeneration, implicates nodal glial disruption as a possible initiating factor in glaucomatous axonopathy — and a novel target for early therapeutic intervention.

Disclosures: M. Terzic: None. C.M. Dengler-Crish: None. M.A. Smith: None. S.D. Crish: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.20/C34

Topic: B.09. Glial Mechanisms

Support: NIH-T32
NEI R01-EY033816
P30-EY026877
Research to Prevent Blindness, Inc.

Title: Compartmentalized camp signaling in optic nerve head astrocytes modulates neurodegeneration in glaucoma

Authors: *D. VILLAFRANCA-BAUGHMAN¹, J. MAYA², M. S. KAPILOFF³, J. L. GOLDBERG⁴;

¹Stanford University, Ophthalmology, Fac. of Med., Redwood City, CA; ²Stanford Univ., Palo Alto, CA, ; ³Stanford Univ., Los Altos, CA; ⁴Byers Eye Institute--Ophthalmology, Stanford Univ., Palo Alto, CA

Abstract: Purpose : How does compartmentalized cyclic-AMP (cAMP) signaling influence astrocyte-mediated neurodegeneration in glaucoma? Optic nerve head (ONH) astrocytes play a critical role in regulating neuroinflammatory responses and supporting retinal ganglion cell (RGC) survival. Although distinct subcellular pools of cAMP are known to control various astrocytic functions, their specific roles in the glaucomatous ONH remain unclear. Here, we investigate whether targeted modulation of cAMP levels—specifically increasing nuclear cAMP via a calcium-sensitive soluble adenylyl cyclase (sAC)—in ONH astrocytes can alter neurodegenerative outcomes in a mouse model of ocular hypertension (OHT).

Methods : OHT was induced in young/adult CD1 mice by intracameral injection of magnetic microbeads (N = 7 mice per group). To modulate compartmentalized cAMP levels in ONH

astrocytes, we employed adeno-associated virus (AAV) vectors engineered to either constitutively elevate nuclear cAMP or to buffer cAMP levels in the nucleus or cytoplasm. Three weeks post-OHT induction, RGC survival was evaluated using retinal immunolabeling.

Results : Preliminary data indicate that AAV-mediated elevation of nuclear cAMP in ONH astrocytes significantly promotes RGC survival following three weeks of OHT induction. In contrast, buffering nuclear cAMP revokes this neuroprotective effect, while modulation of cytoplasmic cAMP did not produce a comparable impact on RGC survival. These findings suggest that nuclear cAMP signaling in ONH astrocytes is a critical determinant of neuroprotective responses in the context of glaucoma.

Conclusions : Our study demonstrates that targeted modulation of nuclear cAMP levels in ONH astrocytes via AAV vectors significantly influences neurodegenerative outcomes in a mouse model of glaucoma. These results underscore the importance of compartmentalized cAMP signaling in the ONH and point to nuclear cAMP as a promising therapeutic target for preserving RGCs and mitigating neurodegeneration. Future studies will focus on elucidating the molecular pathways downstream of nuclear cAMP that drive astrocyte-mediated neuroprotection in glaucoma.

Disclosures: **D. Villafranca-Baughman:** None. **J. Maya:** None. **M.S. Kapiloff:** None. **J.L. Goldberg:** None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.21/C35

Topic: B.09. Glial Mechanisms

Support: NIH Guanosine Grant

Title: Purines dynamically mediate reactive astrocytes in inflammation

Authors: *K. CALDWELL, A. E. ROSS;
Univ. of Cincinnati, Cincinnati, OH

Abstract: In neuroinflammation, astrocytes can adapt to a reactive state, undergoing morphological and molecular changes that result in altered cytokine production, receptor expression, and neurochemical release. Purines have come to the forefront as biomarkers of interest due to their role in the modulation of major neurotransmitters. Specifically, nucleoside derivatives, adenosine and guanosine, have increased in recognition due to their neuroprotective and immunomodulatory roles in the central nervous system (CNS). While adenosine has been extensively studied under pathological conditions, astrocytes have been identified as a primary source of extracellular adenosine during injury; the role of guanosine remains underexplored. Despite evidence showing that exogenous guanosine reduces neuroinflammatory damage, the mechanisms by which guanosine modulates astrocyte function during inflammation remain

poorly defined. In this study, we investigate how guanosine influences astrocyte reactivity by engaging with purinergic receptors and activating the PI3K/AKT signaling pathway, leading to downstream changes in cytokine production, receptor regulation, and astrocyte phenotype. We utilized primary astrocyte cell culture treated with lipopolysaccharide (LPS) to induce a reactive astrocyte phenotype. Immunocytochemistry and flow cytometry were used to capture changes in astrocyte reactivity and surface receptor expression. ELISA assays quantified proinflammatory and anti-inflammatory cytokine release from these cells. Additionally, western blotting was used to assess expression levels of adenosine receptors (A1R and A2AR), equilibrate nucleoside transporters (ENT1 and ENT2), and PI3K/AKT pathway components. The use of selective PI3K/AKT inhibitors provided mechanistic insight into guanosine's signaling actions. Collectively, this approach aims to uncover novel pathways by which guanosine modulates astrocyte behavior during neuroinflammation, potentially revealing new therapeutic strategies for neurodegenerative diseases.

Disclosures: K. Caldwell: None. A.E. Ross: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.22/C36

Topic: B.09. Glial Mechanisms

Support: NIH T32 DA050558-03

Title: Astrocyte coordination of dopaminergic disease

Authors: *L. OTSUKA, E. BORRELLI;
Microbiology and Mol. Genet., Univ. of California, Irvine, Irvine, CA

Abstract: Over 15 million adults in the United States alone suffer from severe mental illnesses. Among these, schizophrenia (SZ), a chronic neuropsychiatric disorder, typically manifests in adolescence and affects as many as 1 in every 300 worldwide. Despite this relatively common rate of occurrence, the etiology of SZ remains largely unknown. Due to the efficacy of neuroleptics, which primarily target the dopamine D2 receptor (D2R), chronic alterations in dopamine (DA) signaling have long been implicated in the genesis of SZ. Similarly, drugs of abuse such as methamphetamine (MA) are known to induce SZ-like psychotic states through disruption of DAergic transmission throughout the brain. This heterogeneity in the onset of psychotic disorders suggests a combination of developmental, environmental, and epigenetic factors in the etiology of SZ. Therefore, we utilize a unique transgenic mouse model (DA-D2RKO mice) in which DA neuron-specific ablation of presynaptic D2Rs leads to loss of control over DA release, widespread epigenetic reprogramming of cortical neurons, and psychotic-like behavioral phenotypes. Importantly, newly emerging research has established crucial roles for astrocytes in regulating neurotransmitter homeostasis in the brain, including the recent

identification of D2Rs expressed on perisynaptic astrocyte processes (PAPs). Therefore, we sought to characterize astrocytic contributions and responses to dysregulation of DA signaling from two distinct perspectives: genetic, as in DA-D2RKO mice, and pharmacological, employing a model of MA-induced psychosis. Behavioral assessment of motor sensitization to MA revealed a striking inhibition in DA-D2RKO mice compared to their wild type (WT) littermates - a phenotype recapitulated in WT animals by chemogenetic manipulation of ventral tegmental area (VTA) astrocytes. We find that lack of control over DA signaling leads to aberrant astrocyte neurotransmitter cycling and neuronal dendritic spine structures in the VTA, highlighting the importance of this control in driving proper glial synaptic tuning. Finally, in-vivo imaging of the VTA following MA administration implicates a novel role for local DA release in regulating astrocyte activity and inhibitory feedback onto DA neurons. Taken together, we provide evidence of a coordinated astrocyte-neuron response to DA signaling that, for better or worse, shapes dopaminergic circuitry in the brain.

Disclosures: L. Otsuka: None. E. Borrelli: None.

Poster

PSTR155: Astrocytes: Disease Mechanisms II

Location: SDCC Halls B-H

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Program #/Poster #: PSTR155.23/C37

Topic: B.09. Glial Mechanisms

Support: 100332977-UALVIEP/24-1

Title: Diabetic Encephalopathy-associated glial markers in the Zucker Diabetic Fatty Rat as a model of Type 2 Diabetes

Authors: *A. M. OROZCO, M. ISLAS-ISLAS, R. A. VAZQUEZ-ROQUE;
Neuroplasticity and Metabolism, Inst. of Physiology, Meritorious Autonomous Univ. of Puebla (BUAP), Puebla, Mexico

Abstract: Diabetes is a chronic metabolic disorder with a great health burden worldwide. Type 2 Diabetes (T2D) is characterized by a functional failure and decrease of pancreatic β -cells volume and/or number, which is accompanied by varying degrees of peripheral insulin resistance, decreased insulin secretion, and increased hepatic glucose production, all leading to the common presentation of sustained hyperglycemia. The complications presented by patients with T2D are of relevance to the central nervous system, such that the term “diabetic encephalopathy” was originated to name the cognitive impairment, as well as the neurophysiological and structural changes in the brain caused by the pathophysiology of diabetes itself, which include: mitochondrial dysfunction, oxidative stress, neuroinflammation, and gliosis, as well as vascular damage, glucose toxicity, blood-brain barrier alterations and insulin resistance. Emerging evidence suggests that glial reactivity is closely linked to mitochondrial dysfunction, which may exacerbate neuron vulnerability and cognitive decline.

In this study we investigated how glial activation correlates with alterations in mitochondrial integrity, as well as cell death and inflammation markers in a model of T2D (ZDF rat). We used a combination of immunofluorescence markers as well as mitochondrial probes in the Hippocampal region (Dentate Gyrus, DG, and CA1) of Lean ZDF and Hyperglycemic Obese ZDF rats (n=6) of 13 weeks of age. Our results demonstrate a differential expression of astrocyte, microglial, and inflammation markers (GFAP, Iba1, and COX2) in comparison to the control, as well as an apparent change in morphology in astrocytes. Mitochondrial viability was measured by the Mitotracker probe Red CMXRos, and was found to be decreased in the DG diabetic group as well. Additionally we measured cell death by Acridine Orange, which was found to be increased in both regions in the diabetic group. These results are consistent with findings of a decrease in neuron density, atrophies in neuron morphology, as well as inflammation markers reported previously by our lab and in the literature in the diabetic hippocampus, as compared to controls. These findings suggest a bidirectional relationship that supports the mechanisms behind diabetic encephalopathy.

Disclosures: A.M. Orozco: None. M. Islas-Islas: None. R.A. Vazquez-Roque: None.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.01/C38

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

Support: 2024 TRSA John P. McGovern Fellowship
NIH Grant U01AA025932
NIH Grant R01AA027768
NIH Grant R01AA030293

Title: Early-stage corticostriatal circuit hyperactivity impairs cholinergic function and cognitive flexibility in an alzheimer's model

Authors: *Y. HUANG^{1,2}, X. XIE², Z. HUANG², R. CHEN^{2,3}, H. GANGAL², K. M. SOUZA^{2,1}, X. WU², D. S. REDDY^{2,1}, J. CHIN⁴, J. WANG^{2,1,3};

¹Texas A&M Inst. for Neurosci., College Station, TX; ²Dept. of Neurosci. and Exptl. Therapeut., Texas A&M Univ. Hlth. Sci. Ctr., Bryan, TX; ³Interdisciplinary Fac. of Toxicology, Texas A&M Univ., College Station, TX; ⁴Dept. of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Cognitive flexibility deficits are a hallmark of early-stage Alzheimer's disease (AD), but the underlying circuit mechanisms remain poorly understood. Here, we show that the 5xFAD mouse model of AD pathology exhibited early deficits in instrumental reversal learning, indicating cognitive inflexibility preceding spatial memory deficits. This impairment was associated with excessive neuronal reactivation in the medial prefrontal cortex (mPFC) and dorsomedial striatum (DMS), key regions for goal-directed behavior. Electrophysiological

recordings revealed that mPFC neurons in young 5xFAD mice were hyperexcitable and received elevated excitatory input. Moreover, the mPFC-to-direct pathway medium spiny neuron (dMSN) circuit and the dMSNs themselves were selectively hyperactive. These hyperactive dMSNs exerted increased inhibitory control over cholinergic interneurons (CINs) in the DMS, coinciding with reduced CIN firing and diminished striatal acetylcholine (ACh) release. Critically, sustained chemogenetic inhibition of the mPFC-to-DMS circuit in 5xFAD mice reduced cortical A β accumulation, normalized glutamatergic transmission in both the mPFC and DMS, restored striatal ACh levels, and rescued reversal learning deficits. Together, these findings identify a hyperactive mPFC-to-DMS circuit that disrupts corticostriatal and cholinergic signaling, contributing to cognitive inflexibility in 5xFAD mice. Targeting this circuit may offer a therapeutic strategy to preserve cognitive function in the early stages of AD.

Disclosures: Y. Huang: None. X. Xie: None. Z. Huang: None. R. Chen: None. H. Gangal: None. K.M. Souza: None. X. Wu: None. D.S. Reddy: None. J. Chin: None. J. Wang: None.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.02/C39

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

Support: Louisiana State University School of Veterinary Medicine (LSU-SVM)
CORP grant
National Science Foundation grant (IOS 2137023)
National Institute of Health grant (R01MH132018-01A1)

Title: Amyloid beta alters mPFC encoding of temporal order task.

Authors: *I. LIM, O. OGUNDELE;
Comparative Biomed. Sci., Louisiana State Univ., Baton Rouge, LA

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder linked to dementia. Clinical diagnosis of AD occurs in the mid to advanced disease stage when patients exhibit signs of memory loss or dementia. Likewise, in AD experimental models, animals are assessed in the mid-to-late stages when behavioral phenotypes are discernible. The goal of the current study was to detect mPFC encoding of TOR tasks over a chronic duration before and after toxic or non-toxic A β lesioning (48 days). Furthermore, by recording from a fixed electrode, approximate putative neuron populations were sampled before and after lesioning. The current study deploys *in vivo* PFC recording in mice during TOR tasks to detect changes in putative PFC encoding of TOR tasks in naïve mice (baseline) and after toxic A β ₍₂₅₋₃₅₎ or control A β ₍₃₅₋₂₅₎ lesioning. TOR recognition index had a positive correlation with increasing firing rate (FR) of putative units during correct (old) object exploration intervals. Furthermore, the percentage distribution of putative units with FR increase during old object intervals was more

than the recent object intervals. Interestingly, in A β ₍₂₅₋₃₅₎ ensembles, the positive correlation between TOR performance and pyramidal FR was diminished. In addition, there was a reduction in the percentage of units with FR increase during old object exploration. The positive correlation between the FR and recognition index was retained in control A β ₍₃₅₋₂₅₎ ensembles. Taken together, our results showed that toxic A β lesioning impacts TOR memory encoding by altering memory encoding patterns associated with object recognition and discrimination.

Disclosures: I. Lim: None. O. Ogundele: None.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.03/C40

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

Support: NIH Grant R01 AG054104
NIH Grant R01 AG064231

Title: Locus Coeruleus Activation Advances Cognitive Impairment and Tau Pathology without Influencing Amyloid Pathology in an Alzheimer's Knock-in Mouse Model

Authors: *C. LY, P. V. FENIK, S. C. VEASEY;
Ctr. for Sleep and Circadian Neurobio., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Chronic sleep disruption (CSD) is a common occurrence worldwide and is considered an independent risk factor for Alzheimer's disease (AD). Previous work supports roles for both increased neuronal activity and reduced glymphatic clearance in amyloid- β and tau responses to CSD. However, distinct temporal and regional patterns of amyloid- β and tau pathologies in AD suggest a primary role for neural circuit involvement in AD pathogenesis. Sleep disruption increases the activity of locus coeruleus neurons (LCn), which project to the brain regions most vulnerable in AD. We hypothesized that LCn activity drives regionally distinct amyloid and tau responses in AD. Using a mutant amyloid precursor protein knock-in mouse model (APPSAA KI) of AD pathology, we determined the effects of 12 weeks of intermittent LCn chemogenetic activation on neurobehavior and pathology. We found that chronic activation of LCn led to persistent reductions in sleep time, impaired memory and reduced center avoidance in an open field and increased phosphorylated tau at two pathogenic sites (Thr217 and Thr231) in the LC, entorhinal cortex and dentate. In contrast, there were no differences observed in amyloid plaque. We conclude that chronic LCn stimulation imparts entorhinal and hippocampal tau neural injury, indicative of an LC - limbic system circuit influencing tau phosphorylation and progression of AD. Neural circuits underlying the link between sleep disruption and AD must be understood to identify effective therapies for the disease. Here we found that activation of locus coeruleus neurons is sufficient to induce lasting impairments in sleep and memory and induce limbic system tau injury consistent with AD temporal-regional differences.

Disclosures: C. Ly: None. P.V. Fenik: None. S.C. Veasey: None.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.04/C41

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

Support: National Science Foundation Graduate Research Fellowship

Title: Studying the impacts of early-life and adult stress on AD pathology and stress-vulnerable circuits

Authors: *J. SANTOYO;
MIT, Cambridge, MA

Abstract: Alzheimer's Disease (AD) is a highly debilitating disease with major individual and societal impacts. Given the lack of effective treatments for AD, there is an urgent need to understand the risk factors that contribute to its development and invest in research on preventative and early-detection strategies. Notably, stress exposure in early life and adulthood is emerging as a critical risk factor for AD, with recent epidemiological meta-analyses suggesting that increased early-life stress (ELS) exposure is associated with nearly a 2-fold increase in dementia incidence. Here, we present results demonstrating specific effects of ELS, adult stress, and their combined impact on AD pathology and cognition. Specifically, we optimized a computational pipeline for multi-region brain analyses to identify brain regions where ELS and adult stress may act synergistically and to systematically profile the impacts of each unique stressor. We report that both early-life and adult stress drive distinct effects on AD-related pathology, with ELS appearing to exacerbate brain-wide accumulation of amyloid plaques, one of the hallmarks of AD, while adult restraint-stress appears to primarily drive localized effects on inflammatory processes. We predicted that, due to the lasting effects of ELS on anxiety and stress regulation, ELS may heighten susceptibility to adult stress, leading to a compounded impact on AD pathology. Indeed, we observe that ELS drives an increase in anxiety-linked behaviors in the elevated-plus maze, light-dark task, and in open-field tests. Furthermore, we tested whether restraint-evoked c-fos activation would differ between the mice previously exposed to ELS & Restraint and those exposed to Restraint alone, and we found that the ELS-exposed mice showed hypoactivity across prefrontal cortical regions, including infralimbic, anterior cingulate, primary motor, secondary motor, insula, and piriform cortices. Anxiety measures and c-fos hypoactivity in the dual-hit group predicted elevated amyloid-beta plaque counts in focal regions (particularly in the ventromedial PFC, orbitofrontal cortex, retrosplenial cortex, and dentate gyrus), as well as widespread reductions in microglia and astroglia counts. We propose additional experiments to probe the transcriptional effects of these distinct stressors as well as circuit-specific rescues.

Disclosures: J. Santoyo: None.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.05/C42

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

Support: Daniel J. Epstein Breakthrough Alzheimer's Disease Research Fund

Title: Theta and gamma frequency forniceal deep brain stimulation rescues recognition and spatial memory in a 5xFAD mouse model of Alzheimer's Disease

Authors: I. A. CHEN¹, M. A. PEREZ¹, N. C. ZEPEDA², *D. J. LEE¹;

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Abstract: Alzheimer's Disease (AD) is a neurodegenerative disorder marked by disrupted functional connectivity and progressive cognitive decline. In addition to pathognomonic amyloid beta deposition, tau hyperphosphorylation and synaptic loss, AD involves impaired septohippocampal theta oscillations critical for learning and memory. Thus, neuromodulation has emerged as a treatment modality for such circuitopathy. The fornix has been postulated as a promising target for deep brain stimulation (fx-DBS), as it is crucial for memory regulation. While standard DBS typically employs high-frequency gamma (130-180 Hz) stimulation, there have been several studies that suggest low-frequency theta oscillations (5-12 Hz) are essential for learning and memory. Here, we assess the differential effects of theta- versus gamma-frequency fx-DBS on recognition and spatial memory in a 5xFAD mouse model of AD. Male 5xFAD (n = 25) and wild-type (WT; n = 42) mice were evaluated at 38-40 weeks of age using Novel Object Recognition (NOR), Elevated Plus Maze (EPM), and Barnes Maze (BM) tasks to assess memory and behavior. Mice received either theta, gamma, or sham fx-DBS for 10 consecutive days (8 hours/day). For NOR, stimulation conditions had no effect in discrimination index among WT mice (p = 0.694). However, 5xFAD mice receiving theta fx-DBS showed improved recognition memory compared to their sham DBS counterparts (p = 0.00445) and were indistinguishable from WT controls (p = 0.993), suggesting rescue of recognition memory to baseline WT levels. There was no difference between 5xFAD theta and gamma groups (p = 0.283), though theta showed a trend towards improvement. For EPM, 5xFAD theta mice spent significantly less time in open arms compared to 5xFAD sham DBS (p = 0.0167), suggesting reduced disinhibition and normalization of anxiety-like behavior. 5xFAD theta performance did not differ from WT sham DBS (p = 0.813), supporting restored behavior to WT levels with theta DBS. During the BM task, performance of WT subgroups were similar. Theta-stimulated 5xFAD mice had significantly reduced escape latencies relative to 5xFAD sham DBS (p = 0.0098) and were indistinguishable from WT controls (p = 0.00051), indicating that theta fx-DBS rescued spatial learning impairments. While 5xFAD gamma DBS had a trend towards improved performance compared to 5xFAD sham DBS (p = 0.0547), there was no difference between 5xFAD theta and

gamma groups ($p = 0.141$). Collectively, these findings highlight theta-frequency fx-DBS as a potentially more robust therapeutic modality for circuit-level restoration and cognitive rescue in AD.

Disclosures: I.A. Chen: None. M.A. Perez: None. N.C. Zepeda: None. D.J. Lee: None.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Program #/Poster #: PSTR156.06/C43

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

Support: National Institute on Aging, grant AG067049

Title: Impact of sex and age on hippocampal long-term depression in wild type and APP/PS1 mice

Authors: *Y. DU, A. SNYDER, A. LAWRENCE, K. B. DORE;
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Abstract: The NMDA receptor (NMDAR) is a crucial excitatory receptor in the brain, essential for synaptic plasticity, the molecular basis of learning and memory. Beyond its well-known ion-flux dependent function, NMDARs have been found to have an ion-flux independent function, thought to be important for structural plasticity. However, previous studies have primarily investigated this function in young male rodents, leaving a gap in understanding its role across sexes and ages. Given recent evidence of sex differences in the effects of NMDAR antagonists on synaptic plasticity and memory, we investigated ion-flux dependent and independent LTD in adult and aged wild type and APP/PS1 mice, considering sex differences. We employed two different low-frequency stimulation protocols to induce NMDA-dependent and -independent LTD, with and without the NMDAR antagonist L689,650, which blocks NMDAR ion-flux but not glutamate binding. Our results show that ion-flux independent NMDAR LTD was observed in adult (2-4-month-old) WT female mice and aged (16-23-month-old) female APP/PS1 mice, but not in males. We also detected classic NMDAR-dependent LTD in both adult and aged female APP/PS1 mice, suggesting that in female mice, the determinant factor for susceptibility to LTD is AD phenotype. In contrast, we observed NMDAR-dependent LTD in both aged WT and aged APP/PS1 male mice, suggesting that in male mice, age is the determinant factor. These findings suggest that different forms of LTD contribute variably to synaptic weakening in a sex- and age-dependent manner. Finally, this study underscores the need to revisit and expand seminal findings on LTD to better understand how it changes across life and presents differently in male and female animals.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Program #/Poster #: PSTR156.07/C44

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

Support: Purdue Institute for Integrative Neuroscience pilot grant

Title: Visual familiarity induced oscillations are altered in 5xFAD modeled Alzheimer's disease

Authors: *K. CRAGG¹, M. YIN², V. SALDARRIAGA³, A. A. CHUBYKIN³;

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Abstract: Alzheimer's disease is a neurodegenerative disease that commonly results in cognitive and memory impairment. The hippocampus, widely accepted as integral in memory encoding and retention, has been a primary target for study and is a hotspot for Alzheimer's disease (AD) biomarkers, such as amyloid-beta and hyper-phosphorylated tau aggregates. However less studied is how similar biomarkers and degradation present in cortical areas impacts their function and contributes to AD symptoms. We have previously shown that visual familiarity induces theta oscillations 4-8Hz in the primary visual cortex (V1) of mice. These oscillations are stimulus specific and appear after multiple days of repeated visual stimulus presentation. Disruption to these oscillations impairs the ability of mice to perform in learned visual discrimination tasks, emphasizing their link to visual memory. Excitation/inhibition balance and circuit connectivity are critical for the induction of these familiarity oscillations. Therefore, the disruption to this circuit in AD may contribute to poor learning, memory formation, and recall. However, which parts of the familiarity circuit in V1 are most impacted by AD and how this alters the oscillatory activity has yet to be characterized. To address this gap in knowledge, we conducted acute extracellular silicon probe recordings in V1 of aged B6 wildtype and B6-5xFAD mice before and after 3 days of familiarity training. We find that current source density flow is significantly altered in 5xFAD mice compared to WT. This circuit disruption in 5xFAD mice correlates with familiarity induced oscillations which have significantly smaller second cycle peak to trough amplitudes in local field potentials. Moreover, individual unit analysis showed that a majority of oscillating units are not preferentially firing at this cycle in 5xFAD mice. This may represent that critical components of the circuit have experienced degeneration, thus altering the familiarity response. Overall this work marks an important first step in understanding the impact of AD on early sensory processing and how that translates to cognitive and memory impairment.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

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Program #/Poster #: PSTR156.08/C45

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

Support: MRC Grant UKDRIEdin007

Title: Accelerated Oscillations and Reduced Inhibition Drive Early Hippocampal Hyperactivity in Alzheimer's Disease

Authors: *S. KANG^{1,2}, M. LIU^{1,2}, A. TOPÇU^{1,2}, J. GAN^{1,2};

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Abstract: Hippocampal hyperactivity is a consistent yet mechanistically unresolved feature of early Alzheimer's disease (AD), observed in at-risk individuals and animal models prior to cognitive symptoms. While functional imaging has revealed abnormal hippocampal activity, the circuit-level changes that drive this phenomenon during the early phase of amyloid pathology—when A β is largely soluble—remain unclear. To investigate these early network alterations, we conducted high-density silicon probe recordings in the hippocampus in awake, head-fixed APP^{swe}/PS1 Δ E9 (APP/PS1) mice navigating a linear track within a virtual reality (VR) environment. This allowed us to assess hippocampal dynamics under behaviorally relevant conditions. Following analysis of single units and local field potentials (LFPs), we observed increased burst firing in CA1 pyramidal neurons and a significant reduction in the activity of fast-spiking interneurons. Spectral analysis of LFPs revealed a clear shift toward faster network oscillations, with increased power in the theta and beta activity in APP/PS1 mice. These changes suggest a breakdown in inhibitory control, where reduced engagement of inhibitory neurons—combined with enhanced pyramidal cell bursting—contributes to a disrupted excitation-inhibition balance within the hippocampal network. Our findings provide in vivo evidence that early soluble A β burden disrupts hippocampal rhythm generation and inhibitory regulation in behaving animals. Accelerated hippocampal oscillations, particularly during active task engagement, may serve as a translatable biomarker of early circuit dysfunction in AD and a potential therapeutic target before the onset of cognitive decline.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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

Support: NIH Grant R21AG067008-01 (EJK)
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NRF RS-2025-00522887 (JC)
25YB1210 (SP)

Title: Sharp-wave ripple-associated corticolimbic dynamics and risky decision-making in an Alzheimer's disease mouse model

Authors: *E. KIM¹, S. PARK³, B. P. SCHUESSLER¹, J. CHO⁴, J. J. KIM^{1,2};

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Abstract: While Alzheimer's disease (AD) research has traditionally focused on memory impairments, recent human studies suggest that AD also affects other cognitive functions, such as decision-making (DM) under risk and ambiguity—abilities essential for everyday life. Notably, DM deficits may precede memory loss, positioning risky DM as a potential early marker of AD. Previously, we reported that amyloid pathology disrupts behavioral flexibility and reduces hippocampal sharp-wave ripples (SWRs) in 5XFAD mice using a naturalistic “approach food-avoid predator” paradigm. In this study, we examined how amyloid load influences SWR-associated hippocampal-prefrontal dynamics during risky foraging decisions, along with theta-related oscillatory changes. Male and female 5XFAD and wildtype (WT) mice (4-9-month-old) were implanted with tetrodes in the medial prefrontal cortex (mPFC) and dorsal hippocampus (dHPC; dCA1) and tested in a risky DM task. Animals progressed through nest habituation, foraging training, and predator testing in a T-maze offering grain-based and chocolate-flavored pellets. Predator testing consisted of pre-predator, predator, and post-predator recording sessions. During the predator session, a puppet eagle surged forward when mice approached the preferred (risky) pellet. WT mice adapted by shifting preference to the non-preferred (safe) pellet, whereas 5XFAD mice persistently chose the risky option. Although both groups exhibited SWRs, 5XFAD mice showed significantly reduced dCA1 SWR frequency across all sessions. In WT mice, SWR frequency increased in response to the predator, while in 5XFAD mice, it remained unchanged. Peri-SWR activity analyses during pre-predator and predator sessions revealed that foraging under predatory risk elevated dHPC firing around SWR onset in both groups, but 5XFAD mice exhibited delayed SWR-modulated firing. Critically, mPFC neurons in WT mice showed SWR-modulated activity during the predator session, an effect absent in 5XFAD mice, indicating disrupted dHPC-mPFC coordination. At the decision point, hippocampal theta activity increased under predatory threat in WT mice compared to the pre-predator session, whereas 5XFAD showed no significant changes. In contrast, mPFC theta activity did not vary with threat level in either group. Together, these findings suggest that A β pathology reduces SWR frequency, disrupts SWR-driven modulation of corticolimbic dynamics, and impairs risk-induced hippocampal theta enhancement during adaptive DM. These circuit-level disruptions may complement the proposed mechanistic link between amyloid accumulation and impaired risk-based behavior in AD.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.10/C47

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

Title: Impact of Alzheimer's disease on suprachiasmatic nucleus connectivity, sleep regulation and circadian rhythm.

Authors: *H. CALLIGARO¹, B. KHOV¹, K. NOEL², L. VAN ROSMALEN¹, R. RAMASAMY¹, V. ROTHENBERG¹, K. KIM³, M. ELLISMAN⁴, S. PANDA⁵;

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Abstract: Circadian disruption, notably sleep disturbances, serves as an early indicator of Alzheimer's disease (AD), preceding cognitive symptoms like memory loss. The suprachiasmatic nucleus (SCN) governs biological rhythms and receives direct retinal input via melanopsin-expressing retinal ganglion cells (mRGCs) to synchronize with environmental light cycles. The anatomical and functional basis for circadian disruption in AD remains unclear. Here, we explored the multi-level relationships between gene expression, SCN connectome, and regulations of sleep and circadian rhythms in the APP/PS1 mouse model. The sleep architecture of APP/PS1 mice displayed significantly reduced rapid-eye-movement sleep, associated with a reduced daily core body temperature amplitude and locomotor hyperactivity. Lastly, APP/PS1 mice showed decreased circadian fluctuation in metabolic activity and an impaired response to acute light pulse stimulation or phase shift. The physiological functions are known to be, at least in part, regulated by the SCN. We noted several modifications in SCN connectomics using serial blockface electron microscopy (SBEM), including a reduction of the dendro-dendritic chemical synapse network that receives a large part of the retinal input and is thought to be crucial for synchronicity between SCN neurons. In addition, we observed multiple signs of dystrophy, including modifications of the shape of dendrites and cell soma, accumulation of aggregated lysosomes, and swelling of axons. At the same time, we investigated the changes in gene expression using spatial transcriptomics. The SCN presents changes in the expression of genes associated with synapse formation, cell adhesion, and neurite growth. These results suggest that, despite the absence of amyloid plaques in the ventral hypothalamus, APP/PS1 mice still undergo profound gene expression changes, impacting connectomics and physiological functions. Further investigation will evaluate non-pharmacological approaches to mitigate the observed circadian disruptions.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Program #/Poster #: PSTR156.11/C48

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

Title: Changes in Audition and Functional Connectivity in 5xFAD Mouse Model of Alzheimer's Disease

Authors: *C. BOWE¹, R. GARGIULLO², V. ESHO², L. WILLIAMSON², K. COBB², J. MAI², C. RODGERS³;

¹Emory Univ., Avondale Estates, GA; ³Neurosci., ²Emory Univ., Atlanta, GA

Abstract: The pathological hallmarks of Alzheimer's disease (AD) are amyloid beta plaques, tau neurofibrillary tangles, and neurodegeneration. Relatively little is known about how these pathologies act on neural circuits to cause cognitive symptoms. Studies in people with AD and mouse models found evidence of impaired communication within brain networks like the default mode network, described as changes in “functional connectivity”. Additionally, there is also evidence of central auditory dysfunction in AD, suggesting that this change in functional connectivity could be the cause of central auditory dysfunction. Using an animal model, we can use methods that are more accurate and invasive than commonly used techniques such as FMRI to measure changes in neural activity, like hyperexcitability, that lead to disruptions in functional connectivity that affect behavior. To answer the question of how amyloidosis leads to central auditory dysfunction and disruption in brain networks, we use a mouse model of amyloidosis (5xFAD) and perform tests of peripheral, central, and spatial hearing at 3, 6 and 9 months. Preliminary data currently shows that 5xFAD mice show few signs of peripheral hearing loss on auditory brainstem response (ABR), but significant evidence of central auditory dysfunction starting at 6 months on startle testing, a test where mice are placed in a box and startled with a noise at random time points. On a spatial hearing task where the mice must choose which speaker is making a noise within a maze, no difference was observed in performance between 5xFAD models and controls. We have also implanted tetrodes into the auditory cortex and hippocampus of mice as they passively listen to sounds and analyze neural activity in both regions as well as functional connectivity between both regions to see if 5xFAD mice shows signs of hyperexcitability and disrupted brain communication. Enhancing our understanding of how AD pathology acts on neural circuits to cause cognitive symptoms will allow us to explore new therapeutic targets for neural modulation methods.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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

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NIH/NIGMS 5P20 GM121310-05
NIH/NIA R03 AG062883-01
Alzheimer's Association AARF-16-443613

Title: A potential role for sex hormone receptor and gonadotropin receptor signaling in Alzheimer's disease-related disruptions of circadian entrainment

Authors: *M. RUHMANN¹, W. D. TODD, III²;
¹Zoology and Physiol., ²Zoology and Physiology, Program in Neurosci., Univ. of Wyoming, Laramie, WY

Abstract: Alzheimer's disease (AD) is associated with progressive disruption of entrained circadian rhythms, and sexual dimorphisms in both AD and circadian function have been well established. However, whether sex differences in AD and circadian function share a common mechanism is unknown. Due to aging and menopause, testosterone and estrogen levels decrease, both of which have been shown to be potentially neuroprotective in diseases such as AD and Parkinson's. Gonadotropin [follicle stimulating hormone (FSH) and luteinizing hormone (LH)] levels increase with menopause and have been suggested to contribute to the fact that two thirds of AD patients are women. Yet, it is unclear whether increased gonadotropin receptor signaling also contributes to sex differences in AD-related circadian dysfunction. In the TAPP (APPSwe-Tau) mouse model of AD, we recently showed that females develop AD-related pathology and disruptions of entrained circadian rhythms much earlier than males. Markers of circadian dysfunction were strongly associated with the development of hyperphosphorylated Tau (pTau) pathology in lateral parabrachial (LPB) neurons that project to the circadian system, including the suprachiasmatic nucleus (SCN, the master circadian pacemaker) and its primary axonal relay, the adjacent subparaventricular zone (SPZ). It has also been shown that gonadectomy (GDX) in male mice contributes to both a delay and blunting of free running wheel running. In this current study, we examine the sexually dimorphic role of sex hormone receptor and gonadotropin receptor expression and signaling on entrained rhythms of core body temperature (Tb) and locomotor activity (LMA) in female and male wild-type (WT) and TAPP mice. We performed GDX at ages relevant for the development of AD pathology in TAPP mice. Our preliminary findings suggest that GDX increases variability in markers of circadian entrainment in WT mice compared to shams and increases circadian disruption and LPB pTau in GDX compared to sham TAPP mice, and these effects are nuanced in a sex-specific manner. We also collected tissue from the LPB and SCN/SPZ regions and are using RNAscope to determine changes in sex hormone receptor and gonadotropin receptor expression and how these differences correlate to circadian disruption. We hypothesize that there will be sexually dimorphic changes in gonadotropin receptor expression in the LPB, as both FSH and LH concentrations significantly increase with GDX and have been associated with increased deposition of AD pathology. Additionally, we hypothesize that sex hormone receptor changes in the SCN due to GDX may contribute to circadian dysfunction in Tb and LMA rhythms.

Disclosures: M. Ruhmann: None. W.D. Todd: None.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Alzheimer's Association AARF-16-443613

Title: Behavioral Consequences of a Bidirectional Circadian-Olfactory System Circuit across Aging in Mice with and without Alzheimer's Disease Pathology

Authors: *Q. JEFFS¹, W. BONDS¹, J. EDWARDS¹, W. D. TODD, III²;
²Zoology and Physiology, Program in Neurosci., ¹Univ. of Wyoming, Laramie, WY

Abstract: Alzheimer's disease (AD) is the leading cause of dementia, affecting over 45 million patients globally. Patients experiencing preclinical AD start to exhibit behavioral disturbances before the onset of cognitive impairment and memory loss, the most common of which include circadian and olfactory disruptions. Previous work has demonstrated the circadian and olfactory centers of the brain have functional similarities and influence each other. However, the mechanisms underlying such bi-directional interactions are unknown. Research has shown that there are daily time-dependent increases in cFos expression, a marker of neuronal activation, in circadian regions in response to olfactory stimuli, suggesting a pathway connecting olfactory structures to the circadian system. Here, we present preliminary data proposing a bidirectional pathway between the two systems utilizing an additional forebrain structure as a relay. To further investigate this circuit and its potential role in AD-related olfactory and circadian dysfunction, we are currently assessing olfactory detection and discrimination in wild-type (WT) and AD-model mice as well as the impact of induced circadian desynchronization on olfactory detection and discrimination in WT mice. To assess olfactory abilities, we are performing a habituation-dishabituation task involving three non-social odors. To induce circadian desynchronization in WT mice we are subjecting them to a 10:10 light:dark cycle. Additionally, we are performing retrograde tracing to demonstrate the existence of an indirect circuit underlying the observed behavioral interactions between the olfactory and circadian systems that has not been confirmed in previous literature. A better understanding of such circadian-olfactory interactions may improve their use as biomarkers for preclinical AD and may also provide opportunities for early interventions that can slow the progression of the disease.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Alzheimer's Association Grant AARF-16-443613

Title: Investigating Subcircuits for Alzheimer's Disease-related Circadian Disturbances Using P301-L Mutant Tau and Chemogenetic Manipulations

Authors: *E. D. GWALTNEY¹, A. E. WARFIELD², P. GUPTA³, B. L. ROBERTS¹, W. D. TODD, III³;

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Abstract: A common aspect of circadian dysfunction in Alzheimer's disease (AD) is a "phase delay" characterized by later acrophases and bathyphases of locomotor activity (LMA) and body temperature (Tb) rhythms. In many AD patients, this phase delay is strongly associated with sundowning syndrome, a poorly understood clinical phenomenon that is characterized by wandering, agitation, and aggression during the late afternoon and early evening. In the TAPP (APPSwe-Tau) mouse model of AD, we recently showed that the development of hyperphosphorylated Tau pathology (pTau) in lateral parabrachial neurons of the brainstem is strongly correlated with a similar phase delay and increased aggression around the active-to-rest phase transition. We further categorized two types of pTau-expressing LPB neurons, dynorphin-expressing (pDyn) and cholecystokinin-expressing (CCK) neurons. We have found that both neuronal subpopulations project to the major circadian structures of the hypothalamus, the suprachiasmatic nucleus (SCN, the master circadian pacemaker) and its major axonal target, the subparaventricular zone (SPZ). In our ongoing study, we are testing the hypothesis that pTau in the subpopulations of this LPB to SCN/SPZ pathway underlie different components of AD-related circadian dysfunction. To test this hypothesis, we used Cre-mouse lines and an AAV that expresses mutant P301-L, and subsequently pTau, in these LPB subpopulations that differentially project to the circadian system. We performed biotelemetry recordings of LMA and Tb rhythms before and after the expression of Cre-dependent pTau in these LPB subpopulations. Interestingly, our preliminary findings suggest that expression of pTau in the pDyn versus CCK LPB subpopulations results in opposing effects on different entrained rhythms. We also chemogenetically manipulated both the pDyn and CCK LPB subpopulations to test their function. Activation of the pDyn subpopulation led to an acute phase advance in Tb rhythms. We are currently analyzing the results of activating the LPB CCK subpopulation on Tb

and LMA rhythms. Knowing that CCK neurons can act in an excitatory or inhibitory fashion, we also plan to use slice electrophysiology coupled with optogenetics to understand the synaptic strength of inhibitory and excitatory inputs from these CCK LPB neurons onto the SCN and SPZ.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Program #/Poster #: PSTR156.15/C52

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

Support: R01 RF1AG081767
Evelyn F McKnight Brain Institute

Title: Novel treadmill escape learning task for assessing interval timing in the TgF344-AD rat model of Alzheimer's Disease

Authors: *R. J. DOUGHERTY¹, G. V. MAZURIK¹, I. E. LOVATO², S. L. COWEN^{1,3};
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Abstract: Multiple aspects of time perception are impaired in individuals with Alzheimer's disease (AD). Deficits in the ability to track the passage of time at the milliseconds, seconds, and minutes scale are all symptoms of AD and parallel the widespread deficits in episodic memory that are a hallmark of the disease. Numerous studies have identified temporal perception impairments in AD patients, and it remains a key feature assessed by clinicians in diagnosis. Despite this, few studies have investigated whether animal models of AD also express deficits in time interval estimation. Consequently, the neural underpinnings of altered time processing in AD remain unclear. The TgF344-AD rat model exhibits key pathological features of AD such as amyloid-beta plaques, neurofibrillary tangles, neuronal loss, and gliosis, making it well-suited to study the neural basis of AD-related cognitive impairments. However, efforts to study cognition in the TgF344-AD model have been complicated by motivational and hedonic feeding deficits which emerge during early stages of adulthood, particularly in females (Ostlund et al., 2025). These characteristics make it challenging to motivate TgF344-AD animals to perform the appetitive operant behaviors often used to assay various aspects of learning and memory. We sought to overcome these limitations by developing an aversive treadmill escape learning paradigm to assess time interval estimation in TgF344-AD rats. The preliminary study included 4 female transgenic rats (aged 12-13 months) comprised of both TgF344-AD (n = 2) and wild-type control (WT; n = 2) animals. Rats were trained to perform a time estimation task requiring them to wait for 5s before responding with a nose-poke. The task was unique in that animals were

forced to walk or run on a moving treadmill, and the treadmill only stopped if the nose-poke was performed at the specified delay interval. Nose-poke responses occurring before the specified interval were penalized by increasing the speed of the treadmill, thus requiring rats to estimate elapsed time to withhold responding during the delay. Preliminary results indicated that rats in both the TgF344-AD and WT groups acquired the nose-poke response to stop the treadmill within a single training session, as response times decreased across the session to a median of 1.22s by the final 5 trials. Further, median response times increased during the delay training phase towards the 5s delay mark, suggesting that rat's estimations of the interval improved with training. These results indicate that the treadmill escape learning task may provide a promising avenue for assessing facets of temporal cognition in TgF344-AD rats.

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Poster

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Program #/Poster #: PSTR156.16/C53

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

Title: Resting state EEG changes correlate with changes in clinical and volumetric brain measures after 6-months of Spectris AD sensory stimulation in mild-to-moderate Alzheimer's disease participants

Authors: B. L. JACKSON¹, O. LAUFER², G. ISSACHAR², J. RIDDLE¹, M. HERNANDEZ¹, Z. MALCHANO¹, A. BOASSO¹, *C. V. SESHAGIRI¹, M. HAJOS¹;

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Abstract: Sensory stimulation is an emerging therapeutic approach for the treatment of Alzheimer's disease (AD). A recent randomized, sham-controlled, feasibility study (OVERTURE, NCT03556280) in mild-to-moderate AD participants showed that 6-months of daily home-use of Spectris™ AD (Cognito Therapeutics, Cambridge, MA), an investigational sensory stimulation device, significantly slowed cognitive (MMSE) and functional (ADCS-ADL) decline and brain atrophy (volumetric MRI). Resting-state EEG (rs-EEG) was collected at baseline and 6-months via a 32- or 64-channel wet cap system (ANT-Neuro). EEG were pre-processed and estimates of the power in EEG frequency bands as well as the peak alpha frequency were determined (Firefly Neuroscience). We investigated whether changes in rs-EEG metrics from baseline to 6-months in the active group were correlated with 6-month changes in clinical and volumetric MRI. To reduce sensitivity to outliers, correlations were assessed via biweight midcorrelation. As this was an exploratory analysis, corrections for multiple comparisons were not performed. Consistent with findings from other groups showing shifts in EEG power from higher (alpha-beta) to lower frequencies (delta-theta) with AD severity, measures of EEG slowing correlated with observed clinical and volumetric MRI outcomes.

Specifically, some of the strongest correlations were revealed between smaller temporal volume loss and decrease in the ratio between theta (4-8Hz) power and beta1 (12-18Hz) power ($r=0.69$, $p=0.0012$, $n=19$), increases in beta1 relative power ($r=0.72$, $p = 0.001$, $n=17$), and increases in peak alpha frequency ($r=0.75$, $p < 0.001$, $n=17$) over the treatment period. Better cognitive outcomes (MMSE) were associated with changes in hemispheric alpha asymmetry towards the right hemisphere ($r = 0.77$, $p < 0.001$, $n=18$), and better functional outcomes (ADCS-ADL) were associated with decreases in the ratio of delta to beta1 power ($r = 0.66$, $p = 0.003$, $n=18$). These preliminary results show that EEG measures, including slowing, correlate well with the observed 6-month effects of Spectris AD sensory stimulation treatment in a mild-to-moderate AD cohort. While these associations need to be confirmed in a larger population, they may provide important, measurable markers of a therapeutic effect.

Disclosures: **B.L. Jackson:** A. Employment/Salary (full or part-time): Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **O. Laufer:** A. Employment/Salary (full or part-time): Firefly Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Firefly Neuroscience. **G. Issachar:** A. Employment/Salary (full or part-time): Firefly Neuroscience. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Firefly Neuroscience. **J. Riddle:** A. Employment/Salary (full or part-time): Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **M. Hernandez:** A. Employment/Salary (full or part-time): Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **Z. Malchano:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics. **A. Boasso:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **C.V. Seshagiri:** A. Employment/Salary (full or part-time): Cognito Therapeutics. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. **M. Hajos:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cognito Therapeutics. F. Consulting Fees (e.g., advisory boards); Cognito Therapeutics.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.17/C54

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

Title: Cerebellar seeding of amyloid- β highlights underrecognized role in Alzheimer's Disease

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Abstract: Alzheimer's disease (AD) is the leading cause of neurodegeneration and the seventh leading cause of death in the United States. While most AD research has focused on the cerebrum, the cerebellum remains understudied despite its emerging role in both cognitive and motor functions. Imaging studies from the Schmammann lab have demonstrated cerebellar involvement in AD pathology and revealed functional connectivity between cerebellar and cerebral regions critical for cognition. A deeper understanding of cerebellar contributions in AD would inform region-specific disease progression and guide the development of precise, novel gene therapy strategies. Prior work has shown that parenchymal seeding of amyloid-beta (A β) fibrils in pre-pathogenic APP mice induces plaque formation resembling that of the fibril donor, offering a valuable model to study targeted regional involvement. Applying this approach to the cerebellum enables evaluation of its contribution to disease progression in early-stage APP animals. APP/Psen1 mice (mixed sex, $n=8$) received stereotaxic injections of A β 42 fibrils into the cerebellum at four months of age. Two months post-seeding, mice underwent behavioral testing - including balance beam, fear conditioning, and open field assays - compared to age-matched non-seeded APP/Psen1 controls (mixed sex, $n=7$). Following behavioral analysis, brains were collected for histological evaluation of glial activation (Iba1, Gfap), plaque deposition, (Thioflavin-S) and cerebellar integrity (Calbindin). Seeded mice exhibited significantly increased freezing behavior on day 2 of fear conditioning relative to controls, suggesting altered memory processing. Thioflavin-S staining confirmed increased plaque deposition in the cerebellum of seeded animals compared to controls. Preliminary findings indicate that cerebellar seeding with A β 42 induces localized plaque pathology and behavioral alterations. Increased freezing behavior may reflect compensatory or maladaptive memory responses. Ongoing analyses are quantifying glial responses and evaluating secondary effects in connected cerebral regions. These results support the cerebellum's involvement in AD progression and highlight its potential as a novel therapeutic target.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

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

Support: NIH Grant R01AG075338
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Title: Neuronal GLT1 mediates the early effects of AB42 on hippocampal activity and episodic memory

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Abstract: Synapses are critical targets of Alzheimer's disease (AD), a highly prevalent neurodegenerative disease associated with accumulation of extracellular amyloid- β peptides. Although amyloidosis and aggregation of the 42-amino acid amyloid- β (A β 42) have long been considered pathogenic triggers for AD, clinical evidence suggesting normal cognition can persist even in the presence of elevated levels of A β 42 challenges this hypothesis. To resolve this conundrum on the role of A β 42 in regulating synaptic activity, we used an adeno-associated viral vector approach that triggers extracellular accumulation of A β 42. We show that the initial stages of A β 42 accumulation increase excitatory and inhibitory transmission in hippocampal region CA1, disrupting the timing of hippocampal signaling and producing deficits in short term spatial memory. Interestingly, these changes are dependent on an increased expression of the glutamate transporter GLT-1 in CA1 pyramidal cells, suggesting that neuronal expression of this transporter is a critical mediator the early pathology of A β 42 accumulation, and the synaptic dysfunction seen in the early stages of AD. These findings identify neuronal GLT-1 as key players in the pathogenesis of AD.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Program #/Poster #: PSTR156.19/C56

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

Support: NTNU Enabling Technologies
Central Norway Regional Health Authority
NorFab, project number 295864
ETH Postdoctoral Fellowship

Title: Microengineered neural networks for mechanistic studies of neurodegenerative diseases

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Abstract: Neurodegenerative diseases are characterized by accumulating pathological proteins, progressive synaptic and neuronal loss, and dynamic alterations of structural and functional connectivity. These pathological events often spread through interconnected brain regions and engage complex cellular and network level responses. While *in vivo* models can provide valuable systemic insights, they lack the precision and control necessary to dissect early stage disease mechanisms and microscale network alterations following disease initiation. Engineered cellular platforms present a promising approach to study localized and circuit level dysfunctions within highly controllable microenvironments. In this study, we present modular microfluidic platforms with up to 12 nodes, designed to reconstruct hippocampal and cortical microcircuits *in vitro*. Neural populations are cultured in spatially segregated chambers connected by microtunnels that permit only axonal outgrowth, enabling the formation of modular neural microcircuits. Tesla valve inspired tunnel geometries promote unidirectional, hierarchical connectivity between distinct populations. Integration with nanoporous microelectrode arrays (MEAs) further enables noninvasive, high resolution recordings of spatiotemporal network dynamics. These engineered circuits capture key features of brain like organization, including signal segregation, integration, and synchronous dynamics across spatially separated network regions. To demonstrate the utility of these platforms for disease modeling, we applied Alzheimer's disease relevant insults including amyloid beta exposure and hypoxic stress. Our results show localized disruption of functional connectivity within targeted chambers, while connected populations showed emerging and strengthened functional connectivity, suggesting network-level plasticity in response to localized pathology. While initial platform validation was conducted using rat cortical and hippocampal neurons, we are now incorporating human iPSC derived neuronal subtypes to enhance physiological relevance. We are also exploring electrical stimulation for targeted neuromodulation to restore function and prevent circuit breakdown. By scaling down to smaller neural populations, we can study in detail the spread of toxic protein aggregates and their impact on functional decline. These multi-nodal microfluidic platforms provide a scalable and adaptable system for investigating disease progression, pathology propagation, and therapeutic response at the microcircuit level, applicable to a broad range of neurodegenerative disorders.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.20/C57

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

Title: Disrupted social behavior and prefrontal encoding in Alzheimer's Disease

Authors: B. CURD¹, I. ANTHONY², V. NGUYEN³, N. JOHNSTON², D. KWAK², A. CHIKUNI², *N. A. FROST²;

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Abstract: Alzheimer's disease (AD) is a progressive, age-related, and highly prevalent neurodegenerative illness marked by deficits in short-term memory, navigation, social interaction, and emotional regulation due to early pathological changes in affected neuronal circuitry. Human patients often undergo social withdrawal early in the course of the disease. The disease pathology involves the accumulation of extracellular amyloid-beta (A β) plaques and intracellular tau neurofibrillary tangles, and early changes in circuit excitability. The medial prefrontal cortex (mPFC) is a critical regulator of complex behaviors including social interactions, but how exactly AD pathology alters the cortical circuit function underlying these behaviors has not yet been described. To understand how A β accumulation alters both behavioral repertoires and prefrontal circuit activity during social behavior, we used the APP-SAA knock-in (KI) mouse model of AD, which contains three pathogenic mutations in the APP gene in the endogenous locus. We first examined social interactions in KI mice and controls expressing 3 humanizing mutations in the APP gene (WT). We found that KI mice spent significantly less time interacting with a sex-matched juvenile intruder. To more carefully examine how the behavioral ethogram is altered in these mice we performed UMAP clustering of pose estimation inferred using a Social LEAP Estimates Animal Poses model trained in our laboratory which identifies multi-animal pose information on a frame by frame basis within behavioral videos to identify individual mice and track their location and movements over time. We extracted 19 features from these inferred positions and performed UMAP clustering to reduce dimensionality; this generated groups of frames clustered by inter- and intra-mice relationships. Comparison to manually labeled frames revealed clusters enriched for specific active and passive social behaviors which differed in their abundance, in a genotype-specific manner. We then examined calcium activity underlying specific social interactions. These studies revealed elevated mPFC activity in KI mice with resultant increased activity of cross-hemispheric output neurons and decreased network flexibility. Together, these studies demonstrate pathological changes in mPFC circuitry underlying a complex behavioral phenotype in a knock-in model of Alzheimer's Disease.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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Program #/Poster #: PSTR156.21/C58

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

Support: NIH Grant 1RF1NS129878-01

Title: Loss of TDP-43 in Prefrontal GABAergic Neurons Leads to Cognitive Impairment

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Abstract: TAR DNA-binding protein 43 kDa (TARDBP, or TDP-43) is a nuclear protein essential for RNA processing and splicing. Abnormal cytoplasmic accumulation of TDP-43 is a shared pathological hallmark of several neurodegenerative disorders, including amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD), and a significant subset of Alzheimer's disease (AD) cases. While previous studies have shown that loss of TDP-43 in excitatory neurons leads to neurodegeneration, its role in inhibitory neurons remains unclear. Here, we investigated the functional importance of TDP-43 in GABAergic neurons of the prefrontal cortex (PFC) using a conditional knockout mouse model. Selective depletion of TDP-43 in these neurons at the PFC led to marked GABAergic neuronal loss and impaired performance in various cognitive tasks. Notably, enhancing the activity of the remaining PFC GABAergic neurons via chemogenetic stimulation significantly improved cognitive function. These findings uncover a previously underappreciated role of TDP-43 in maintaining neural network integrity and cognitive function. They also suggest that targeting GABAergic circuit may hold therapeutic potential for TDP-43 linked AD and AD related dementias (ADRD).

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Poster

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

Support: NIH Grant 1R21AG077498-01
NIH Grant NS100440
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NIH Grant DC017091
NIH Grant AG062196

Title: Temporal lobe hyperexcitability in mild cognitive impairment

Authors: *P. PRABHU¹, K. KUDO⁴, F. SYED², J. H. KRAMER², K. VOSSEL⁵, R. LA JOIE⁶, S. NAGARAJAN⁷, K. RANASINGHE³;

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Abstract: Early detection of neural dysfunction in Alzheimer’s disease (AD) is critical for distinguishing pathological aging from normal cognitive decline. An important index of neural dysfunction in AD is altered excitation-inhibition (E/I) balance of cortical networks, which previous studies have shown to be reliably captured by the aperiodic component of the neural power spectrum (i.e. $1/f$ slope). Specifically, flatter slopes indicate greater E/I imbalance. This study used high spatiotemporal resolution magnetoencephalography (MEG) imaging to examine the regional patterns of abnormalities in aperiodic slope in individuals with AD-predementia—mild cognitive impairment (MCI) due to AD compared to amyloid-beta-negative individuals ($A\beta$ -CN). Resting-state MEG recordings were acquired from participants including 30 $A\beta$ + MCI and 20 age-matched $A\beta$ -CN. 60 seconds of artifact-free data were used for the quantitative analyses. Power spectral densities were computed for each participant across 210 cortical regions (Brainnetome atlas), and $1/f$ slope was estimated in the 15-50 Hz range. Group-level comparisons were performed using independent-samples t-tests for each region, and statistical significance was corrected for multiple comparisons using a 10% false discovery rate (FDR). Patients with MCI due to AD showed flatter aperiodic slopes compared to age-matched $A\beta$ -CN individuals indicating higher E/I ratio (Figure 1). The regional involvement of increased E/I in MCI patients include inferior temporal and posteriori temporo-parietal cortices. The regional patterns involved in E/I imbalance in early AD are indeed the most vulnerable regions to AD-tauopathy as shown in previous imaging studies. This study demonstrates that aperiodic slope derived from brief resting-state MEG recordings can detect cortical network alterations in the earliest stage of AD pathology against normal aging.

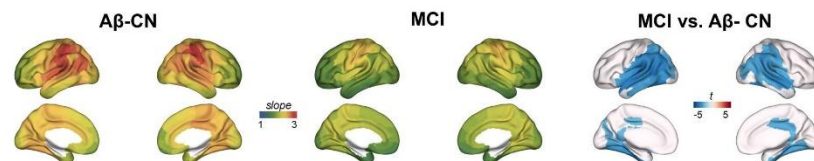


Figure 1: Reduced aperiodic slope (right panel) in MCI (middle panel) when compared to age-matched $A\beta$ -CN (left panel) individuals.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

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Program #/Poster #: PSTR156.23/C60

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

Support: NIH Grant 5R00AG068602
Karen Toffler Charitable Trust
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Title: Longitudinal electrophysiology recordings show hippocampal and entorhinal neurons silenced by tau pathology can spontaneously reactivate in ThyTau22 mice

Authors: ***T. J. ZWANG**^{1,3}, **J. ZHANG**⁴, **R. GELB-BICKNELL**⁵, **N. WOLF**², **V. CHANCHYKOV**², **E. AGASTRA**², **A. HOLBROOK**⁴, **R. E. BENNETT**^{1,3}, **B. HYMAN**^{1,3};
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Abstract: The accumulation of tau proteins is a hallmark of Alzheimer's disease that correlates with cognitive impairment and neuron death. Both human studies and animal models show that tau pathology induces electrophysiological changes that relate to subsequent cognitive decline. To understand the changes in activity as tau pathology accumulates, we used implantable flexible electronics to simultaneously track hippocampal and entorhinal neuronal activity over multiple months in awake and behaving ThyTau22 mice, a model of tauopathy with MAPT G272V/P301S mutations. We were able to detect changes in single-neuron firing activity and network-level neuronal activity that progress with aging and tau accumulation, including the observation of a number of silenced neurons in ThyTau22 mice that were not present in WT mice. In ThyTau22 mice, ~4% of neurons are silent within a given week compared to <0.5% of WT neurons. Markov chain analysis shows that silenced neurons have a ~50% probability of reactivating the following week, independent of brain region, which suggests that neurons which appear silent in cross-sectional data may instead be transiently inactivated by tau pathology in longitudinal data. Over 6 months, 26% of all ThyTau22 neurons were silent for at least one week and 97% of this subset of neurons were transiently inactivated. Transiently inactive neurons were silenced for an average of 3 weeks and half fully recovered their activity within 12 weeks of silencing. Correlated activity between pairs of neurons within the hippocampus, within the entorhinal cortex, or connecting both regions are significantly less likely to persist across weeks in ThyTau22 mice when compared to WT mice. Within ThyTau22 mice, neurons that recover from silencing show further destabilized correlated activity with other neurons compared to those that remained consistently active. These findings suggest that while individual neurons silenced by tau pathology can spontaneously recover over several months, this process may impair brain function by disconnecting them from other neurons.

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rights/patent holder, excluding diversified mutual funds); Novartis, Dewpoint. F. Consulting Fees (e.g., advisory boards); AbbVie, Avrobio, Biogen, BMS Cell Signaling, Genentech, Ionis, Novartis, Seer, Takeda, Vigil, Voyager.

Poster

PSTR156: Neural Circuits and Alzheimer's Disease

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.24/C61

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

Support: U54 AG054345B
R01 AG079877

Title: Coordinate structural and functional alterations of hippocampal-cortical circuitry in *App*^{SAA} mice

Authors: *E. BLOSS, J. POMEROY-TUCK, M. SASNER, G. R. HOWELL;
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Abstract: The hippocampus is a critical site for organizing and storing episodic memories. Dense connectivity to prefrontal cortical (PFC) circuits allow hippocampal representations to guide adaptive behaviors. Hippocampal and PFC functions are highly vulnerable to decline during the progression of Alzheimer's disease. Such decline plausibly results from the disconnection of the long-range pathways that link these associative circuits. Here, we use a humanized APP mouse line containing Swedish, Arctic, and Austrian mutations (*App*^{SAA}) to show that a cognitive task requiring hippocampal-to-PFC activity coincides with two distinct modes of synapse loss. 12-month-old *App*^{SAA} and B6 mice showed equivalent learning between an auditory cue paired with a brief foot shock (assayed by behavioral freezing during the tone). *App*^{SAA} and B6 mice readily extinguished the freezing response to the cue in a new context. B6 mice reliably retrieved the cue-dependent associative memory in the original context, while *App*^{SAA} mice did not. Interestingly, *App*^{SAA} mice that did not undergo extinction had intact cue-dependent freezing responses in the original context, suggesting that the deficit in *App*^{SAA} mice is driven by new competing memories 'overwriting' older ones. By leveraging viral strategies to gain access to the CA1-to-PFC projection neurons that mediate performance in this task phase, we reconstructed synaptic connectivity on their dendrites in area CA1 and their axons in PFC. Our results show revealed two distinct forms of synapse loss: a robust effect (~50% loss) on dendrites that localize to plaques, and a much milder form at plaque-free locations (~20% loss). Although axons showed dystrophic swellings at plaques, reconstructions of axons in PFC at plaque-free sites revealed that bouton density was unchanged. Ongoing experiments seek to determine whether this selective postsynaptic sensitivity generalizes to PFC projection neurons, to decouple memory retrieval from synapse loss by manipulating the activity of CA1-to-PFC neurons, and to determine the mechanistic distinction between the two modes of synapse loss. Collectively, our results suggest that *App*^{SAA} mice can form and store memories, but that accurate

memory retrieval is impacted by competing memory traces. Precisely how such competition relates to either or both modes of synapse loss within the CA1-to-PFC pathway remains unclear.

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Poster

PSTR156: Neural Circuits and Alzheimer's Disease

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

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NIH Grant R01MH135565 (to S.J.A.)
Chan Zuckerberg Initiative Collaborative Pairs Grant (to C.C.K. and S.J.A.)

Title: The night watch: how midlife sleep guards neural networks underlying memory in Alzheimer's

Authors: *F. RAVEN¹, J. KRAVCHENKO², B. BUNCE², N. SONIKA², A. HE², A. VAN KAMPEN², K. O. MCDONALD², C. C. KACZOROWSKI², S. J. ATON²;

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Abstract: Disturbances in sleep and memory are among the most common health concerns for elderly, disrupting the quality of life of older adults and their families. Within the aging population, Alzheimer's disease (AD) is the leading cause of dementia, affecting over 6 million Americans age 65 and older. Recent findings suggest that midlife sleep disturbances are associated with increased risk for subsequent AD diagnosis, although the mechanisms linking early sleep disturbances and late-life memory impairments remain unknown. In this study, we used the AD-BXD mouse panel—a genetically diverse panel of strains with mixed C57Bl6 and DBA2 background—and assessed the effects of 5xFAD causal familial AD alleles. Our data show that reduced sleep during midlife predicts greater cognitive decline later in life. We find that AD neuropathology is pronounced in regions important for both sleep regulation and memory—especially in mice genetically susceptible to cognitive decline—and correlates with memory problems at old age. Moreover, AD-related neuropathology reduces somatostatin-positive (SST+) interneurons—a population essential for memory processing and sleep regulation—in cognitively susceptible, but not resilient mice. The density of remaining SST+ interneurons in hippocampal and thalamic structures correlated with memory performance. Therefore, SST+ interneuron loss may link age-related sleep disruption, cognitive deficits, and AD pathology. In a parallel study using aged, non-AD mice, we tested whether chemogenetic activation of SST+ interneurons could rescue age-related deficits in hippocampus-dependent memory function. We find that effects of hippocampal SST+ interneuron activation on memory depends on the age and sex of the animal, restoring memory function in aged male, but not

female mice. Uncovering how midlife sleep contributes to memory problems in AD, and how SST+ interneurons change during aging and disease pathogenesis, could pave the way for developing new therapeutic strategies to combat AD-related cognitive decline later in life.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.01/C63

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

Support: NSERC CGS-D (DW)
NIH RF1-AG087504 (HY)
NIH U19-AG079774 (HY)

Title: Suvorexant ameliorates sleep-deprivation-associated acceleration of Alzheimer's-like pathologies in progressive transgenic mouse models of tauopathy

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Abstract: Tau proteinopathy is a major contributor to diseases including Alzheimer's disease (AD), progressive supranuclear palsy, and frontotemporal dementia. Sleep loss is potential modifiable risk factor associated with disease and dementia risk, but needs more research according to the 2024 Lancet Commission on modifiable risk factors in AD. Specifically, understanding the links between dementia and sleep circuitry is a critical step needing investigation. The loss of wake-promoting noradrenergic neurons in the locus coeruleus (LC) and orexinergic neurons in the lateral hypothalamus early in AD, as well as pathological tau localization to the LC in Braak stage 0, highlights potential links between sleep and dementia. We have shown the acceleration of AD-like pathologies in human APP^{NL-G-F} knock-in mice following a 2-wk sleep deprivation (SD). As a result, we sought to investigate the impact of a sleep promoting dual orexin receptor antagonist, suvorexant, during a 2-wk SD in 3 human tau knock-in mouse models (MAPT, MAPT⁽¹⁰⁺³⁾, MAPT^{(10+3)/S305N}) at 6-, 12-, and 18mo (n=8/group/sex). Our SD paradigm involves aversive light during the 12-hour wake-dominant light cycle and constant randomized on-and-off high frequency tones ranging from 1000-10000 Hz at a maximum of 100 db. Immediately following SD, we found reduced attempted sleep/quiet wakefulness by locomotion in our 6mo MAPT^{(10+3)/S305N} mice, the line with the greatest tau pathology, treated with 10 mg/kg/day suvorexant. We also observed nesting changes with 12mo

MAPT^{(10+3)/S305N} mice showing improved nest scores while 18mo MAPT^{(10+3)/S305N} mice scored lower than our saline group. As nesting can be indicative of stress levels, and we have previously shown improved nest scoring and elevated corticosterone in SD mice, it is possible these reduced nest scores are a result of reduced stress following suvorexant treatment. Indeed, we observed reductions in plasma corticosterone levels in these 18mo MAPT^{(10+3)/S305N} mice. This coincided with recognition memory improvements in our oldest mice scoring better in a novel object recognition test with suvorexant treatment vs vehicle. We are currently exploring the neuropathology and proteostasis changes in the sleep-memory circuit looking across genotype, age, and treatment. This data highlights both the potential benefits of suvorexant treatment in tauopathy models and provides insight into optimal treatment times based on age/pathological staging. Following the completion of this project, we aim to clarify the impact of SD on tau and other AD-like pathologies while potentially uncovering a novel therapeutic strategy to improve AD outcomes.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.02/C64

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

Support: NIH Grant R01AG084728

Title: Novel neutral sphingomyelinase 2 (nSMase2) inhibitor attenuates tau propagation in mouse model of Alzheimer's disease

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Abstract: Extracellular vesicles (EVs) have been shown to play a role in the prion-like spread of phosphorylated tau (p-tau) in Alzheimer's disease (AD). The formation of EVs is, in part, triggered by the enrichment of membrane ceramides, which can be produced from sphingomyelin by the enzyme neutral sphingomyelinase 2 (nSMase2). As such, nSMase2 inhibition has been identified as a therapeutic target for blocking the EV-mediated propagation of pathological tau. However, there are no nSMase2 inhibitors clinically available. Our lab previously identified phenyl (*R*)-(1-(3-(3,4-dimethoxyphenyl)-2,6-dimethylimidazo[1,2-*b*]pyridazin-8-yl)pyrrolidin-3-yl)carbamate (PDDC), the first nanomolar potent (IC₅₀ = 300-600 nM), brain-penetrant, orally bioavailable nSMase2 inhibitor. Despite its excellent

pharmacokinetic properties in mice, PDDC has poor solubility and unexpectedly showed very poor systemic exposure in higher species including rats, dogs, and primates, limiting its translational potential. To address this, we have designed a new series of PDDC analogs and identified an analog termed PDDC-7B with a > 5,000-fold increase in aqueous solubility (0.001 vs 5.52 mg/mL) and > 2-fold higher plasma exposure in rat following oral administration (0.484 ± 0.024 vs 1.21 ± 0.13 mg/mL at 0.5 h and 0.77 ± 0.11 vs 2.22 ± 0.32 mg/mL at 2 h post dose). Next, we evaluated the efficacy of PDDC-7B in a tau propagation mouse model, in which an adeno-associated virus encoding P301L/S320F double mutant human tau (AAV-hTau) was stereotactically injected into the CA3 region of the left dorsal hippocampus of 10-week-old C57/BL6 mice. AAV-hTau mice were treated daily with PDDC-7B (50 mg/kg, intraperitoneal) or vehicle for six weeks (n=7-8/group/sex), after which p-tau transfer to the contralateral hippocampus was quantified by immunofluorescence and ELISA. For each method, the p-tau signal in the contralateral hippocampus was normalized by that of the ipsilateral (injected) hippocampus to account for injection variability (expressed as a percentage). AAV-hTau mice treated with PDDC-7B exhibited a significant reduction in p-tau staining intensity in the contralateral dorsal hippocampus compared to vehicle controls (2.658 ± 1.153 vs $38.35 \pm 9.653\%$; $p < 0.01$). PDDC-7B also significantly reduced total p-tau level in the contralateral hippocampus relative to vehicle treatment (23.62 ± 13.32 vs $92.88 \pm 9.539\%$; $p < 0.01$) as measured by ELISA. These findings demonstrate that PDDC-7B may be a therapeutic for slowing the progression of tau pathology in AD.

Disclosures: **P.A. Pietri:** None. **M. Huang:** None. **A. Ranjit:** None. **L. Tenora:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on JHU patents covering small molecule neutral sphingomyelinase 2 inhibitors. This arrangement was reviewed and approved by JHU in accordance with its conflict-of-interest policies. **Y. Zheng:** None. **R. Rais:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on JHU patents covering small molecule neutral sphingomyelinase 2 inhibitors. This arrangement was reviewed and approved by JHU in accordance with its conflict-of-interest policies. **B.S. Slusher:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor on JHU patents covering small molecule neutral sphingomyelinase 2 inhibitors. This arrangement was reviewed and approved by JHU in accordance with its conflict-of-interest policies.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.03/D1

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

Support: NIA R01 AG068330
NIA R01AG093847

Bright Focus Foundation A20201775S
P20 GM148326
Coins for Alzheimer's Trust (CART)

Title: Katp channel inhibition as a therapeutic strategy in tauopathies: linking metabolism, microglia, and neuroinflammation

Authors: *S. M. TURNER¹, J. GRIZZANTI⁴, A. SNIPES¹, R. IRMEN², C. ASHLEY¹, S. L. MACAULEY³;
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Abstract: Neuroinflammation plays a key role in the progression of Alzheimer's disease (AD) and other tauopathies, suggesting that modulating microglial activity may offer a promising therapeutic strategy. Microglia, the resident immune cells of the brain, play a complex role in AD particularly in the propagation of tau pathology. Initially protective, dysregulated reactive microglia contributes to chronic inflammation, neurodegeneration, and pathological tau spread. Reactive microglia is tightly linked to cellular metabolism and excitability, potentially through ATP-sensitive potassium (KATP) channel activity. These metabolic sensors respond to changes in cellular energy status and influence inflammatory responses, which could provide a novel route for dampening the pathological activity of microglia in AD. Glyburide is an FDA approved sulfonylurea used to treat type 2 diabetes by inhibiting KATP channel activity, but also holds promise for modulating neuroinflammatory processes. Therefore, we evaluated the effects of KATP channel inhibition on tau pathology and reactive microglia using a slow-release glyburide pellet. Pellets were implanted in P301S PS19 mice, a model of tauopathy, at 5 months of age. Interstitial fluid (ISF) tau and lactate levels were measured via microdialysis after 3 months of treatment, revealing a reduction in ISF tau and a downward trend in ISF lactate, suggestive of decreased tau release and neuroinflammation. Analysis of hyperphosphorylated tau and neurofibrillary tangles indicated that glyburide reduced AT8+ tau pathology in the hippocampus and cortex of male mice, but not females. Complementary transcriptomics analysis further highlighted microglia as key mediators of glyburide's therapeutic effects. Specifically, upregulated pathways in response to treatment included macroautophagy, mitochondrial ATP synthesis, and protein translation, collectively indicating alterations in cellular metabolism and energy regulation potentially underlying reactive microglia and neuronal function. Concurrently, pathways associated with reactive microglia, neuroinflammation, ATP-sensitive potassium channel activity, and ion transport were downregulated. These findings suggest that attenuating neuroinflammation and modulating the excitability dependent release of tau may be neuroprotective in tauopathy. Together, these findings support a mechanism in which KATP channel inhibition with glyburide reduces neuronal excitability and tau pathology via microglial modulation, revealing a promising therapeutic strategy to delay the onset or slow the progression of AD.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.04/D2

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

Title: Effects of a PPAR delta agonist T3D-959 in a tauopathy mouse model

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Abstract: Background: Elevated levels of p-tau (phosphorylated tau) is directly correlated with neurodegeneration and neuropathogenesis in Alzheimer's disease (AD). The presence of ApoE allele is a significant genetic risk factor for the progression of AD. PPAR- δ , a nuclear receptor highly expressed in CNS neurons, regulates metabolic processes that helps boost mitochondrial function and improve quality protein control; processes that deteriorate as neurodegeneration progresses. This makes PPAR- δ an appealing candidate for neurodegenerative diseases such as Alzheimer's. Here we assess the effect of PPAR-delta agonist, T3D, on a mouse model of tauopathy P301S/E4 against a saline control group. **Method:** T3D was administered intraperitoneally at 50mg/kg/day, 3 days a week from ~4 to ~11 month of age. Neurological testing was performed every alternate month. Behavior studies such as Object Recognition Memory test (ORM), Object Location Memory (OLM), and Y maze studies were conducted at 7, 9 and 11 months. p-tau staining was performed to compare phosphorylated tau staining in Treated vs control mice. **Result:** The weight of T3D-959 treated mice appear to deteriorate less compared to saline treated mice. Not much difference was seen in the overall neurological exam scores. In behavioral studies, T3D-959 treated mice subjected to OLM performed the long-term memory task significantly better compared to saline treated mice. Significant superior performance of the T3D-959 treated mice were observed at 11 months of age ($p=0.02$, $n=5$ per group, two-tailed t-test; error bars = s.e.m.), indicative of better long-term hippocampal memory function upon treatment with T3D-959. There was no significant difference in the ORM and Y-maze test. p-tau staining ($n=1$) of the hippocampus appears to show a correlation with discrimination index (DI) of behavior (OLM) studies with relatively less p-tau staining in T3D treated mice which had high positive DI. **Conclusion:** OLM testing evaluates dorsal hippocampus long term memory function and is transcription based. Y-maze is non-transcription based and studies short-term memory function and spatial recognition. Several relevant brain regions, including the entorhinal cortex and ventromedial prefrontal cortex, are required for ORM. Significantly higher discrimination index (DI) scores were observed with OLM testing at 11 months of age in the T3D-959 treatment group compared to saline, which demonstrates that T3D rescues hippocampal long term memory function better than saline. This is a potentially important finding that indicates that T3D-959 can impact the hippocampus to preserve long term memory function.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.05/D3

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

Title: Repairing synaptic plasticity with a KIBRA-derived peptide to reverse memory loss in aging and tauopathy models

Authors: *L. YAO, T. E. TRACY;
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Abstract: Impaired long-term potentiation (LTP) in the hippocampus is commonly associated with memory deficits in both aging and aging-related neurodegenerative diseases including Alzheimer's disease (AD). In a mouse model of pathological tau hyperacetylation (tauKQ^{high} mice), we recently demonstrated that lentivirus-based overexpression of the C-terminal domain of KIBRA (CT-KIBRA) in hippocampus reverses both LTP impairment and memory deficits in the mice despite the accumulation of pathogenic tau in the brain. KIBRA is a postsynaptic scaffold protein that interacts with multiple synaptic proteins critical for synapse function, including PKM ζ and PKC γ . Its levels were decreased in AD patients, and knockout of KIBRA in mice impaired LTP and caused memory loss. Thus, KIBRA-mediated synaptic repair represents a promising therapeutic avenue for reversing memory loss. To design a therapeutic strategy that could be translational for synapse repair, here, we engineered a cell-permeable KIBRA-derived peptide (KB_{pep}) to mimic the functional properties of KIBRA. Using co-precipitation methods, we confirmed that KB_{pep} interacts with different PKC isoforms, including PKM ζ and PKC γ . We used a chemical long-term potentiation (cLTP) induction method to study postsynaptic trafficking of GluA1-containing AMPA glutamate receptors (AMPA receptors) during LTP in cultured rat hippocampal neurons and in human induced pluripotent stem cell (iPSC)-derived glutamatergic neuron tauopathy models. In hippocampal neurons, pathogenic tau blocked GluA1-containing AMPAR insertion into postsynaptic spines during LTP, and KB_{pep} treatment restored the AMPAR delivery to the postsynaptic surface despite the expression of pathogenic tau. In human iPSC-derived neurons with the V337M *MAPT* mutation that causes frontotemporal dementia, cLTP-induced postsynaptic AMPAR insertion was blocked while KB_{pep} treatment reinstated AMPAR trafficking during LTP. To study the effects of KB_{pep} *in vivo*, KB_{pep} was continuously delivered to the lateral ventricle of tauKQ^{high} mice, which have impaired long-term potentiation (LTP) in dentate gyrus (DG) and hippocampal-dependent memory impairment. KB_{pep} treatment rescued LTP in DG and restored pattern separation and spatial memory in tauKQ^{high} mice. Furthermore, we found that KIBRA levels were reduced in aged wild-type mice and KB_{pep} treatment rescued LTP and improved memory performance in the aged wild-type mice, suggesting its therapeutic potential beyond disease models. These findings support the therapeutic potential of KB_{pep} in reversing aging and tauopathy-related synaptic plasticity impairment and memory loss.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.06/D4

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

Support: NIH R01AG076610-0
Alzheimer's Association AARFD-24-1312259
BrightFocus Foundation A2022017F

Title: Protective role of the niacin receptor HCAR2 in tau pathology

Authors: I. CORONEL¹, D. SONI¹, P. MARTINEZ², C. RANGEL-BARAJAS¹, A. OBLAK¹, C. A. LASAGNA-REEVES², G. E. LANDRETH¹, ***M. MOUTINHO**¹;

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Abstract: The microtubule-associated protein tau has been implicated in the pathogenesis of several neurological disorders collectively known as tauopathies, which includes conditions such as frontotemporal lobar degeneration (FTLD)-tau or Alzheimer's disease (AD). Currently, there are no effective disease-modifying treatments for patients with tauopathies. Interestingly, higher intake of niacin (nicotinic acid) correlates with reduced risk of AD, which suggests that niacin may protect against pathogenic tau-induced neurodegeneration. Niacin can activate the HCAR2 receptor which has been shown to be protective in models of Parkinson's disease, neuroinflammation and multiple sclerosis. We have also recently reported that HCAR2 activation with niacin is protective in an amyloid mouse model. However, the impact of an HCAR2-directed therapeutic strategy has not been explored for tauopathies. We hypothesized that HCAR2 activation with niacin can limit the progression of tau pathology. To investigate the role of HCAR2 on tau pathology, we analyzed how the deletion of *Hcar2* gene affected the pathology in the tauopathy mouse model PS19. We also treated PS19 mice with niacin by daily oral gavage (100 mg/kg) for 30 days to activate HCAR2. The effects of niacin treatment on disease-associated motor phenotype, neuronal loss and tau species were assessed. Our findings indicate that HCAR2 expression is significantly elevated in hippocampal microglia of PS19 mice. Genetic deletion of the *Hcar2* in PS19 mice increased tau oligomers, insoluble tau and tau seeding, accompanied by accelerated onset of motor deficits. Treatment with niacin was neuroprotective and improved motor deficits in PS19. These data highlight the potential protective role of HCAR2 in tauopathies and the use of niacin formulations as a pharmacological therapy. Additional studies are necessary to determine the exact mechanism by which HCAR2 can mitigate tau pathology.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.07/D5

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

Support: T32 GM007752
T32 AG066596
R01 AG074273

Title: Dissecting the Molecular Mechanism of Beta Hydroxybutyrate in Alzheimer's Disease

Authors: *L.-A. M. ROSSITTO¹, L. LEHMANN⁴, J. DI SILVESTRI², D. E. MUNOZ-MAYORGA³, X. CHEN⁵;

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disease marked by brain accumulation of amyloid beta plaques, tau neurofibrillary tangles, and increased gliosis. Recent studies show brain and body metabolism changes in AD, sparking a growing interest in metabolism-based therapies, such as the ketogenic diet. Dietary interventions have inherent challenges in the treatment of cognitive impairments in older adults, calling for the development and evaluation of a ketomimetic for AD. β -hydroxybutyrate (BHB), the main ketone body produced during ketosis, is a likely candidate. Despite promising preclinical and clinical results using ketogenic diet for AD intervention, it remains unknown if BHB alone is sufficient to alter AD-driving pathologies such as tau. In this presentation, we demonstrate that a BHB-precursor diet can ameliorate toxic tau pathology in the P301S-Tau transgenic (PS19) mouse model, especially highly aggregated and insoluble tau. Using both *in vitro* models and biochemical assays in combination with systematic approaches including snRNA sequencing and mass spectrometry-based tau interactomics, we interrogate the molecular properties of BHB and their influence on tau proteostasis. Overall, we find that BHB modulates neuronal proteostasis networks and reduces tau pathogenesis.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

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Program #/Poster #: PSTR157.08/D6

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

Support: Alzheimer's Association Grant 24AARG-1193678

Title: Lithiated gold nanoparticles as promising therapy for Alzheimer's disease

Authors: *G. PULIATTI¹, B. CANNATA², N. CASTAGNO³, L. SPOSITO¹, M. ALBINI¹, A. GRASSI³, C. GRASSI¹, A. BUONERBA³, R. PIACENTINI¹;

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Abstract: Glycogen Synthase Kinase 3 β (GSK-3 β), is a hub kinase whose deregulation has been linked to mood disorders and neurodegenerative diseases, including Alzheimer's disease (AD). Although significant efforts have been made to develop drugs that modulate this kinase, most candidates failed to reach the clinical use. The lithium cation (Li⁺) is a potent GSK-3 inhibitor, that modulates kinase activity by inducing its phosphorylation at Ser9 (pGSK-3 β -S9). Unfortunately, the systemic use of lithium is limited by its toxicity, especially for kidneys and thyroid. Currently, lithium salts are administered only orally to treat neuropsychiatric disorders, but safe doses are ineffective against other GSK-3-dependent illnesses, which require higher, toxic doses. Thereby, discovering novel lithium administration routes, that reach the target organ(s) (e.g., the brain) bypassing the systemic administration and without damaging other organs, would be highly beneficial. In this context, we developed a tool consisting of gold nanoparticles (AuNPs) functionalized with glutathione and charged with Li⁺ in the outer corona. In water, they form aggregates of 250 nm in diameter (a-LiG-AuNPs). a-LiG-AuNPs internalize cells by endocytosis and efficiently release Li⁺ in the cytosol, thus inducing an increase of pGSK-3 β -S9 (+2.2 $\pm$ 0.3 folds at 3 mEq/L Li⁺; p<0.001), even at Li⁺ concentration normally resulting ineffective with lithium salts (0.15 mM), without resulting cytotoxic. When applied intranasally in healthy C57BL/6 mice, a-LiG-AuNPs efficiently reached the brain, particularly the hippocampus, resulting in a +130% increase in pGSK-3 β -S9 levels (p<0.01 vs. vehicle) after 5 months of treatment (3 μ L/nostril/day from a 100 mg/mL stock solution, 5 days/week with 10-day rest periods). Notably, this occurred without significantly altering plasma lithium concentrations (0.08 $\pm$ 0.01 mmol/L in vehicle-treated vs. 0.14 $\pm$ 0.02 mmol/L in a-LiG-AuNP-treated mice) and without inducing gliosis or affecting the animals' general health status. From a therapeutic perspective, we found that a-LiG-AuNP spared murine hippocampal neurons from the synaptotoxic action of tau oligomers in vitro. More importantly, a-LiG-AuNPs intranasal treatment significantly improved memory of 12 months-old 3 $\times$ Tg-AD mice treated until 14 months of age (65.9 $\pm$ 1.6% vs. 48.6 $\pm$ 1.7% of preference index; p<0.01), assessed by Novel object recognition paradigm, while reducing tau load. Collectively, a-LiG-AuNPs offer a promising tool for brain-specific Li⁺ delivery, potentially beneficial for treating GSK-3 β -dependent neurological diseases such as AD, and avoiding the Li⁺ side effects.

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Piacentini: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Università Cattolica del Sacro Cuore.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.09/D7

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

Support: National Research Foundation in Republic of Korea
(2021R1A2C3005704)
Institute for Basic Science (IBS- R025-A1)

Title: Excitatory Neuronal ERBB4 Drives Early Pathophysiology of Alzheimer's Disease

Authors: *S. LEE¹, W.-S. CHUNG²;

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Abstract: Neuroinflammation and synapse loss synergistically contribute to cognitive decline in Alzheimer's disease (AD). Although microglial hyper-phagocytic activity has been shown to mediate synapse loss, the exact mechanisms underlying these pathologies remain obscure. Here, we first demonstrate that astrocytes and microglia increase the phagocytic elimination of excitatory synapses, but significantly decrease their elimination of inhibitory synapses during AD progression, suggesting neuroinflammation may be dispensable for early AD synapse loss. Instead, through single-nucleus RNA sequencing (snRNAseq), we identified the emergence of Disease-Initiating Excitatory Neurons (DIENs), characterized by ectopic *ErbB4* expression, as the earliest major alteration in an AD mouse model. Notably, specific deletion of *ErbB4* in 5XFAD excitatory neurons abrogated abnormal neuronal network activities and synapse loss, as well as reactive gliosis, amyloid plaque deposition, and cognitive deficits. Conversely, overexpression of *ErbB4* in wild-type (WT) excitatory neurons recapitulated these key AD phenotypes in the absence of amyloid plaques. Subsequent snRNAseqs following *ErbB4* deletion and overexpression confirm that excitatory neuronal *ErbB4* is both sufficient and necessary to induce DIEN and reactive gliosis. Together, these findings reveal that the early pathophysiology of AD arises largely due to aberrant *ErbB4* expression in excitatory neurons, and that targeting excitatory neuronal *ErbB4* may thus represent a novel therapeutic strategy for mitigating multiple neurodegenerative diseases.

Disclosures: S. Lee: None. W. Chung: None.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

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Program #/Poster #: PSTR157.10/D8

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

Support: PNRR-MCNT2-2023-12377366 Finanziato dall'Unione europea – Next Generation EU – PNRR M6C2 - Investimento 2.1 Valorizzazione e potenziamento della ricerca biomedica del SSN

Title: Developing new therapeutic strategies to counteract synaptic and cognitive deficits in Alzheimer's disease by targeting zDHHC enzymes

Authors: S. FUSCO^{1,2}, F. NATALE^{1,2}, M. TROPEA³, M. RINAUDO^{1,2}, N. GAROFALO¹, F. PASTORE², R. SOLLAZZO¹, D. D. LI PUMA^{1,2}, C. RIPOLI^{1,2}, D. PUZZO^{3,4}, *C. GRASSI^{1,2}; ¹Dept. of Neurosci., Univ. Cattolica del Sacro Cuore, Rome, Italy; ²Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; ³Dept. Biomed. and Biotechnological Sci., Univ. of Catania, Catania, Italy; ⁴Oasi Res. Institute-Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS), Troina, Italy

Abstract: Protein post-translational modifications play a critical role in the modulation of synaptic function, and their dysregulation contributes to the onset and progression of neurodegenerative disorders. S-palmitoylation is a post-translational modification catalyzed by zinc finger DHHC domain containing (zDHHC) S-acyltransferases, which affects both the localization and activity of proteins involved in synaptic plasticity and amyloid- β metabolism. Western blotting and acyl-biotinyl exchange assay were used, respectively, to assess zDHHC expression and protein S-palmitoylation levels in: (i) hippocampi of 3 $\times$ Tg-AD mice and Alzheimer's disease (AD) patients; and (ii) neurons and brain organoids derived from human induced pluripotent stem cells obtained from skin biopsies of AD patients. In vivo zDHHC inhibition was achieved by stereotaxic injection of lentiviral particles harboring short hairpin RNA targeting zDHHC7 into the hippocampus of 9-month-old female 3 $\times$ Tg-AD mice exhibiting a clear AD-like phenotype. A broad-spectrum investigation of zDHHC7 targets was conducted through palmitoyl-proteome analysis of the hippocampus from zDHHC7-silenced 3 $\times$ Tg-AD mice. In the same mice, we also assessed synaptic plasticity via long-term potentiation recordings at CA3-CA1 synapses, and evaluated memory performance using the Novel Object Recognition and Novel Object Location tests. Our results demonstrated significant increases in both zDHHC7 expression and synaptic protein S-palmitoylation in the hippocampi of 3 $\times$ Tg-AD mice and AD patients. Hippocampal silencing of zDHHC7 counteracted synaptic plasticity and cognitive deficits in 3 $\times$ Tg-AD mice. Palmitoyl-proteome analysis identified numerous zDHHC7 molecular targets potentially involved in the onset and progression of neurodegeneration. Finally, we developed locked nucleic acid-containing antisense oligonucleotides targeting zDHHC7 and demonstrated their silencing efficacy in both in vitro and in vivo models. Collectively, our data suggest that aberrant protein S-palmitoylation plays a critical role in hippocampal synaptic plasticity and memory deficits observed in experimental models of AD, highlighting zDHHC7 as a new target for therapeutic interventions against cognitive decline in

AD patients. Moreover, our findings identify novel and readily translatable therapeutic approaches to modulate zDHHC enzymes and their targets in neurodegenerative disorders.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.11/D9

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

Support: USC Stem Cell NIH T32 PhD Fellowship
Diana Jacobs Kalman/AFAR Scholarships for Research in the Biology of Aging

Title: Pharmaceutical rejuvenation of aged neural stem cells to enhance cognition in age-related and Alzheimer's disease-associated cognitive decline

Authors: *W. NGUYEN¹, M. SHARIQ³, M. A. BONAGUIDI²;
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Abstract: Adult neural stem cells (NSCs) generate new neurons that modify existing neural circuits to support learning and memory. This process, known as adult neurogenesis, relies on NSCs transitioning from a quiescent to an activated state to enter the proliferative phase, which, unfortunately, is compromised at early chronological age. To better target this premature aging of NSCs, our lab compared single-cell transcriptomic trajectories of NSCs in young and older mice as they shift from quiescence to activation. Our analyses revealed a gene signature that is robustly activated as young NSCs proliferate but not in aged NSCs. Using *in silico* screening and subsequent *in vivo* validation, we identified SS as a leading candidate compound that successfully reactivates this transition signature, rejuvenating NSCs in middle-aged rodents and improving cognitive performance.

Building on these findings, we extended our validation to Alzheimer's disease (AD), where NSC exhaustion and neurogenesis dysregulation is exacerbated, contributing to more severe cognitive deficits. In both 5xFAD and 3xTg-AD mouse models, we observed significantly reduced NSC numbers, proliferation, and neurogenesis compared to age-matched wild-type controls. Remarkably, SS treatment via intracerebroventricular infusion for just six days significantly enhanced NSC proliferation in 5xFAD mice at both 6 and 8 months of age, which corresponds to early and advanced stages of cognitive impairment in this model. These results highlight that NSC dysfunction is accelerated in AD and demonstrate that SS effectively rejuvenates NSCs by

targeting aging-related mechanisms, offering a promising therapeutic approach for AD-related cognitive decline.

Disclosures: W. Nguyen: None. M. Shariq: None. M.A. Bonaguidi: None.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.12/D10

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

Title: Multiplexed in vivo screening of biologics at scale discovers novel “portal” receptors and mechanisms for enhanced delivery of therapeutic molecules to the CNS

Authors: *K. A. SCEARCE-LEVIE¹, N. MEHTA¹, K. DUFFY¹, I. ALBUJA¹, F. ANAM¹, A. ANAND¹, J. AVERA¹, S. CARROLL¹, M. CASE¹, A. GARCIA¹, A. GEREW¹, H. HADDAD², Y. HO-RATH¹, R. MEHMOOD¹, M. NICHOLS¹, M. PRESCOTT¹, S. RAVICHANDRAN¹, E. SWANSON¹, P. OGDEN¹;

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Abstract: Central nervous system (CNS) diseases are difficult to treat in part due to the blood-brain barrier (BBB), which prevents many therapeutics from reaching the brain at efficacious concentrations. Receptor-mediated transcytosis (RMT) shows promise for transporting macromolecules across the BBB, but current targeting methods lack CNS specificity and cell-type selectivity. The number of validated "Portals" (BBB receptors with demonstrated RMT in vivo) is limited due to historical screening constraints.

In order to discover Portals with differentiated properties, we conducted the most comprehensive in vivo evaluation of potential CNS shuttles to date, screening candidates against over 300 potential Portal targets in mice, and characterizing scores of those in multiplexed non-human primate studies. Our novel pooled in vivo screening technology, mCodes™, allowed us to simultaneously assess quantitative tissue distribution for up to 100 molecules per animal with high precision.

This approach revealed an expanded set of Portal targets capable of facilitating RMT across the BBB. Detailed pharmacokinetic and biodistribution analyses of select novel Portals demonstrate distinct properties compared to well-characterized targets like transferrin receptor (TfR) and CD98. Novel portals were discovered that demonstrated optimal characteristics for therapeutic strategies targeting extracellular pathologies like Abeta, as well as intracellular pathologies like Tau. These portals offer promising avenues for further research and development in the pursuit of effective treatments for CNS diseases.

These newly identified Portal receptors may enable unprecedented control over biodistribution, enhancing CNS delivery, cell-type specificity, and regional targeting, while reducing peripheral effects. By substantially expanding the known CNS Portal landscape, our work provides a

foundation for developing biologics with precisely engineered tissue distribution profiles that are sculpted to meet the intended product profiles for specific therapeutic approaches.

Disclosures: **K.A. Searce-Levie:** A. Employment/Salary (full or part-time): Manifold Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Manifold Bio, Denali Therapeutics. **N. Mehta:** A. Employment/Salary (full or part-time): Manifold Bio. **K. Duffy:** A. Employment/Salary (full or part-time): Manifold Bio. **I. Albuja:** A. Employment/Salary (full or part-time): Manifold Bio. **F. Anam:** A. Employment/Salary (full or part-time): Manifold Bio. **A. Anand:** A. Employment/Salary (full or part-time): Manifold Bio. **J. Avera:** A. Employment/Salary (full or part-time): Manifold Bio. **S. Carroll:** A. Employment/Salary (full or part-time): Manifold Bio. **M. Case:** A. Employment/Salary (full or part-time): Manifold Bio. **A. Garcia:** A. Employment/Salary (full or part-time): Manifold Bio. **A. Gerew:** A. Employment/Salary (full or part-time): Manifold Bio. **H. Haddad:** A. Employment/Salary (full or part-time): Manifold Bio. **Y. Ho-Rath:** A. Employment/Salary (full or part-time): Manifold Bio. **R. Mehmood:** A. Employment/Salary (full or part-time): Manifold Bio. **M. Nichols:** A. Employment/Salary (full or part-time): Manifold Bio. **M. Prescott:** A. Employment/Salary (full or part-time): Manifold Bio. **S. Ravichandran:** A. Employment/Salary (full or part-time): Manifold Bio. **E. Swanson:** A. Employment/Salary (full or part-time): Manifold Bio. **P. Ogden:** A. Employment/Salary (full or part-time): Manifold Bio.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.13/D11

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

Title: Development of a highly potent, brain penetrant and allosteric RIPK1 inhibitor for the treatment of neurodegenerative diseases

Authors: *Y. XU, Y. JIANG, Y. REN, W. FAN, S. AGARWAL, Y. WU;
Sironax, Boston, MA

Abstract: Receptor-Interacting Serine/Threonine-Protein Kinase 1 (RIPK1) is an important regulator at the crossroads of cell survival, apoptosis, and necroptosis. It functions as a key modulator of inflammatory and cell death signaling downstream of tumor necrosis factor receptor 1 (TNFR1). RIPK1 mediates apoptosis through interactions with FADD and caspase-8, or necroptosis via RIPK3 and MLKL, particularly when caspase-8 is inhibited. Pathologically, dysregulation of RIPK1 signaling contributes to numerous human diseases. Aberrant activation of RIPK1-mediated cell death pathways is implicated in neurodegenerative diseases (e.g., ALS and Alzheimer's disease), ischemia-reperfusion injuries, and inflammatory disorders such as inflammatory bowel disease (IBD) and psoriasis. Mice bearing kinase-dead mutants of RIPK1 live normally and are resistant to tissue damage in various disease models. Furthermore, genetic

studies have linked mutations in RIPK1 to rare autoinflammatory syndromes characterized by systemic inflammation. SIR9900 is a highly selective, potent, brain penetrant and allosteric RIPK1 inhibitor developed by SIRONAX. **Methods:** In mouse SIRS models, SIR9900 was first dosed orally at 1, 3, 10, 30, 100mg/kg, followed by TNF injection. SIR9900's activity was measured through the reduction of the levels of cytokines, amelioration of hypothermia and protection of epithelial damage of the GI tract. In mouse AD model, 5xFAD mice were dosed with SIR9900 via orally gavage at either 100mg/kg qd or bid for 30 days, after which cytokine level from different brain regions were measured to reflect SIR9900's activity. In the mouse EAE model, SIR9900 was administered through oral gavage once daily at either 100 or 300mg/kg for 21 days. Clinical score and plasma NfL were used to reflect compound activity. **Results and conclusions:** SIR9900 significantly and dose dependently reduced cytokine production, protected epithelial damage on GI and reduced mortality rate in the SIRS model. SIR9900 significantly reduced neuroinflammation in the AD mouse model and significantly delayed disease onset of the EAE model. SIR9900 is a potent, selective and brain penetrant RIPK1 inhibitor that exhibited good activities in vitro and in multiple in vivo preclinical models.

Disclosures: **Y. Xu:** A. Employment/Salary (full or part-time): Sironax. **Y. Jiang:** A. Employment/Salary (full or part-time): Sironax. **Y. Ren:** A. Employment/Salary (full or part-time): Sironax. **W. Fan:** A. Employment/Salary (full or part-time): Sironax. **S. Agarwal:** A. Employment/Salary (full or part-time): Sironax.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.14/D12

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

Title: Atbfinder-guided antibiotics ameliorate urinary tract infection-associated cognitive decline and delirium in patients with neurodegenerative disorders

Authors: *G. TETZ;

Structural Biol., Human Microbiology Inst., New York, NY

Abstract: Background Urinary tract infections (UTIs) in patients with neurodegenerative diseases are associated with cognitive decline. Conventional phenotypic and genotypic antimicrobial susceptibility testing (AST) methods frequently fail to ascertain optimal and effective antibiotics. Particularly in elderly patients, AST-guided antibiotic therapy is incapable of mitigating UTI and culminates in alleviated cognitive impairment. AtbFinder is a novel diagnostic test designed for selecting the most effective antibiotics for difficult-to-treat infections. AtbFinder, for the first time, selects antibiotics contingent upon a “whole community response” by identifying those that target the entire microbial community at the infection site, in contrast to traditional AST that focuses solely on the response of a single dominant pathogen. This study aimed at evaluating the application of AtbFinder in determining antibiotics for the

treatment of UTI-associated cognitive decline in patients with neurodegenerative disorders.

Methods Fifteen patients (8 with Alzheimer's disease, 7 with other forms of dementia) with persistent UTI-associated cognitive decline, including three with UTI-associated delirium, were enrolled. The patients were suffering from symptomatic UTIs, as documented in their medical records. The cognitive decline was reported to be ≥ 3 points (3.6 ± 0.4), in compliance with the Mini-Mental State Examination (MMSE), as compared to that prior to UTI incidence. All patients had received at least two courses of AST-guided antibiotic therapy for UTI during the past two months, which failed to ameliorate UTI symptoms without increasing the MMSE score by >1 point. None of the patients were administered antibiotic therapy for at least 5 days. Assessments were performed using the MMSE, OBS Scale, GDS-15. Dementia and delirium were diagnosed according to DSM-IV criteria. **Results** Thirty days after completion of antibiotic therapy selected with AtbFinder, 15 of 15 (100%) patients did not have a UTI (clinically and laboratory-confirmed). The antibiotic therapy selected using AtbFinder varied among patients and lasted from 7 to 12 days. The number of broad-spectrum antibiotics used was reduced by 65% compared to the recommendations based on the standard AST before the selection of antibiotics with AtbFinder. Three patients (100%) who were diagnosed with delirium at baseline were not delirious and did not develop delirium during the past four weeks after the end of antibiotic therapy. The MMSE score increased in all 15 patients (100%) by 4.8 ± 0.5 points ($p < 0.01$) within four weeks after completing antibiotic therapy.

Disclosures: G. Tetz: None.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.15/D13

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

Support: University of Galway Hardiman Research Scholarship (A.O. and A.K.)
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Health Research Council of New Zealand (R.L.F., H.J.W., A.K.; 3723033)

Title: Treatment of β -amyloid-induced increased tonic conductance and cognitive deficits by an $\alpha 5$ GABA inverse agonist

Authors: *A. O'CONNELL¹, Y. ZHAI¹, C. KEIGHRON², K. PEPPERCORN⁴, H. J. WALDVOGEL⁵, R. L. FAULL⁶, J. M. MONTGOMERY⁷, L. QUINLAN³, A.

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Abstract: Alzheimer's disease (AD) is a chronic progressive neurodegenerative disorder characterized by cognitive impairment, which may arise from disruptions in the excitatory/inhibitory balance within the brain. Gamma-aminobutyric acid (GABA), the principal inhibitory neurotransmitter in the central nervous system, plays a crucial role in maintaining the excitatory/inhibitory balance and regulating neuronal activity involved in memory. In AD, changes in $\alpha 5$ GABA A receptor ($\alpha 5$ GABAAR) expression and activity increase tonic inhibition, disturbing the neuronal excitatory/inhibitory balance and ultimately impairing cognitive processes. Therefore, targeting $\alpha 5$ GABAAR offers a promising therapeutic strategy. This study examined the potential of an $\alpha 5$ GABAAR-selective inverse agonist, $\alpha 5$ IAs, in treating β -amyloid-induced cognitive deficits and the mechanism underlying this using ex vivo microelectrode array and patch clamp electrophysiology. $\alpha 5$ IA significantly reduced β -amyloid-induced long-term spatial memory deficits and long-term potentiation. $\alpha 5$ IA reversed A β -induced increases in neuronal excitability, as indicated by input-output curves, and mitigated elevated tonic conductance. These findings highlight $\alpha 5$ IA's ability to restore excitatory/inhibitory balance and cognitive function. The selective targeting of $\alpha 5$ -GABAARs and enhancing the efficacy of $\alpha 5$ -GABAAR inverse agonists, such as $\alpha 5$ IA represents a promising direction in developing novel AD therapies.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.16/D14

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

Support: NIH Grant AG059640
NIH Grant AG062429-06

Title: Using biomarkers to try to predict memantine effects in Alzheimer's Disease

Authors: *N. R. SWERDLOW^{1,3}, J. SPROCK^{1,3}, C. E. GONZALEZ³, J. MIN DIN¹, J. MINHAS¹, J. TALLEDO BENRUBI¹, J. MOLINA^{1,3}, Y. JOSHI^{1,3}, G. LÉGER², L. POWELL², B. K. RANA⁴, L. DELANO-WOOD¹, G. A. LIGHT^{1,3};

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San Diego Healthcare System, VISN-22 MIRECC, San Diego, CA; ⁴Psychiatry, Moores UCSD Cancer Ctr., La Jolla, CA

Abstract: Background: A “personalized medicine” approach of selecting interventions based on patients’ characteristics (“biomarkers”) may be particularly valuable for treatments that benefit only a subset of patients. The NMDA antagonist, memantine (MEM), slows clinical progression of Alzheimer’s Disease (AD) in some individuals, but this effect is heterogeneous in magnitude and duration. Here we assessed whether the acute cognitive or neurophysiological response to MEM challenge, or other baseline clinical and genetic characteristics, predicted sensitivity to MEM’s therapeutic effects in AD. Methods: We enrolled 30 individuals with mild-to-moderate severity AD (M:F = 13:17; mean (range) age (y) = 71.6 (56-82); MoCA mean (range) = 16.4 (2-23) and 24 healthy comparison subjects (HCS) (M:F = 12:12; mean (range) age (y) = 65 (52-81); MoCA mean (range) = 27.1 (20-30). AD participants were characterized based on cognitive (Repeatable Battery for the Assessment of Neuropsychological Status (RBANS)) and neurophysiological (mismatch negativity (MMN), auditory steady state response (ASSR), prepulse inhibition (PPI)) measures and based on changes in these measures after an acute “challenge” with MEM (20 mg). We then assessed whether these measures predicted clinical change over a 24-week open-label trial of MEM (10 mg bid; primary outcome measures: Alzheimer’s Disease Assessment Scale - Cognitive Subscale (ADAS-cog), Geriatric Depression Scale (GDS) and the Neuropsychiatric Inventory Questionnaire (NPI-Q)). Results: The 20 mg MEM “challenge” was well tolerated. Baseline cognitive (RBANS; $p < 0.0001$) and neurophysiological measures (MMN amplitude ($p < 0.05$), P3a latency ($p < 0.0005$), ASSR power ($p < 0.03$) and coherence ($p < 0.04$), PPI ($p < 0.03$)) were impaired in AD participants vs. HCS; deficits in a subset of measures in AD subjects were modestly reduced by acute MEM challenge. Overall, AD participants showed no significant clinical changes across 24 weeks of MEM treatment; subgroups exhibited either small cognitive gains or deterioration. Clinical sensitivity to MEM was not strongly predicted either by baseline experimental measures or by sensitivity of these measures to acute MEM challenge. Conclusions: A challenge dose design failed to identify biomarker predictors of clinical sensitivity to MEM among participants with mild-to-moderate severity AD. We report impairment in specific measures in AD participants, and in some cases their opposition by MEM, that might inform future efforts to identify treatment biomarkers in AD.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.17/D15

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

Support: Scottish Rite Charitable Foundation Grant

Title: Procognitive effects of $\alpha 5$ -GABAA positive allosteric modulation in a transgenic mouse model of Alzheimer's disease

Authors: *J. CHEN^{1,2}, C. MEZO GONZALEZ¹, M. MARCOTTE¹, D. SHARMIN⁴, J. M. COOK⁴, E. SIBILLE^{1,2,3}, T. D. PREVOT^{1,2,3};

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Abstract: Alzheimer's disease (AD) is a progressive and debilitating neurodegenerative disorder. Despite drug development advancements in recent years, directly targeting amyloid and tau pathologies still has limitations in meaningfully improving patients' quality of life. Our research identified the $\alpha 5$ -subunit of the GABAA receptor ($\alpha 5$ -GABAAR) as a promising therapeutic target, due to its vulnerability to aging and its regulatory role in multiple facets of cognition. Our group developed a novel molecule, GL-II-73, that acts as a preferential positive allosteric modulator at the $\alpha 5$ -GABAAR. Chronic treatment with GL-II-73 has been shown to reverse working memory deficits and neuronal shrinkage in preclinical models of amyloid deposition and tau tangles. However, the exact biological mechanism underlying these procognitive effects has not been clarified by direct genetic approaches. This project proposes to demonstrate the requirement of positive allosteric modulation at the $\alpha 5$ -GABAAR in the regulation of cognitive functions, using a double-transgenic mouse model of amyloid load, genetically designed to be insensitive to $\alpha 5$ -GABAAR potentiation. We hypothesize that, following chronic treatment, the drug-sensitive strain will show better cognitive performance than the drug-insensitive strain, despite both groups having amyloid pathology. Specifically, 5xFAD^{tg/+} mice, as a model of progressive amyloid load, were crossed with *Gabra5*^{ki/ki} mice, who bear a point mutation rendering their allosteric site of the $\alpha 5$ -GABAAR insensitive to GL-II-73 binding. Double transgenic animals and their wildtype littermates (n=12/sex/group) underwent three weeks of GL-II-73 treatment, administered through drinking water (30 mg/kg). Multiple facets of cognition were subsequently assessed, including working memory in Y-Maze alternation task, spatial learning in Morris Water Maze, and cognitive flexibility in Noldus Phenotyper Cognition Wall. Compared to untreated controls, 5xFAD^{tg/+} mice chronically treated with GL-II-73 showed statistically significant advantage in completing cognitive tasks, including reduced latency in spatial navigation (p<0.05); this treatment effect was only observed in the drug-sensitive wildtype group, and not the drug-insensitive *Gabra5*^{ki/ki} strain. Our early findings suggest the necessary role of $\alpha 5$ -GABAAR potentiation in a mouse model of AD for improving performance in specific cognitive functions by GL-II-73. Future research will further explore the efficacy of $\alpha 5$ -GABAA positive allosteric modulation through neuronal and molecular analyses.

Disclosures: J. Chen: None. C. Mezo Gonzalez: None. M. Marcotte: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Damona Pharmaceuticals. D. Sharmin: None. J.M. Cook: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Damona Pharmaceuticals. E. Sibille: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Damona Pharmaceuticals. T.D. Prevot: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.18/D16

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

Title: Hyp-101 reduced tau-associated pathology and cognitive dysfunction via OGA inhibition.

Authors: *H. KIM, S. BAEK, J. IM;
Central Res. Institute, Hyper Corp., Seoul, Korea, Republic of

Abstract: Alzheimer's disease (AD) is the leading cause of dementia. Its neuropathological features include the accumulation of extracellular amyloid-beta plaques and intracellular neurofibrillary tangles (NFTs), both of which contribute to neuronal damage and the progressive decline in cognition. NFTs consist of hyperphosphorylated tau proteins. The phosphorylation of tau is dynamically regulated by tau kinases, phosphatases, and O-GlcNAcylation. Importantly, O-GlcNAcylation has been shown to suppress tau hyperphosphorylation, reducing tau aggregation and neurotoxicity. This suggests that enhancing tau O-GlcNAcylation through inhibition of O-GlcNAcase (OGA) may serve as a promising therapeutic approach. Thiamet-G, while demonstrating high selectivity and efficacy as an OGA inhibitor, faces challenges in crossing the blood-brain barrier in Alzheimer's disease patients owing to its suboptimal membrane permeability. In this study, we designed a novel OGA inhibitor scaffold inspired by Thiamet G and its binding profile with OGA, leading to the discovery of a lead compound HYP-101. HYP-101 demonstrated potent and selective inhibition of OGA ($IC_{50} = 0.053 \mu M$) without affecting β -hexosaminidase. It also showed blood-brain barrier permeability ($-\log Pe = 4.4$) and exhibited no toxicity in HT-22 hippocampal neuronal cells. Moreover, in a P301L tau-overexpressing cell model, the compound reduced tau phosphorylation via OGA inhibition. In vivo, oral administration every other day-starting two weeks after intracerebral ventricular injection of streptozotocin significantly improved cognitive performance in mice, while increasing brain O-GlcNAc levels and reducing levels of hyperphosphorylated tau. These findings support the therapeutic potential of OGA inhibition as a strategy to alleviate tau-related pathology and cognitive deficits in Alzheimer's disease.

Disclosures: H. Kim: A. Employment/Salary (full or part-time): Full-time. S. Baek: A. Employment/Salary (full or part-time): Full-time. J. Im: A. Employment/Salary (full or part-time): Full-time.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.19/D17

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

Title: Modulation of ERK/MAPK Signaling and Neuroinflammatory Responses by Hesperidin in Aluminum Chloride-Induced Hippocampal Neuropathology

Authors: ***R. S. ORIA**¹, O. M. IJOMONE²;

¹Human Anat., Univ. of Cross River State, Okuku/Yala, Nigeria; ²Dept. of Anat., Univ. of Med. Sciences, Ondo, Ondo, Nigeria

Abstract: Neuroinflammation represents a pivotal pathological hallmark of neurodegenerative disorders, including Alzheimer's disease (AD). Objective: This study investigated the neuroprotective potential of Hesperidin, a citrus bioflavonoid with established anti-inflammatory properties, against aluminum chloride (AlCl₃)-induced neuroinflammation and associated neurodegeneration within the hippocampal formation (CA1 and CA3 subfields). Twenty-five adult male Wistar rats were randomly allocated into five experimental groups: Group A (Control) received vehicle (normal saline); Group B received AlCl₃ (100 mg/kg/day) alone; Group C received Hesperidin (100 mg/kg/day) alone; Group D received AlCl₃ plus Hesperidin (50 mg/kg/day); Group E received AlCl₃ plus Hesperidin (100 mg/kg/day). All treatments were administered orally via gavage daily for four weeks. Post-treatment assessments included: neurobehavioral evaluation of short-term spatial memory (Morris water maze); quantification of hippocampal proinflammatory cytokine levels (TNF- α and IL-1 β) via ELISA; histological examination (H&E staining) of neuronal morphology in CA1/CA3; and immunohistochemical analysis of microglial activation (IBA-1 immunoreactivity) and ERK/MAPK pathway activity (phospho-ERK expression). Administration of AlCl₃ alone elicited significant neuropathological alterations, including: pronounced deficits in spatial memory performance; a marked elevation ($p < 0.05$) in hippocampal TNF- α and IL-1 β concentrations; extensive neurodegeneration evidenced by neuronal necrosis, eosinophilic cytoplasm, and vacuolation; robust microgliosis indicated by increased IBA-1⁺ cell density; and significant upregulation of phospho-ERK immunoreactivity within the hippocampus. Concurrent administration of Hesperidin with AlCl₃ produced a dose-dependent attenuation of these pathological indices. Specifically, Hesperidin co-treatment ameliorated memory impairment, reduced proinflammatory cytokine levels, preserved neuronal cytoarchitecture, suppressed microglial activation, and mitigated ERK/MAPK pathway hyperactivation. These findings demonstrate that Hesperidin conferred significant neuroprotection against AlCl₃-induced hippocampal damage. The protective mechanisms likely involve the preservation of neuronal histomorphology, suppression of neuroinflammatory cascades (including cytokine release and microgliosis), and modulation of the ERK/MAPK signaling pathway. Hesperidin thus represents a promising candidate for mitigating neuroinflammation and neurodegeneration relevant to AD pathology.

Disclosures: R.S. Oria: None. O.M. Ijomone: None.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.20/D18

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

Title: Masupirdine (SUVN-502), a Pure 5-HT₆ Receptor Antagonist: Phase-3 Study for the Treatment of Agitation in Patients with Dementia of Alzheimer's Type

Authors: *A. K. SHINDE, V. GOYAL, P. JAYARAJAN, V. BENADE, J. RAVULA, S. JETTA, S. PANDEY, R. SUBRAMANIAN, R. ABRAHAM, A. MOHAMMED, R. NIROGI; Suven Life Sci. Ltd, HYDERABAD, India

Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder frequently accompanied by neuropsychiatric symptoms (NPS). Among the NPS, agitation is common and is characterized by emotional distress in conjunction with excessive motor activity, verbal aggression, or physical aggression. The monoamine neurotransmitter systems, which play a key role in behavioral regulation, are notably disrupted in AD. The serotonergic system is critically involved in modulating aggression and impulsivity. Therefore, pharmacological agents that target monoamine neurotransmission especially through the serotonergic pathway may offer therapeutic benefit in managing agitation. Serotonin-6 (5-HT₆) receptors have distinct localization and specific distribution in brain regions involved in mood and behavior regulation. Several clinically used psychotropic drugs act as 5-HT₆ receptor antagonists, suggesting that these receptors may be promising therapeutic targets for managing agitation. Masupirdine is a potent, selective, and orally active 5-HT₆ receptor antagonist. In preclinical studies, administration of Masupirdine produced a rapid and statistically significant attenuation of aggression-like behaviors in the resident-intruder paradigm and the dominant-submissive assay. Furthermore, Masupirdine was found to modulate monoaminergic neurotransmission, suggesting a potential mechanism underlying its behavioral effects. Post hoc analyses of a Phase 2 clinical study of Masupirdine in patients with AD (NCT02580305) indicated that the treatment significantly improved agitation/ aggression, and related domains (symptoms), as measured by the neuropsychiatric inventory scale. Based on the observation from animal models and AD patients, Masupirdine is currently being evaluated in a Phase-3 pivotal global study (NCT05397639; EudraCT: 2021-003405-22) for the treatment of agitation in patients with dementia of the Alzheimer's type. This study will assess Masupirdine at doses of 50 mg and 100 mg, compared to placebo, in approximately 375 patients recruited from the USA and Europe. The primary endpoint is the change in scores on the Cohen-Mansfield agitation inventory items that align with the international psychogeriatric association agitation criteria domains. The key secondary efficacy endpoint is the modified Alzheimer's disease cooperative study-clinical global impression of change score related to agitation. Results from the Phase-3 study will inform the utility of Masupirdine in treating agitation in patients with dementia of the Alzheimer's type. Phase-3 study data readout is anticipated in 2026.

Disclosures: **A.K. Shinde:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **V. Goyal:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **P. Jayarajan:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **V. Benade:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **J. Ravula:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **S. Jetta:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **S. Pandey:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **R. Subramanian:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **R. Abraham:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **A. Mohammed:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd. **R. Nirogi:** A. Employment/Salary (full or part-time): Suven Life Sciences Ltd.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.21/D19

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

Support: Clinical and Translational Science Award (UL1 TR001439) from the National Center for Advancing Translational Sciences, National Institutes of Health

Title: Neurological risk and protective associations of amoxapine and trifluoperazine: Retrospective cohort analysis from real-world data

Authors: ***O. MALIK**¹, S. DANN², A. CHOPRA³, X. FANG^{1,4,5};

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Abstract: Trifluoperazine (TFP) and amoxapine (AXPN) are FDA-approved psychotropic medications with established central nervous system activity. Although initially indicated for psychiatric disorders, the neuropharmacological profile of these drugs raises the possibility of impacting long-term neurological outcomes. Previous preclinical studies have suggested immunomodulatory and neuroprotective potential, but human data remain limited. The current study aims to determine whether exposure to TFP or AXPN is associated with an altered risk for neurodegenerative or neurological conditions compared to an age- and sex-matched cohort treated with fluoxetine. Data were obtained through a retrospective cohort study using anonymized electronic health record data from a large federated real-world data network. Patients aged 18 to 90 years were treated with either TFP, AXPN, or fluoxetine. Mutually exclusive cohorts were formed using a 1:1 matching of patients by age and sex. Ten neurological conditions were examined as outcomes, including Alzheimer's and Parkinson's disease, multiple sclerosis, mild cognitive impairment, epilepsy, and restless leg syndrome. Measures of association were evaluated through risk and odds ratios. Outcomes achieving statistical

significance were further analyzed using Kaplan-Meier survival analysis and time-to-event measurement. The 834 member AXPB cohort showed no significant statistical differences in neurological outcomes compared to fluoxetine. The 1,854 member TFP cohort showed a significantly reduced risk of MCI ($p < 0.001$) and RLS ($p < 0.001$) development, and a significantly longer event-free survival period compared to fluoxetine. Although a higher incidence rate of epilepsy was noted in the TFP cohort, Kaplan-Meier analyses did not show a statistically significant difference in time to event ($p = 0.082$). Proportional hazard assumptions were met for all models examined. Overall findings suggest a significantly lowered risk of mild cognitive impairment and restless leg syndrome for TFP compared to fluoxetine, while AXPB and fluoxetine showed no significant differences. The findings suggest potential neurological effects of TFP and support the need for further investigation into its repurposing potential for neuroprotection.

Disclosures: O. Malik: None. S. Dann: None. A. Chopra: None. X. Fang: None.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.22/D20

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

Support: Epstein foundation

Title: Development of novel STING inhibitors for treatment of Alzheimer's disease

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia, characterized by amyloid plaques, Tau tangles, synaptic loss and chronic neuroinflammation. The cGAS-STING pathway, a key mediator of innate immunity, not only defends against pathogens but also contributes to chronic inflammation in aging and neurodegeneration. Preclinical studies in AD models demonstrate that persistent cGAS-STING activation exacerbates neuroinflammatory processes, whereas genetic or pharmacological inhibition of this pathway attenuates inflammation and ameliorates disease phenotypes. Here, we report a series of novel, high-potency STING inhibitors through structure-based drug design and systematic structure-activity relationship (SAR) analyses. Using SN-011 as our hit compound, we optimized key pharmacological properties including potency, aqueous solubility, metabolic stability, and BBB permeability by medicinal chemistry approaches, including bioisosteric replacement strategies employing triple bonds as linker to disrupt π - π stacking interactions in the biphenyl tail group, followed by nonaromatic bicyclic rings as bulkier substitution of phenyl subunit of SN-011, leading to significantly increased kinetic solubility and potency. Furthermore,

we optimized the head group by replacing the 4-F-phenyl moiety with a smaller ethyl group, which reduced molecular weight while increasing lipophilicity, obtaining our two lead compounds YQ-1-23 and YQ-1-76 with potent improved BBB permeability. The therapeutic potentials of our lead compounds were evaluated using both *in vitro* system and *in vivo* AD mouse models, which showed significant improvement in efficacy compared to parental compound SN-011 and reference STING inhibitor H-151. In summary, our research developed a series of highly potent and druggable STING inhibitors, which not only provide chemical tools for perturbation of cGAS-STING pathway, but also created an integrated platform for accelerated development of novel STING-targeted therapeutics for the treatment of neurodegenerative conditions associated with neuroinflammation, including AD.

Disclosures: Y. Qin: None. Z. Zhao: None.

Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.23/D21

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

Title: Effect of biotin and lipoic acid on behavior and motor function in a model of Alzheimer's disease

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Abstract: Neurodegenerative diseases are a heterogeneous group of central nervous system disorders, with Alzheimer's (AD) being the most prevalent. AD is marked by the presence of β -amyloid plaques, neurofibrillary tangles, oxidative stress, and inflammation, leading to cognitive and motor deficits. Nutraceuticals such as biotin (B) and lipoic acid (LA) have shown neuroprotective properties, but their combined effects remain unexplored. This study aimed to evaluate the individual and combined effects of B and LA on behavior and motor function in a rat model of AD. Male Wistar rats (300 ± 50 g) were maintained under standard bioterium conditions following Mexican Official Standard (NOM-062-ZOO-1999). Animals were assigned to five groups (n=5): 1) Control (Ct); 2) AD (AlCl_3 , 100 mg/kg, p.o.); 3) AD+B (AlCl_3 + B, 5 mg/kg, i.p.); 4) AD+LA (AlCl_3 + LA, 50 mg/kg, i.p.); 5) AD+B+LA (AlCl_3 + B + LA). Behavioral tests included Y-maze, novel object recognition (NOR), grip strength, and open field test (OFT). Data were analyzed using ANOVA and Tukey's post hoc test ($p \leq 0.05$). In the Y-maze, AD+B rats (2.3 ± 0.37) outperformed AD rats (1.6 ± 0.24) and were not significantly different from controls (3.4 ± 0.24). NOR revealed improved short-term memory in Ct (76.1 ± 12.8), AD+B (83.5 ± 8.4), and AD+LA (81.4 ± 9.3) versus AD (19.9 ± 10.0), with no differences

in long term or working memory. Grip strength was higher in Ct (9.91 ± 0.06), AD+B (9.26 ± 0.17), AD+LA (9.46 ± 0.24), and AD+B+LA (9.47 ± 0.24) vs. AD (6.76 ± 0.47). OFT results showed lower anxiety in AD+B (19.6 ± 4.0) compared to AD (10.6 ± 1.9). In conclusion, biotin ameliorated all tested behavioral and motor deficits, with performance similar to controls. LA improved short term memory and strength but did not affect anxiety. While no synergistic effect was observed, the combination enhanced grip strength. These results suggest that biotin and lipoic acid may alleviate certain cognitive and motor symptoms of neurodegeneration in a rat model of Alzheimer's disease.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.24/D22

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

Support: 2024 Student Endeavors Grant
Central Michigan University Neuroscience Program
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The John G. Kulhavi Professorship in Neuroscience
E. Malcolm Field and Gary Leo Dunbar Endowed Chair in Neuroscience
at CMU

Title: Therapeutic Potential of Trans- β -2-styryl Boronic Acid in Mitigating Alzheimer's Pathology at Early and Advanced Stages in 5xFAD Mice

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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-beta ($A\beta$) plaque accumulation, neurofibrillary tangles composed of hyperphosphorylated tau, and chronic neuroinflammation. Although boron is a naturally occurring trace element found in plant-derived foods like fruits and leafy greens, it is not currently classified as an essential nutrient. Boron has been proposed as a potential therapeutic agent for Alzheimer's disease due to its ability to scavenge harmful free radicals, thereby reducing oxidative stress. This study's objective is to investigate the behavioral and

neuropathological effects of the boronic acid derivative trans- β -2-styryl boronic acid (TBSA) in the 5xFAD mouse model of AD may offer new avenues for therapeutic development. Male and female 5xFAD and wild-type mice aged 6 and 12 months were stratified by genotype and treatment group. Mice received either TBSA (0.5 mg/kg body weight in 0.5% methylcellulose) or an equivalent volume of vehicle via oral gavage every other day (QOD) for 60 days. Prior to treatment, all animals underwent behavioral assessments including the open field and novel object recognition (NOR) tasks to establish baseline measures of locomotion, exploration, recognition memory, and object discrimination. Post-treatment behavioral testing included repetition of open field and NOR, as well as the Morris Water Maze to evaluate spatial learning and memory. At study endpoint, fixed brain tissue was sectioned coronally at 30 μ m and stained for glial fibrillary acidic protein (GFAP), ionized calcium-binding adapter molecule 1 (IBA-1), and co-stained with MOAB-2 and nanocurcumin to assess amyloid pathology and glial activation. Preliminary behavioral analyses suggest a mild improvement in memory performance following TBSA treatment. Histological evaluation of cortical brain sections demonstrated a qualitative reduction in both the size and density of amyloid plaques in TBSA-treated 5xFAD mice compared to vehicle-treated controls at both age groups. These findings support the hypothesis that TBSA may exert disease-modifying effects by attenuating amyloid burden and cognitive decline in AD, warranting further investigation into its mechanistic targets and long-term efficacy.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

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Program #/Poster #: PSTR157.25/D23

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

Support: Basque Government (IT1454-22)
BIOEF (BIO22/ALZ/010) EITB Telemaratón
SGIKER-UPV/EHU facilities

Title: Cannabinoid CB1 modulation of long-chain sphingolipid components of myelin involves S1P1 receptor signaling in a rat lesion model of dementia of the Alzheimer's type

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Abstract: In Alzheimer's-type dementia (DAT), cognitive deficits are linked to changes in both the cholinergic system and myelin in memory-related brain regions. Cannabinoid treatments can modulate these alterations in a rat DAT model with a specific lesion (192IgG-SAP) of cholinergic neurons in the nucleus basalis magnocellularis (NBM). Endocannabinoids (eCBs), derived from membrane lipids, activate CB1 signaling, increasing ceramides, which are precursors of sphingosine 1-phosphate (S1P), mainly via S1P1 receptors. This study examined lipid species related to myelin and S1P1 signaling after subchronic WIN55,212-2 treatment (0.5 mg/kg for 5 days) in this rat model. Learning and memory were assessed using the passive avoidance (PA) test in four groups (aCSF, 192IgG-SAP, aCSF+W, 192IgG-SAP+W). Myelin structure was analyzed via MBP immunodetection, S1P1 activity by [³⁵S]GTPγS autoradiography, and lipid composition by MALDI-MSI. Lesion and treatment influenced PA performance. MBP levels were reduced in the 192IgG-SAP group in cortical layers I-II but were restored to control levels with WIN treatment. In corpus callosum, MBP increased significantly in 192IgG-SAP+W versus 192IgG-SAP. Lipidomics showed that WIN treatment altered specific myelin-related lipids, including sulfatides (e.g., ST(d18:1/18:0), ST(d18:1/24:0)), phosphatidylethanolamines (e.g., PE 36:0+K⁺), and phosphatidylserines (e.g., PS(P-20:0/22:2)+Cl⁻). In white matter, long-chain ceramides (e.g., Cer 42:2;O₂+H-H₂O) and galactosylceramides (e.g., GalCer 42:2;O₂+K⁺) were increased. S1P1 activity increased in globus pallidus and hippocampus in aCSF+W, but decreased in corpus callosum. In 192IgG-SAP+W, it rose in hippocampus and dropped in amygdala. In NBM, S1P1 activity was nearly abolished by the lesion, with no effect from treatment. Some lipid intensities (e.g., oleoylcarnitine, hexosylceramides) correlated with S1P1 activity in NBM. In summary, WIN55,212-2 promoted remyelination via remodeling of myelin lipid composition, associated with changes in S1P signaling. These findings suggest cannabinoid-induced modulation of the sphingolipid pathway may offer therapeutic potential for neurodegenerative diseases involving demyelination.

Keywords: Sphingolipid, Cholinergic, CB1 receptor, S1P

Supported by the Basque Government (IT1454-22), BIOEF (BIO22/ALZ/010) EITB Telemaratón, and SGIKER-UPV/EHU facilities.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.26/D24

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

Title: Dimethyl fumarate ameliorates amyloid-beta generated cognitive deficits by inhibiting necroptosis in rats

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Abstract: Alzheimer's disease (AD) is a major neurodegenerative disorder characterized by progressive cognitive dysfunction. Necroptosis process plays a pertinent role in the neurobiology of AD, which is governed by receptor-interacting protein kinases (RIPK) and mixed lineage kinase domain-like protein (MLKL). Herein, we examined the effect of dimethyl fumarate (DMF) in C6 cell line and amyloid-beta oligomer (A β) AD model. DMF treatment reversed the C6 cell viability and expression of RIPK1, RIPK3, and MLKL in Lipopolysaccharide (LPS) model. We will confirm these results by employing annexin V/propidium iodide staining in flow cytometry. Intracerebroventricular (ICV) injection of A β in rats developed the cognitive deficits in Morris water maze (MWM), open-field test, Y-maze, and novel object recognition test (NORT). Administration of DMF, at 25 and 50 mg/kg doses via peroral route for 14 days, showed a decrease in escape latency and increased exploration of target quadrant in a probe trial of MWM test. DMF-recipient rats also displayed exploration of novel arms and novel object in Y-maze and NORT, respectively. The locomotor activity remained unchanged across the treatment groups in open field test. In molecular studies, we estimated the expression of necroptosis mediators (RIPK1, RIPK3, and MLKL), proinflammatory cytokines and oxidative mediators in hippocampus/frontal cortex using RT-qPCR and ELISA. DMF reduced oxidative processes by decreasing lipid peroxidation, and increasing antioxidant enzymes like superoxide dismutase, catalase, and glutathione. Moreover, DMF treatment decreased the levels of IL-6, TNF- α , and CRP cytokines in frontal cortex. We also planned NeuN and thioflavin T immunofluorescence staining for understanding the amount of hippocampal damage. A significant downregulation of RIPK1, RIPK3, and MLKL gene expression was observed in the hippocampus following DMF treatment indicated the inhibition of necroptosis. Our results indicate the cognitive improvement and neuroprotective effects of DMF in A β -induced AD model by modulating the necroptosis signalling. We suggest that the selective targeting of necroptosis process may open new treatment avenues for AD.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

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Program #/Poster #: PSTR157.27/D25

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

Support: NRF MSIT RS-2024-00441331
NRF MSIT RS-2025-00519518

Title: Epigenetic profiling of ZMYM3 in AD, development of miRNA LNA site blockers using PLGA based ApoE-targeted drug delivery platform

Authors: *J. PARK¹, K. CHOE², M. KANG¹, M. KIM¹;

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Abstract: Alzheimer's disease (AD) remains incurable, and current treatments provide only symptomatic relief without arresting neurodegeneration. Emerging evidence implicates epigenetic dysregulation and microRNA (miRNA) activity in this therapeutic gap. By sequencing circulating miRNAs, we found miR-4271 to be significantly up-regulated in AD patients relative to those with mild cognitive impairment. Postmortem brain analyses showed that ZMYM3—a brain-enriched zinc-finger MYM-type protein—was markedly reduced and epigenetically dysregulated in AD. Murine and neuronal studies confirmed that miR-4271 directly suppresses ZMYM3 translation. To restore ZMYM3, we engineered a locked-nucleic-acid (LNA) blocker targeting the miR-4271 seed sequence and encapsulated it in ApoE-functionalized poly(lactic-co-glycolic acid) (PLGA) nanoparticles for intranasal delivery. We will next extend miRNA profiling, generate an AAV-mediated miR-4271 overexpression model in APP/PS1 mice, and create CRISPR/Cas9-based ZMYM3 knockouts in human iPSC-derived neurons. RNA-seq and ChIP-seq will delineate the ZMYM3-dependent epigenetic network governing synaptic integrity and neuroinflammation. Following intranasal administration of the ApoE-PLGA-LNA formulation, we will evaluate brain uptake, ZMYM3 restoration, normalization of histone acetylation, and behavioral rescue in spatial memory and novel-object recognition tasks. Collectively, this work aims to validate ZMYM3-targeted epigenetic modulation via miR-4271 blockade as a non-invasive, disease-modifying strategy for AD.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

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

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PICOENTECH Co., Ltd. (Seongnam-si, Republic of Korea)

Title: Yeast Aldehyde-Reducing Composition Attenuates Oxidative and Aldehyde Stress in *C. elegans*, *Drosophila*, and 5XFAD Mouse of AD Models

Authors: *S. YI¹, C. KIM¹, H. KWON², J. LEE²;

¹Konkuk University/College of Vet. Med., Seoul, Korea, Republic of; ²PICOENTECH Co., Ltd., Seongnam, Korea, Republic of

Abstract: Alzheimer's disease (AD) progression is driven by the convergence of amyloid- β (A β) aggregation, reactive oxygen species (ROS) production, and lipid-derived reactive aldehydes, such as 4-hydroxynonenal (4-HNE), which collectively amplify mitochondrial dysfunction and synaptic loss. Astrocytic NOX4 is a prominent CNS ROS source; once activated, it initiates a myeloperoxidase (MPO)/osteopontin (OPN) signaling loop that accelerates lipid peroxidation, triggers glial ferroptosis, and perpetuates neuroinflammation. Because both ROS and aldehyde stress are intertwined drivers of AD pathology, agents that concurrently quench ROS and detoxify aldehydes may provide broad disease-modifying benefit. We examined a yeast-derived aldehyde-reducing composition (ARC) for its capacity to mitigate oxidative and aldehyde stress across three evolutionarily distinct AD models. In *Drosophila melanogaster* carrying eye-specific human tau overexpression (GMR > hTau), ARC was evaluated by gross ommatidial architecture and p-Tau/total Tau ratios, revealing a consistent trend toward preserved eye morphology and reduced tau burden. In *Caenorhabditis elegans*, ARC lowered whole-animal ROS, delayed paralysis in the A β -expressing strain CL4176, protected dopaminergic neurons in the 6-OHDA-challenged BZ555 line, and improved locomotor thrashing, demonstrating efficacy against both AD- and Parkinsonian-type insults. Finally, 10-month-old 5XFAD mice received oral ARC (20 units/kg/day for 30 days); hippocampal analyses showed decreased immunoreactivity for NOX4, MPO, OPN, and 4-HNE, indicating suppression of the NOX4-centered oxidative/aldehyde cascade in a mammalian brain context. Collectively, these findings suggest that ARC acts at the intersection of oxidative stress, aldehyde detoxification, and glial ferroptosis, providing conserved neuroprotection from nematodes to transgenic mice. By targeting a shared pathogenic axis rather than a single hallmark lesion, ARC emerges as a promising multi-target candidate that warrants further pre-clinical optimization and mechanistic dissection.

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Poster

PSTR157: Alzheimer's Disease Therapeutic Strategies: Pharmaceutical Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.29/D27

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

Support: JPMJSP2151

Title: Endogenous oxytocin neurons regulate cognitive function in scopolamine-induced Alzheimer's model mice

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Abstract: Introduction: Oxytocin (OXT) is a peptide hormone produced in the paraventricular nucleus (PVN) of the hypothalamus. OXT neurons project widely to the brain regions involved in cognitive function. We previously showed that intracerebroventricular administration of OXT improves cognitive performance in mice. To further elucidate the physiological functions of OXT, we employed DREADD to pharmacogenetically activate OXT neurons and examined their impact on cognitive functions. Methods: AAV8-hSyn-DIO-hM3Dq-mCherry was administered to the PVN of OXT-iCre mice (*C57BL/6-Oxt^{tm1.1(Cre)Ksak}*) to express hM3Dq, an excitatory DREADD, specifically in OXT neurons. Subsequently, clozapine-N-oxide (CNO) (1.0 mg/kg, i.p.) was administered to selectively stimulate hM3Dq and specifically activate OXT neurons. Alzheimer's (AD) model mice based on the choline hypothesis were administered scopolamine (0.5 mg/kg, i.p.), a muscarinic receptor antagonist. Cognitive behavior was assessed using the Y-maze and passive avoidance tests. The projection area of OXT neurons was confirmed by immunohistochemical staining for the red fluorescent protein, mCherry. Results: CNO-treated mice exhibited reversal of scopolamine-induced deficits in spontaneous alternation in the Y-maze. In contrast, CNO treatment failed to ameliorate scopolamine-induced reduction in step-through latency in the passive avoidance test. We identified mCherry-positive OXT neurons in the pedunculopontine nucleus and nucleus basalis of Meynert, which are the origins of the cholinergic projections. Discussion: These results suggest that the activation of endogenous OXT neurons in the pedunculopontine nucleus and nucleus basalis of Meynert ameliorates short-term spatial memory impairment in a scopolamine-induced AD mouse model but not fear memory impairment.

Disclosures: N. Wakana: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was supported by JST SPRING, Grant Number JPMJSP2151. J. Takahashi: None. S. Okamura: None. D. Yamada: None. A. Saitoh: None.

Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.01/D28

Topic: C.03. Parkinson's Disease

Support: Grace Science Foundation

Title: Role of NGLY1 expression on the propagation of PD neuropathology

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by a selective loss of midbrain dopaminergic neurons. There are currently no disease-modifying treatments for PD. Lewy bodies, a pathological hallmark of PD, are intracellular inclusions composed of aggregated forms of the presynaptic protein alpha-synuclein (aSyn). Mechanisms for maintaining proteostasis and processing misfolded proteins are dysregulated in PD as a result of environmental insults or genetic perturbations. In turn, this dysregulation results in aSyn aggregation leading to further proteasomal dysfunction and oxidative stress as part of a vicious cycle. Consequently, strategies to increase the antioxidant response and enhance proteasomal activity have the potential to reduce aSyn aggregation and slow PD progression. N-glycanase 1 (NGLY1) is a protein involved in proteostasis whose dysfunction results in NGLY1-deficiency, a congenital disorder of de-glycosylation characterized by developmental delay and aberrant protein accumulation in neurons. Evidence of parkinsonian symptoms associated with NGLY1-deficiency suggests that disruption of NGLY1 activity may result in increased propagation of aSyn aggregates. We hypothesized that NGLY1 deficiency would result in increased spreading of aSyn aggregates, as NGLY1 regulates the transcriptional activity of nuclear factor erythroid-2-like 1 (NFE2L1), an ER-linked transcription factor critical for proteasome biogenesis under conditions of proteotoxic stress. Consistent with this idea, NGLY1 KO HEK293 cells and neurons derived from NGLY1-deficiency patients display impaired proteasome biogenesis when challenged with proteasome inhibitors. However, contrary to our hypothesis, we found that NGLY1 knockout results in decreased spreading of aSyn aggregates in NGLY1 KO HEK293 cells. As one possibility, NGLY1 may modulate the spread of aSyn aggregates *via* its interaction with valosin-containing protein (VCP). Current efforts are now focused on testing the impact of NGLY1 point mutants with decreased VCP-binding capacity on aSyn seeded aggregation in NGLY1 KO HEK293 cells. The results of these studies will yield insights into molecular mechanisms governing aSyn spreading, setting the stage for developing disease-modifying therapies.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

Location: SDCC Halls B-H

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Program #/Poster #: PSTR158.02/D29

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS R03NS108229

Title: Neuroprotective mechanisms of endosulfine- α in cellular models of Parkinson's Disease

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Abstract: Parkinson's disease (PD) and other synucleinopathy disorders are characterized by the presence of aggregates enriched with fibrillar forms of the presynaptic protein alpha-synuclein (aSyn). aSyn undergoes accelerated aggregation in the presence of phospholipid membranes by adopting an exposed alpha-helical structure, a state that favors membrane-induced self-assembly. Endosulfine- α (ENSA), a highly conserved member of the cyclic AMP-regulated phosphoprotein family expressed in the CNS, is a regulator of the ATP-sensitive potassium (K_{ATP}) channel, as well as a binding partner of membrane-associated aSyn. In earlier studies, we found that ENSA inhibited seeded aSyn aggregation in neurons exposed to aSyn preformed fibrils (PFFs). Here, we hypothesized that ENSA could also be exerting a neuroprotective effect through interaction with the sulfonylurea receptor 1 (SUR1) subunit of the K_{ATP} channel to slow neuron dysfunction and degeneration in PD. In support of this idea, the K_{ATP} channel has been shown to play a central role in driving the high vulnerability of dopaminergic neurons in PD. To address our hypothesis, rat cortical cultures plated on microelectrode array (MEA) plates were transduced with adenovirus encoding ENSA-WT, ENSA S109E (a phosphomimic variant of ENSA), or the control protein LacZ downstream of the neuron-specific synapsin promoter and subsequently analyzed for neuronal activity in a Maestro MEA system. Additionally, rat cortical cultures were transduced with virus encoding an ENSA-specific shRNA or a non-targeting control shRNA to assess the impact of ENSA knockdown on neuronal activity. Cortical neurons transduced with ENSA S109E virus exhibited a higher mean firing rate and bursting frequency compared to cells transduced with ENSA-WT or LacZ virus. Unexpectedly, cortical neurons depleted of ENSA via shRNA-mediated knockdown also showed a dose dependent increase in mean firing rate and burst frequency without any changes in synchrony index. From these results, we infer that an ENSA variant unphosphorylated at residue S109 could play a key role in alleviating hyperexcitability in PD through specific interactions with the K_{ATP} channel that differ from those involving pS109-ENSA. Current efforts are focused on replicating these results in human iPSC-derived cortical neurons depleted of ENSA via CRISPR-mediated gene editing. These studies provide valuable insights into the molecular mechanisms underlying ENSA-mediated neuroprotection in PD, ultimately setting the stage for developing new therapies.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.03/D30

Topic: C.03. Parkinson's Disease

Title: A role for casein kinase-2 dysregulation in cortical synaptic dysfunction associated with synucleinopathy disorders

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Abstract: Cortical dysfunction is thought to contribute to the non-motor symptoms associated with Parkinson's disease (PD) and other synucleinopathies. Recent studies have reported functional changes in cortical circuitry in pre-clinical synucleinopathy models, but with limited mechanistic insight. We hypothesized that aSyn aggregation leads to cell signaling perturbations, potentially reflected by alterations of the phosphoproteome, in mouse brain. To address this hypothesis, we utilized a mouse model of aSyn aggregation involving the injection of aSyn preformed fibrils (PFFs) in the cortex or striatum to study the downstream effects of seeded aggregation. Immunohistochemistry revealed that PFF injection in either region leads to the presence of aSyn aggregates that stain positive for the phosphorylation of serine residue 129 (pS129-aSyn) 3 months post-injection in the sensorimotor cortex and connected brain regions. Phosphoproteomic analysis of the sensorimotor cortex revealed significant differences between the PFF- and monomer-injected mice. The results of gene ontology analysis of the phosphoproteomic changes suggested that aSyn PFF administration led to perturbations of synaptic signaling. Further, motif enrichment analysis coupled with kinase prediction indicated that many motifs up-regulated in PFF-injected mice consisted of predicted casein kinase 2 (CK2) phosphorylation sites. CK2, a constitutively active kinase that is dysregulated in multiple disorders, phosphorylates aSyn at residue S129. Additional immunohistochemical analysis revealed that the regulatory beta and catalytic alpha subunits of CK2 were colocalized with pS129-aSyn aggregates in the cortices of PFF-injected mice, and likewise, we observed this co-localization in post-mortem cortical tissue from patients with dementia with Lewy bodies. Punctate CK2 alpha subunit staining was also observed in the nuclei of cortical neuron culture, suggesting that PFF treatment alters CK2 subunit dynamics, in turn leading to the dysregulation of CK2 activity. Given this dysregulation and the role of CK2 in modulating NMDA receptor trafficking, we assessed the activity of rat primary cortical neurons after PFF exposure and noted an increase in bursting, suggesting a hyper-excitability phenotype, compared to control, untreated neurons. Collectively, these findings suggest that aberrant CK2 activity may play a key role in cortical synaptic dysfunction in the brains of individuals with PD and other synucleinopathy disorders.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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Program #/Poster #: PSTR158.04/D31

Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation for Parkinson's Research

Title: Revealing the binding affinities of antibodies targeting biomarkers for Parkinson's disease in the presence of neighboring modifications

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Abstract: Alpha-synuclein (aSyn) aggregation plays a central role in neurodegenerative disorders termed synucleinopathies, including Parkinson's disease (PD). PD diagnosis is based on motor features and nonmotor symptoms, such as autonomic dysfunction and sleep disturbances. However, pathological features, such as dopaminergic neuron loss in the substantia nigra, begin developing decades before clinical symptoms appear, making the discovery and validation of biomarkers a major priority in this field. Furthermore, the clinical and neuropathological overlap between synucleinopathies highlights the need for biomarkers to differentiate these diseases. A variant of aSyn phosphorylated on serine residue 129 (pS129-aSyn) has been extensively characterized as a marker of aSyn pathology, but pY125 and pY136, detected in brains and red blood cells, are less studied. Due to their proximity to pS129 on aSyn, they are highly likely to be influenced by pS129 when analyzed via antibody-based approaches, potentially leading to false-positive or false-negative results. Similarly, human-to-mouse substitutions (D121G and N122S), which are also closely proximal to Y125, are likely to interfere with the quantification of pY125-aSyn in mouse PD models. Here, we examined the binding affinity of antibodies targeting pY125- and pY136-aSyn in the absence or presence of neighboring modifications using biolayer interferometry (BLI), a technique that measures biomolecular interactions in real time by detecting changes in the interference pattern of white light reflected from an optical biosensor surface as molecules associate or dissociate. The presence of pS129 and human-to-mouse substitutions at positions 121 and 122 interfered with the binding of antibodies targeting pY125-aSyn and pY136-aSyn, reflected by an increased equilibrium dissociation constant (K_D), as well as corresponding changes in the association and dissociation rate constants (k_{on} and k_{off}). More pronounced inhibitory effects were observed for modifications at closer proximity to the phosphotyrosine residue. In additional BLI analyses, we found that neighboring phosphorylation events altered the affinity of antibodies targeting the AD biomarkers pT181-tau or pT231-tau for their cognate antigen. Our BLI assay addresses challenges associated with antibody cross-reactivity, characterizing binding affinities, kinetics and specificities of various antibodies, while underscoring the importance of using well-characterized antibodies with specific recognition properties for accurate biomarker quantitation.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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Program #/Poster #: PSTR158.05/D32

Topic: C.03. Parkinson's Disease

Support: NIH Grant AG061251
American Parkinsons Disease Association

Title: Sulfated Heparan Sulfate Chains Are Essential For α -Synuclein Pathology Progression

Authors: *S. DIGRASKAR¹, R. BASH², P. DAS⁴, J. HUH¹, J. ESKO⁵, L. A. VOLPICELLI-DALEY⁶, R. M. COWELL³, P. AGUILAR CALVO¹;

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Abstract: The aggregation and cell-to-cell propagation of α -synuclein (α -syn) are central pathological features of Parkinson's disease (PD) and dementia with Lewy bodies (DLB). While extracellular α -syn is known to contribute to disease progression, the specific neuronal receptors involved in α -syn internalization are not fully understood. Heparan sulfate proteoglycans (HSPGs) are glycoproteins that colocalize with α -syn deposits in Lewy bodies and act as receptors for the internalization of α -syn pre-formed fibrils (PFFs) in immortalized cells. However, whether HSPGs play a role in neuronal uptake and α -syn pathology *in vivo* in vertebrate models remains unknown. We hypothesize that HSPGs modulate α -syn pathology by mediating the *neuronal* internalization of α -syn. HSPGs bind to ligands through the sulfate groups in the heparan sulfate (HS) chains. Thus, to explore the contribution of HS in α -syn pathology *in vivo*, we injected PFFs into the striatum of mice that express lower *neuronal* HS sulfation due to a mutation in *Ndst1*, the enzyme required for N sulfation of HS chains (*NdstSynCre*⁺), and mice with physiological levels of sulfation (*NdstSynCre*⁻). At 16 weeks post intrastriatal bilateral PFF injection, *NdstSynCre*⁺ mice showed ~65% less α -syn deposition in the substantia nigra pars compacta (SNpc), ~52% less in the cortex, and ~47% less in the hippocampus, and reduced behavioral deficits as compared to *NdstSynCre*⁻ mice. Decreasing neuronal HS sulfation did not alter the expression of endogenous α -syn, cause neuronal loss, or modify the behavior of uninjected or monomer-injected *NdstSynCre*⁺ mice, indicating that the pathological and behavioral differences observed between PFF-injected *NdstSynCre*⁺ and *NdstSynCre*⁻ mice are specific to α -syn injection and not the *Ndst1* depletion. Our studies provide the first *in vivo* evidence that neuronal HSPGs act as functional receptors for α -syn internalization and accumulation through their sulfated HS chains. These findings highlight HSPG biosynthesis as a potential therapeutic target in synucleinopathies.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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Topic: C.03. Parkinson's Disease

Support: NTU (NTU-CC-114L891304)
The National Science and Technology Council (NSTC 112-2311-B-002-007-MY3)

Title: Investigating the role of Annexin-A2 in pathogenic α -Synuclein propagation

Authors: *A.-F. LI, P.-J. HUANG, Y.-L. SU, C.-T. WANG;
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Abstract: Parkinson's disease (PD), a second common neurodegenerative disorder in humans, is primarily caused by the misfolding and aggregation of human α -Synuclein (h α -Syn) due to its overexpression or pathogenic mutation, such as A53T. Previous studies indicated h α -Syn-A53T exhibits high toxicity owing to the relatively high propagation and aggregation capacity compared to overexpression of wild-type human α -Syn; however, the underlying mechanism remains unclear. To distinguish its unique pathogenesis and toxicity, we aimed to investigate the potential interactors with h α -Syn-A53T. To answer this question, rat pheochromocytoma (PC12) cells were transfected with plasmids using proximity-dependent biotin identification (BioID2), including the control (Ctrl; pCAGEN-flexible linker-BioID2-HA), the wild-type human α -Syn (hWT), and the pathogenic human α -Syn (hA53T). At 72 hr post transfection, we performed liquid chromatography/mass spectrometry (LC-MS) to detect the potential interactors with h α -Syn or h α -Syn-A53T. Subsequent proteomics analysis revealed that compared to hWT, hA53T increased the abundance of specific biotinylated proteins associated with the cytoskeleton and microtubules. Annexin-A2 (ANXA2) exhibited the most significant enrichment and was selected as a candidate in the follow-up experiments. To validate the potential interaction between h α -Syn and ANXA2, we performed immunofluorescence staining to analyze the spatial colocalization between h α -Syn and ANXA2. We found that hWT and hA53T exhibited a higher colocalization ratio (~30-fold) near the plasma membrane than Ctrl. Subsequently, we performed proximity ligation assays (PLA) to analyze *in situ* interaction between h α -Syn and ANXA2. The hWT-overexpressing cells showed significantly higher PLA signal (~30-fold) than Ctrl (0.2%). Furthermore, the hA53T-overexpressing cells exhibited significantly high PLA signal (~2.3-fold) compared to hWT, suggesting that the A53T mutation may further increase the interaction between h α -Syn and ANXA2 compared to wild-type human α -Syn. These results imply that the toxicity of the A53T mutation may be mediated through this unique interaction, providing valuable insights into potential therapeutic targets for PD.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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Program #/Poster #: PSTR158.08/D35

Topic: C.03. Parkinson's Disease

Support: NIH R01DA058143
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NIH R21NS133384

Title: Brain to Periphery Axis: Midbrain Synucleinopathy Modulates Splenic Immunity

Authors: *J. SEIBOLD¹, A. GOPINATH¹, L. PHAN¹, E. J. MILLER¹, D. BORG², B. I. GIASSON⁴, H. KHOSHBOUEI³;

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Abstract: Parkinson's disease (PD) and midbrain synucleinopathies are characterized by progressive loss of substantia nigra (SNc) dopamine neurons. We and others have demonstrated that in PD, loss of SNc dopamine neurons, or chemogenetic activation of these neurons, modulates peripheral immunity through the midbrain-dorsal vagal complex (DVC)-celiac ganglia-spleen axis. Given that splenic immune cells are modulated by midbrain dopamine transmission, and immune cells are sensitive to biogenic amines including dopamine, serotonin, and norepinephrine, we hypothesized that midbrain dopamine loss in synucleinopathy alters splenic immunity and biogenic amine signaling in the spleen. To investigate this hypothesis, C57BL/6 mice received SNc alpha-synuclein preformed fibrils (PFFs) or saline injection. Twelve months post-injection, spleen and brain tissues were collected for histological and immunological assessments. Brains underwent histological analysis to determine alpha-synuclein pathology and its spread along the midbrain-to-DVC axis and SNc-to-striatum via the medial forebrain bundle. To measure the consequences of midbrain synucleinopathy on splenic immunity, we employed flow cytometry to assess changes in the splenic immunophenotype. Consistent with our prior data demonstrating a midbrain-spleen connection via the DVC, we observed spread of alpha-synuclein pathology from midbrain to DVC neurons, suggesting that PFF injection in the SNc could modulate splenic immunity via a midbrain-DVC-spleen axis. In accordance with alpha-synuclein pathology spread in the DVC, we observed splenic hyperplasia, with splenic CD4⁺ T cells significantly shifted toward a T-memory phenotype compared to saline-injected control animals. Ongoing experiments will utilize fast-scan cyclic voltammetry (FSCV) to measure sub-second fluctuations of biogenic amines from isolated splenic T cells in both saline- and PFF-injected male and female mice. These results will assess whether and how splenic dopamine, serotonin, and norepinephrine signaling are modulated in response to alpha-synuclein pathology. Collectively, these studies represent a transformative step in investigating the mechanistic link between dopamine neuron activity and peripheral immunity, a connection

implicated in neurological and neuropsychiatric conditions where dopamine signaling is disrupted.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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Topic: C.03. Parkinson's Disease

Support: Sastry Foundation Parkinson's Disease Research

Title: Modulation of α -Synuclein Toxicity by Polyamine-Interconversion Enzymes in a *Drosophila* Model of Parkinson's Disease

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Abstract: In Parkinson's disease (PD), pathological aggregation of α -Synuclein contributes to progressive neuronal loss. Recent studies have reported elevated polyamine levels in the serum of PD patients, but the role of polyamine metabolism in disease progression remains unclear. Using a *Drosophila* model, we investigated how polyamine-interconversion enzymes (PAIEs) influence α -Synuclein toxicity in neurons. We found that neuronal knockdown of ODC1, SRM, and SMOX improved survival and motor function in α -Synuclein-expressing flies, while knockdown of SAT1 and SMS worsened these phenotypes. α -Synuclein protein levels correlated with the observed toxicity. Overexpression of SAT1 or SMOX significantly reduced α -Synuclein-induced toxicity. Furthermore, RNA-seq analysis revealed distinct pathway alterations associated with SAT1 and SMOX overexpression in the context of α -Synuclein neurotoxicity. These findings highlight the polyamine metabolic pathway and PAIEs as key regulators of α -Synuclein toxicity, offering new insights and potential therapeutic targets for PD.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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Program #/Poster #: PSTR158.10/D37

Topic: C.03. Parkinson's Disease

Support: W81XWH

Title: Age-dependent propagation of α -synuclein pathology from colon to brain in an intracolonic PFF-induced parkinson's disease model

Authors: *W.-Y. BAE¹, W.-H. CHO¹, I. JEONG¹, S. KIM², E. LEE³, M. JANG², K. LEE³, Y.-S. KIM¹;

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Abstract: Aging is the primary risk factor for Parkinson's disease (PD), yet most experimental studies use young animals, limiting insight into age-related pathogenic mechanisms. Moreover, current PD models focus on the small intestine and vagus nerve, overlooking the role of the colon that plays a critical role in influencing microbiome and gut inflammation. Interestingly, a recent study demonstrated that α -synuclein aggregates in fecal samples of early PD patients. In current study, we investigated whether intracolonic administration of α -synuclein preformed fibrils (PFFs) induces PD-like pathology and whether aging influences pathological progression. We used wild-type (WT) and α -synuclein-overexpressing transgenic mice at young and aged time points. PFF exposure successfully induced pathological features in both WT and transgenic mice. In transgenic animals, PFFs led to behavioral deficits, intestinal inflammation, α -synuclein deposition, glial activation, and loss of dopaminergic neurons in the substantia nigra. In WT mice, we observed a consistent reduction in dopaminergic neurons in aged animals compared to young ones. Notably, phosphorylated α -synuclein at serine 129 (pS129) showed that the spread of pathology from the colon to the brain occurred more rapidly in aged mice. Furthermore, we confirmed rapid transmission of pathological α -synuclein from the colonic lumen to enteric neurons and subsequent propagation to the brain via both the vagus nerve and spinal cord. These findings suggest that the enteric nervous system mediates swift, age-dependent gut-to-brain propagation of pathology. This study introduces a novel colon-targeted PD model and highlights the importance of aging and colonic pathways in PD progression, offering potential new avenues for therapeutic strategies.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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Topic: C.03. Parkinson's Disease

Support: KHIDI Grant RS-2023-00266536

Title: Immunoplate-based seed amplification assay for detection of alpha-synuclein in blood

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Abstract: Introduction: The advent of α -synuclein (α Syn) seed amplification assay (SAA) has transformed the landscape of biological diagnosis in Parkinson's disease (PD), enabling broader clinical application. Although detection of α Syn seeds has been successful in cerebrospinal fluid using SAA, however, the results in peripheral fluids and tissues have been inconsistent. The immunoprecipitation (IP)-SAA method generated excitement for the possibility of detecting α Syn seeds in blood samples. However, the reproducibility of the IP-SAA has been in question as many labs worldwide have struggled to produce consistent results with the method. The aim of the study is to develop a novel SAA method for blood-based detection of α Syn. **Methods:** We enrolled 37 patients with PD and 8 healthy controls (HC). Among PD patients, 17 patients were in moderate-to-advanced stage (Hoehn and Yahr stage ≥ 3) and 20 patients were drug-naïve and in early stage. Rather than conducting conventional IP for α Syn aggregates, we precoated the 96-well plate with the MJFR-1 antibody (anti- α Syn antibody, Abcam) and put the plasma directly into the well for immunocapture of α Syn seeds. After a simple wash, the reaction mixture that includes α Syn monomer and thioflavin T was added, followed by SAA cycles. Each sample was tested in triplicate (3 wells per sample) and mean relative fluorescence units (RFU) were calculated. **Results:** The standard curve using synthetic α Syn fibrils showed dose-dependent increase in RFU. We set 50,000 RFU as a cut-off value for positivity for SAA. All moderate to advanced PD patients showed positive results during 96 hours of quaking. Among 20 drug-naïve and early PD patients, 16 patients showed positive results, and 4 patients showed negative results. Among 8 healthy controls, 7 patients showed negative results, and 1 patient positive negative result. Receiver Operating Characteristics (ROC) analysis revealed that the immunoplate-based plasma SAA had an excellent discriminating power between the PD and HC groups: the area-under-the-curve (AUC) 1.000 in the comparison between the moderate-to-advanced PD and HC, the AUC 0.825 in the comparison between the early PD and HC, and the AUC 0.905 in the comparison between all PD and HC. **Discussion:** We demonstrated that the immunoplate-based plasma SAA successfully amplified the seeds from blood to differentiate patients with PD from healthy controls. This new method is less invasive, cheap, and easily accessible so that it can be widely utilized to define synucleinopathy. Larger sample size and external validation are essential to define its diagnostic performance and reliability.

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Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

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The National Science and Technology Council (NSTC 112-2311-B-002-007-MY3)

Title: The propagation of pathogenic α -Synuclein in a sporadic Parkinson's disease rat model

Authors: *Y.-C. CHENG, P.-J. HUANG, Y.-H. CHEN, Y.-J. CHEN, C.-T. WANG;
Inst. of Mol. and Cell. Biol., Natl. Taiwan Univ., Taipei, Taiwan

Abstract: Parkinson's disease (PD) is a neurodegenerative disease that progresses through four stages, including the prodromal, early, middle, and late stage. The etiology of PD is attributed to the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc) with the presence of Lewy Bodies, mainly composed of human α -Synuclein (α Syn) aggregates due to the pathogenic mutation or overexpression. PD exhibits motor and non-motor symptoms such as visual defects and constipation, suggesting that α Syn aggregates can propagate via bio-fluids or neural connections. However, the time course of α Syn propagation from brain to other systems remains unclear. To answer this question, we established a rat model to mimic the sporadic PD at adulthood by expressing α Syn or its pathogenic mutants in the rat right-side SNc using *in vivo* electroporation, including the sham control (pCAGEN-HA or pCAGEN-BioID2-HA), α Syn, α Syn-A53T, and α Syn-Penta (A30P, E46K, H50Q, G51D, A53T). Successful transfection was confirmed by the presence of α Syn or its aggregates (labeled by pS129) using immunostaining. At 5-7 days post transfection, we found α Syn aggregates in the right-side SNc of the rats expressing α Syn or α Syn-A53T, but not in the sham control. At 2-3 months post transfection, the rats expressing α Syn or α Syn-A53T showed motor defects, suggesting the prodromal stage within 2 months post transfection. Because α Syn can propagate to other organs, we detected retinas, optic nerves, or sigmoid colon to determine the time course of propagation during the prodromal or early stage of PD. We harvested the optical nerves, retinas, and sigmoid colon from transfected rats and determined the presence of α Syn aggregates by immunostaining. At 1 month of transfection, α Syn was found in the choroid of the rats expressing α Syn. At 3 months of transfection, α Syn and its aggregates were found in the choroid, retinas, and optic nerves of the rats expressing α -Syn and its mutants, with relatively high immunoreactivity in the left side compared to the right side, suggesting that α Syn originates from the right SNc. Moreover, the inner plexiform layer and ganglion cells in the left retina displayed the α -Syn immunoreactivity, suggesting that pathogenic α -Syn propagates across retinal neural circuits. In addition, α -Syn was also detected in the duodenum, cecum, and sigmoid colon within 1 month. Thus, at the prodromal stage PD stage, α Syn may propagate from the midbrain to retinas and guts, providing the ways for early PD diagnosis.

Disclosures: Y. Cheng: None. P. Huang: None. Y. Chen: None. Y. Chen: None. C. Wang: None.

Poster

PSTR158: Mechanisms and Propagation of Alpha-Synuclein

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.13/D40

Topic: C.03. Parkinson's Disease

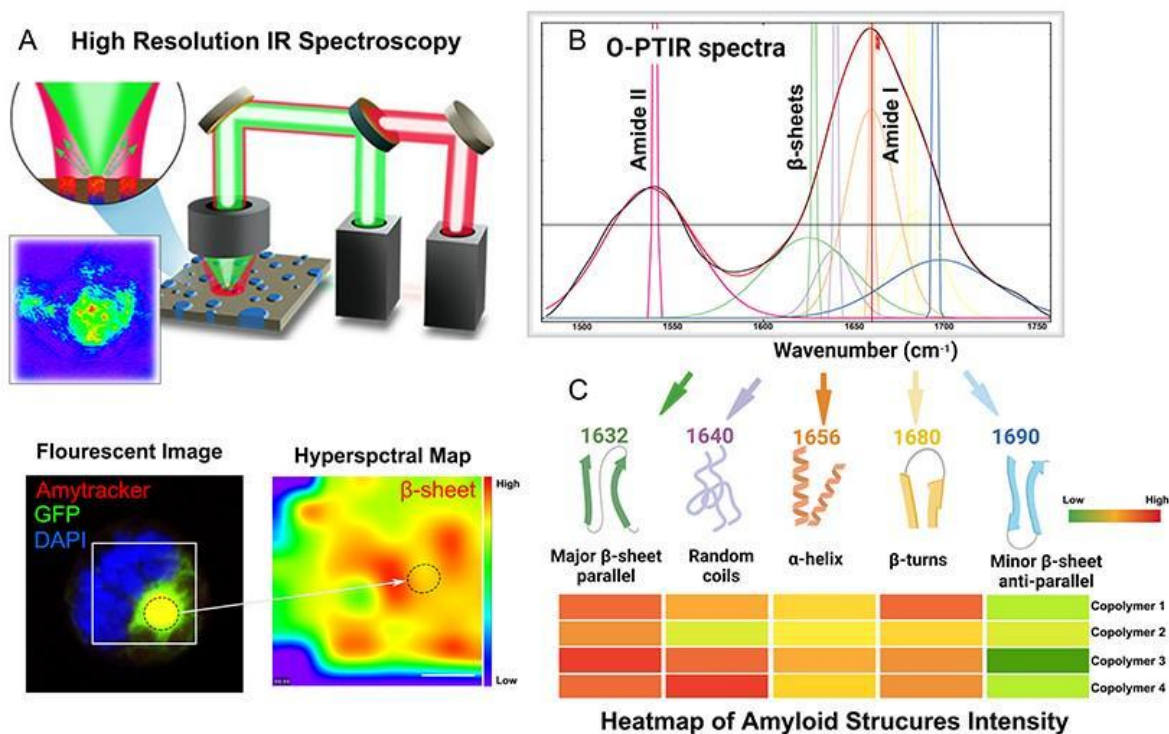
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JPND 2024-02266

Title: Strain-distinct alpha-synuclein and tau cross-seeding uncovered by optical photothermal infrared sub-micron imaging

Authors: X. ZHAN¹, W. LI², E. HATTERER³, J.-P. COURADE⁴, K. PICHÉ⁵, O. KLEMENTIEVA¹, *J.-Y. LI¹;

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Abstract: The co-occurrence of α -synuclein (α Syn) and Tau in synucleinopathies and tauopathies suggests a complex interplay between these proteins. Their cross-seeding enhances fibrillization, leading to the formation of diverse amyloid-specific structures enriched with β -sheets, which may influence their biological functions. However, existing tools cannot differentiate structural polymorphs directly in cells, as conventional microscopic approaches have limitations in providing structural insights into aggregates. As a result, a structurally relevant characterization of amyloids in their native cellular environment has not yet been achieved. In this study, we characterize the structural rearrangements of newly formed α Syn inclusions cross-seeded by different α Syn and Tau preformed fibrils (PFFs) directly in cells, using a correlative approach that combines sub-micron optical photothermal infrared (O-PTIR) microspectroscopy and confocal microscopy. We found that hybrid PFFs synthesized from α Syn, and two Tau isoforms (Tau3R and Tau4R) exhibit variations in α Syn and tau composition. Specifically, structural polymorphs composed of α Syn and Tau3R exhibit the highest β -sheet content and most potent seeding potency, leading to enhanced phosphorylation within cellular inclusions. Importantly, we demonstrate that cellular inclusions inherit structural motifs from their donor seeds and exhibit distinct spatial and structural evolution. By providing subcellular-resolution structural imaging of amyloid proteins, our study uncovers divergent mechanisms of α Syn aggregation induced by α Syn/Tau PFFs in both mixed and hybrid formats.



Disclosures: **X. Zhan:** None. **W. Li:** None. **E. Hatterer:** A. Employment/Salary (full or part-time): Eric Hatterer is an employee of LCB/Novimmune. **J. Courade:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jean-Philippe Courade is owning stocks of Discoveric bio alpha. **K. Piché:** A. Employment/Salary (full or part-time): Kristin is an employee of StressMarq Biosciences. **O. Klementieva:** None. **J. Li:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); The authors received funding from Discoveric bio alpha..

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.01/D41

Topic: C.03. Parkinson's Disease

Title: Relationship between ventricular and thalamic nuclei volumes as assessed by Brainlab amongst a population undergoing Focused Ultrasound (FUS) or Deep Brain Stimulation (DBS) for Parkinson's Disease (PD) or Essential Tremor (ET).

Authors: ***E. L. HARGREAVES**¹, G. ANTONY², M. BRENNAN², C. RAICHLE², R. ZHU², D. DOLCE¹, S. F. DANISH¹;

¹Neurosurg., Jersey Shore Univ. Med. Ctr. (JSUMC), Neptune, NJ; ²Hackensack Meridian Sch. of Med., Hackensack, NJ

Abstract: Ventriculomegaly in the elderly, in the absence of raised cerebral spinal fluid pressure, is typically attributed to reductions in cortical mantle volumes. Here, we examine whether there are any concordant differences in subcortical structure volumes. Specifically, those structures and white matter tracts surrounding the third ventricle. One hundred candidates for FUS or DBS diagnosed with either PD or ET underwent prenavigation scans that involved thin slice T1-weighted Fast Gray Matter Acquisition T1 Inversion Recovery (FGATIR) and/or T1-weighted Fast Spoiled Gradient (FSPGR) axial sequences on a GE 3T Discovery Machine. Candidates were 66 males and 34 females, 52 were DBS candidates and 48 were FUS candidates and 45 were diagnosed with PD and 55 were diagnosed with ET. The Brainlab DBS-Post-op Review module within the Boston Scientific DBS programming platform was used to generate subcortical segmentation volumes of the: Internal Capsule (IC), Caudate, Globus Pallidus (GP externa & interna), Red Nucleus (RN), Putamen, Substantia Nigra (SN pars reticulata & compacta), Subthalamic Nucleus (STN), Thalamus and Anterior (ATN), Ventral Intermediate (VIM), Ventral Posterior Medial (VPM), Ventral Posterior Lateral (VPL) thalamic nuclei, anterior and posterior Commissural (AC/PC) length and the ventricular volume. Ventriculomegaly was defined as where the linear regression slope was greatest between the AC/PC distance and ventricular volume. The determined threshold of 60cm³ ventricular volume allowed for 19 of the 100 candidates to be classified as having ventriculomegaly (n=19, ave=92.21cm³) versus those without (n=81, ave=34.56cm³). Chisquare analyses revealed that more FUS candidates than DBS candidates and more candidates diagnosed with ET than diagnosed with PD were classified as having ventriculomegaly. Although there was a trend to suggest that males were more likely than females to exhibit ventriculomegaly, this difference did not reach statistical significance. Surprisingly, none of the IC, GPe, GPi, or Putamen showed differences between those with ventriculomegaly versus those without. The thalamus itself also exhibited no differences. However, individuals with ventriculomegaly were shown to have statistically larger thalamic nuclei: ATN (139.47%), VIM (116.78%), VPL (118.70%), and VPM (112.53%). Similarly, the caudate exhibited a 110.78% increase in volume for those with ventriculomegaly. Analyses continue to determine which dimensions account for the enlarged volumes, within the thalamic nuclei. These results may have implications for DBS and FUS targeting of VIM in individuals with Ventriculomegaly.

Disclosures: E.L. Hargreaves: None. G. Antony: None. M. Brennan: None. C. Raichle: None. R. Zhu: None. D. Dolce: None. S.F. Danish: F. Consulting Fees (e.g., advisory boards); Medtronic.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.02/D42

Topic: C.03. Parkinson's Disease

Title: Meta-analysis of exercise effects on cognition in persons with parkinson's disease

Authors: *S. O. AHMAD¹, D. L. STILES², K. BROWN³;

¹Occup. Sci. and Occup. Therapy, ²St. Louis Univ., Saint Louis, MO; ³St. Louis Univ., Perryville, MO

Abstract: Background: Parkinson's disease (PD) is a debilitating neurodegenerative disorder affecting millions of people worldwide. PD results in motor and cognitive dysfunction. While there is no proven cure for PD, it is widely agreed upon that aerobic exercises and occupations can help slow the progression of the disease and keep some motor-related symptoms at bay. The most effective forms of exercise to slow the progression of motor symptoms in Parkinson's disease have also been studied. Research Question: This research article aims to compare the differences in outcomes of exercise on Motor versus Cognitive outcomes in Parkinson's Disease, as evaluated by Meta-analysis. Methods: Key terms were Parkinson's Disease and exercise terms. These search terms were then entered to electronic databases: Ovid MEDLINE, SCOPUS, and CINAHL in from March 2018 to May 2023. An ancestral bibliography was also performed. Results: Two reviewers screened the title and abstract records (n=528) found in the initial search. Our review identified 18 studies which met inclusion criteria for meta-analysis. The meta-analysis, found a negative overall effect on patients with PD ($d = -0.03$), and was not significant, CI95% of $-0.13 < \mu < 0.08$, $p > .05$, as the CI includes zero. Additionally, the homogeneity analysis was not significant, $Q(17) = 2.83$, $p > .05$.

Disclosures: S.O. Ahmad: None. D.L. Stiles: None. K. Brown: None.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.03/D43

Topic: C.03. Parkinson's Disease

Support: Swiss National Science Foundation (project number: PZ00P3_202166)

Title: Subthalamic low frequency activity indexing the acute neuropsychiatric state in Parkinson's disease

Authors: *E. BERNASCONI, A. AVERNA, G. TINKHAUSER;
Dept. of Neurol., Univ. Hosp. Bern, Bern, Switzerland

Abstract: Background: The relationship between neurophysiological activity in the subthalamic nucleus (STN) and motor symptoms in Parkinson's disease (PD) patients implanted with deep brain stimulation (DBS) electrodes has been well described. In contrast, the link with neuropsychiatric symptoms in PD is poorly understood. Objectives: To investigate the link between STN activity recorded in chronically implanted PD patients and their neuropsychiatric states / fluctuations. Methods: Resting state STN local field potentials (LFPs) were recorded in

14 PD patients implanted with a brain-sense capable stimulator “Medtronic Percept” in the OFF and ON dopaminergic medication state. The neuropsychiatric states were evaluated using the Neuropsychiatric Fluctuation Scale and the relationship to theta / alpha activity was analyzed. Results: The neuropsychiatric state was significantly improved ON dopaminergic medication. In the medication ON state, STN theta power was significantly increased compared to the medication OFF state. A negative relationship was observed between theta / low alpha power and the Neuropsychiatric State Score in the OFF medication condition. This relationship was most evident with recordings of the DBS electrode's ventral contact pair. Conclusion: Sub-beta frequencies likely derived from the limbic part of the STN can be indicative of acute neuropsychiatric states and may potentially inform future management of DBS patients.

Disclosures: **E. Bernasconi:** None. **A. Aversa:** None. **G. Tinkhauser:** Other; G.T. received financial support from Boston Scientific and Medtronic not related to the present work. Research agreement with RuneLabs not related to the present work, G.T. receives funding from the Swiss National Science Foundation (project number: PZ00P3_202166) and Swiss Parkinson Association..

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.04/D44

Topic: C.03. Parkinson's Disease

Support: NINDS UH3NS103468
NINDS UH3NS129898
Devices donated by Medtronic PLC

Title: Adaptive deep brain stimulation preserved speech intelligibility.

Authors: ***R. RODRIGUEZ CAPILLA**¹, T. W. KEARSE³, J. J. PETERS³, K. MITCHELL², W. M. GRILL³, D. A. TURNER¹, S. L. SCHMIDT³;
¹Neurosurg., ²Neurol., Duke Univ. Med. Ctr., Durham, NC; ³Biomed. Engin., Duke Univ., Durham, NC

Abstract: Deep brain stimulation (DBS) is the primary surgical treatment for the motor symptoms of Parkinson's disease (PD). The subthalamic nucleus (STN) and the globus pallidus (GP) are the most common targets for DBS. While DBS improves the quality of life of patients with PD, it can also cause side effects. Continuous DBS (cDBS) can reduce speech intelligibility and thus hinder the ability of patients to communicate. Adaptive (a)DBS aims to reduce side effects by reacting to patients' instantaneous needs and potentially improving speech intelligibility. The majority of studies of speech in PD patients focused on audio features (e.g., fundamental frequency) rather than intelligibility. We aimed to quantify speech intelligibility (SI) across several cDBS and aDBS paradigms. Here we show a novel method to quantify

intelligibility that automates the process of transcribing and scoring speech, and is sensitive to small differences in intelligibility. All study activities were approved by the FDA and Duke University Health System IRB, and all participants provided written informed consent. Five participants with PD and dual-target (DT) DBS (Medtronic Summit RC+S) participated in monthly clinical research visits. We recorded speech and local field potentials (LFPs) from the STN under five DBS conditions: three cDBS conditions - 100% clinical amplitude at 125 Hz (i.e., clinical settings), 100% amplitude at 75 Hz, and 50% amplitude at 125 Hz - and two aDBS conditions - a reinforcement learning (RL) controller and the embedded, threshold-based controller mode available in the RC+S firmware. After a 300 s wash-in, we prompted participants to read a set of IEEE/Harvard sentences with a microphone set ~50 cm away from their mouths. Participants performed hand grasps for ~10 s after completion of the speech task. We simultaneously recorded LFP during the trial. We developed a computational pipeline using Vosk ASR (Alpha Cephei) to extract speech metrics and transcribe audio. A linear mixed effects model revealed no significant reduction in SI during aDBS compared to 100% cDBS. Only 50% cDBS reduced SI compared to 100% cDBS (Fixed effect size: -0.042 ± 0.016 , $p = 0.0083$). Similarly, hand grasp speed was reduced by 50% cDBS compared to 100% cDBS (-0.6176 ± 0.1739 , $p = 0.0005$). However, both aDBS conditions (and 75 Hz cDBS) were as effective as 100% cDBS in reducing bradykinesia. These results suggest that while clinical settings improved SI, there was no further benefit when using aDBS at levels that maintained bradykinesia suppression. These results highlight how DBS affects intelligibility in persons with PD and provide a new automated approach for analysis of intelligibility.

Disclosures: R. Rodriguez Capilla: None. T.W. Kears: None. J.J. Peters: None. K. Mitchell: None. W.M. Grill: None. D.A. Turner: None. S.L. Schmidt: None.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.05/D45

Topic: C.03. Parkinson's Disease

Support: R01NS100996

Title: Wired for Emotion: Fiber Pathways Linking Deep Brain Stimulation Targets to Apathy Changes

Authors: *K. R. JENKS¹, R. FERNANDEZ-GAJARDO², K. E. GARTNER², J. S. NEIMAT³, N. C. VAN WOUWE⁴;

¹Interdisciplinary Program in Translational Neurosci., ²Neurolog. Surgery, Univ. of Louisville, Louisville, KY; ³Neurosurg., Univ. of Louisville, LOUISVILLE, KY; ⁴Neurosurg., Univ. of Louisville, Louisville, KY

Abstract: Parkinson's disease (PD) primarily affects the function of the basal ganglia, a cluster of brain areas including the subthalamic nucleus (STN) and the globus pallidus internus (GPi). One intervention method involving these specific targets, deep brain stimulation (DBS), has provided motor benefits in patients with PD. However, much is still unknown regarding the behavioral and cognitive consequences of DBS implantation surgery. The objective of this study is to compare apathy changes pre-intervention to post-intervention between the STN and GPi, and to further examine how changes in apathy are reflected in cortical-striatal white matter tracts associated with DBS. Fourteen patients with PD were implanted unilaterally (n=1) or bilaterally (n=13) with depth electrodes in the STN (n=7) or GPi (n=7). Apathy scores were evaluated via the Starkstein Apathy Scale before surgery and at least 6 months after surgery for each patient. The stimulation-based volume of tissue activated area (VTA) of each target was analyzed using both the Lead-DBS and Lead-Group software. Future fiber tract connectivity analyses will determine which white matter tracts are activated by the VTAs (using the PPMI 85 Ewert 2017 structural connectome) and how these tracts correlate with changes in apathy. Furthermore, we will use a connectome to identify anatomical regions associated with changes in apathy by implementing a voxel-wise sweet spot mapping analysis. Initial results show a significant overall increase in apathy from pre-intervention to post-intervention, but not a significant interaction between apathy and target ($p = 0.006$, $F_{1,12} = 11.12$, see Fig. 1). Based on visual inspection of the activated tracts for both GPi and STN subgroups, left-lateralized tracts seem to be associated with these changes in apathy. Discovering the white matter tracts involved with apathy changes post-DBS will be an important step in optimizing DBS programming in the clinic and may also lead to a more patient-centered treatment approach.

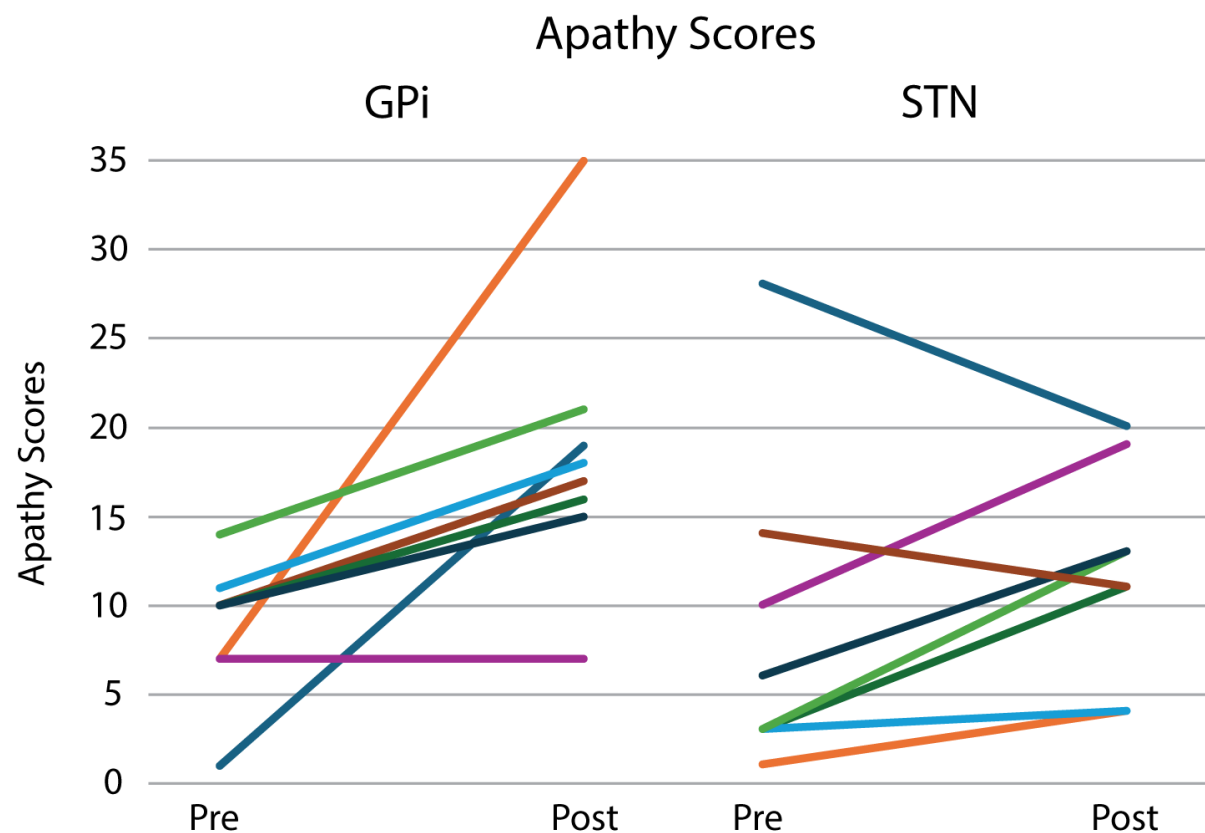


Figure 1. Individual differences in pre-intervention and post-intervention apathy.

Disclosures: **K.R. Jenks:** A. Employment/Salary (full or part-time): University of Louisville. **R. Fernandez-Gajardo:** A. Employment/Salary (full or part-time): University of Louisville. **K.E. Gartner:** A. Employment/Salary (full or part-time): University of Louisville. **J.S. Neimat:** A. Employment/Salary (full or part-time): University of Louisville. **N.C. Van Wouwe:** A. Employment/Salary (full or part-time): University of Louisville.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.06/D46

Topic: C.03. Parkinson's Disease

Support: NIH Grant R01 DC017718

Title: Motor outcomes as a function of lead location in subthalamic nucleus deep brain stimulation for Parkinson's Disease

Authors: ***I. FARMER**¹, F. TABASI¹, A. ROHL¹, K. TJADEN³, C. PATTERSON⁴, D. M. CORCOS⁵, J. D. GREENLEE²;

²Dept Neurosurg, ¹Univ. of Iowa, Iowa City, IA; ³Univ. of Buffalo, Buffalo, NY; ⁴Univ. of Pittsburgh, Pittsburgh, PA; ⁵Dept. of Physical Therapy/Human Movement, Northwestern Univ., Chicago, IL

Abstract: We aimed to evaluate how electrode location relates to change in motor function in subthalamic nucleus deep brain stimulation (STN-DBS) for Parkinson's Disease (PD). Based on prospectively measured functional motor outcomes, we demonstrate how lead location in the STN relates to motor outcomes. Forty bilateral STN-DBS patients with diagnoses of idiopathic PD completed pre- and post-operative evaluations of motor function as measured by the MDS-UPDRS Part III total and sub scores. All assessments were done in the medication OFF state, and post-operative assessments were completed 12 months after electrode implantation in both DBS ON and DBS OFF conditions. Using patient's clinical imaging (co-registered pre-op MRI and post-op CT scans) with LeadDBS (v 3.1), we localized lead placement in Montreal Neurological Institute (MNI) space. Further, we analyzed the relationship between post-op MDS-UPDRS Part III score and active lead contact location using mixed effects modeling. Additional included predictors included age, time since diagnosis, pre-op MDS-UPDRS score, total electrical energy delivered (TEED), levodopa equivalent daily dose (LEDD), and DBS condition (ON vs. OFF). From this large cohort of STN-DBS patients, we demonstrate the relationship between DBS lead location and clinical motor outcomes at 12 months post-operatively.

Disclosures: **I. Farmer:** None. **F. Tabasi:** None. **A. Rohl:** None. **K. Tjaden:** None. **C. Patterson:** None. **D.M. Corcos:** None. **J.D. Greenlee:** None.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.07/D47

Topic: C.03. Parkinson's Disease

Title: Dual Task Gait Performance and Cognitive Function in People with Parkinson's disease

Authors: ***J. BARAJAS**¹, D. S. PETERSON¹, J. WELLER², M. GUDESBLATT², E. OFORI¹;
¹Arizona State Univ., Phoenix, AZ; ²Neurol. Dept., NYU Sch. of Med., New York, NY

Abstract: The addition of a cognitive task can impair gait and increase fall risk for people with Parkinson's disease (PwPD). Prior research has shown that fall-prone PwPD exhibit reduced executive function and attentional capabilities during dual task gait. Understanding the cognitive processes associated with dual task gait performance is critical for reducing the risk of falls in PwPD. Thus, the purpose of this analysis is to examine the preliminary relationships between cognitive function and dual task gait performance in PwPD. Participants (N = 74) completed cognitive assessments that measured global cognition, memory, executive function, visual spatial, verbal function and attention. Gait was assessed under dual task conditions involving serial subtraction (by 3's and 7's) and verbal fluency (animal naming) while walking. Gait outcomes included stride velocity, dual task double support, dual task gait velocity, dual task step length variability, % change velocity, % change double support, % change Functional Ambulation Performance (FAP) and % change step width. Pearson correlations were used to explore associations between cognitive domains and dual task gait outcomes. Partial correlations controlling for age and sex were also performed. Preliminary analyses revealed two significant relationships involving memory. Higher memory scores were positively associated with % change double support ($r=0.412$; $p=0.010$) and negatively associated with % change FAP ($r=-0.323$; $p=0.048$). No other cognitive domains were significantly associated with dual task gait outcomes. These findings suggest that memory may play a unique role in dual task walking in PwPD and contributes to our understanding of dual task interference. Further investigation into this relationship may inform fall risk screenings and future fall prevention interventions.

Disclosures: **J. Barajas:** None. **D.S. Peterson:** None. **J. Weller:** None. **M. gudesblatt:** None. **E. Ofori:** None.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.08/D48

Topic: C.03. Parkinson's Disease

Support: Fixel-Eagles Award

Title: Association of Pavlovian Bias with Apathy and Impulsivity in Patients Receiving Deep Brain Stimulation for Parkinson's Disease

Authors: *C. FLEETING¹, R. S. EISINGER², M. WOOLRIDGE¹, A. GUNDUZ¹;

¹Univ. of Florida, Gainesville, FL; ²Neurol., Univ. of Pennsylvania, Philadelphia, PA

Abstract: Non-motor symptoms of Parkinson's disease (PD), such as impulsivity and apathy, are prevalent and contribute significantly to poor quality of life. A significant barrier to scientific progress is the inability to track these conditions within a timeframe that allows for critical intervention. Recent work has established Pavlovian Bias as a measure of impulsivity in PD with high time resolution. We aim to analyze whether Pavlovian Bias can also serve as a marker for apathy in PD.

A sample of 29 PD patients who received Deep Brain Stimulation (DBS) surgery completed a Go/No-Go task at multiple post-operative visits. We analyzed the relationship between task performance and both the Questionnaire for Impulsive-Compulsive Disorders in PD-Rating Scale (QUIP-RS) and Apathy Scale (AS) scores for impulse control disorder (ICD) and apathy, respectively. We used a mixed-effect model to characterize how each score affects both Action-Reward and Inaction-Avoid-Loss Bias while controlling for age, gender, and time. Relationships were further quantified by generalized linear regression, Spearman and partial correlation, and in terms of comorbidity with Fisher Exact.

When considered independently, both QUIP-RS ($p < 0.05$) and AS ($p < 0.05$) had a significant relationship with Action-Reward but not with Inaction-Avoid-Loss Bias. When considered together with controls and AS-QUIP-RS interaction, AS was found to have a strong partial correlation with Action-Reward bias ($p < 0.01$). Additionally, a significant correlation arose between AS and Inaction-Avoid-Loss Bias ($p < 0.05$), while QUIP-RS remained uncorrelated. Apathy and ICD were highly comorbid ($p < 0.001$) in patients receiving both medical and DBS therapy. QUIP-RS and AS retained correlation ($p < 0.001$) and positive linearity ($p < 0.001$) even when medication metrics and the controls listed above were considered.

These results suggest that Pavlovian Bias retains a strong correlation with established clinical measures of AS and QUIP-RS. Tasks that measure Pavlovian Bias may be used as near real-time as alternatives to monthly self-reported scales. Additionally, despite strong comorbidity, differential effects on Avoid-Loss Bias suggest that apathy and ICD may be assessed simultaneously. More data is needed to generalize these findings, and the impulsivity-apathy interaction term is considerable, calling for further study. In all, this work supports broader clinical and academic use of Pavlovian Bias when assessing apathy and impulsivity during DBS for PD.

Disclosures: C. Fleeting: None. R.S. Eisinger: None. M. Woolridge: None. A. Gunduz: None.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.09/D49

Topic: C.03. Parkinson's Disease

Support: Wild Blueberry Association of North America

Title: Does wild blueberry supplementation improve motor symptoms and performance in people with Parkinson's disease?

Authors: *T. M. GAUSS¹, R. N. ADDISON², D. K. INGRAM³, R. WHIDDON⁴, G. CALEGAN⁴, C. M. CHAMPAGNE³, J. FRANCIS¹, J. M. HONDZINSKI¹;
¹Louisiana State Univ., Baton Rouge, LA; ²DePauw Univ., Greencastle, IN; ³Pennington Biomed. Res. Ctr., Baton Rouge, LA; ⁴NeuroMedical Ctr., Baton Rouge, LA

Abstract: Current medical treatments for Parkinson's disease (PD) primarily focus on increasing dopamine production; however, these treatments often cause side effects such as dyskinesias and balance dysfunction, prompting efforts to explore alternative therapeutic options. While synthetic antioxidant therapies show limited success in counteracting oxidative stress and inflammation, linked to environmental toxins that can contribute to PD, dietary sources of antioxidants, especially polyphenol-rich foods like blueberries, demonstrate neuroprotection in preclinical models. Wild blueberry (BB) ingestion shows improved motor function, reduced oxidative stress and inflammation, and enhanced dopamine activity in animal studies as well as benefits in metabolic, cardiovascular, and cognitive health in humans. Clearly, BB ingestion holds promise for improving motor performance in PD. We investigated whether daily supplementation of BB powder over 8 weeks could improve functional motor performance and PD motor symptoms compared to placebo. Participants with PD were pseudo-randomized (i.e., sex-matched) to receive either BB powder or Placebo. Functional assessments, including standing postural sway with eyes open and closed, gait during normal, fast, and dual-task walking, and clinical assessments were performed before and after intervention while medicated. Outcomes from the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III) on and off medication gave insight into changes in motor symptoms. A mixed model repeated measures ANOVA (GROUP-BB, Placebo x TEST-pre, post) revealed significant effects of TEST on motor function ($P < 0.05$), including an over 6-point decrease UPDRS-III scores off-medication and 7.1 cm/s increase in gait velocity during fast walking. The significant TEST effect for anterior-posterior sway variability with eyes open and interaction for stride length during fast walking ($P < 0.05$) only revealed trends for a decrease in anterior-posterior sway variability with eyes open and decrease in stride length for BB. These data provide evidence that our participants resembled other people with PD, who can appear particularly responsive to expectancy influences and may obscure subtle motor changes between groups. Unlike animal research, the 8-week supplementation period and dosage seemed insufficient to produce obvious motor differences between groups. Subsequent blood analyses may provide greater insight into these outcomes and help determine whether longer and/or altered dose interventions are needed to produce potential benefits of wild blueberry supplementation on motor function in PD.

Disclosures: T.M. Gauss: None. R.N. Addison: None. D.K. Ingram: None. R. Whiddon: None. G. Calegan: None. C.M. Champagne: None. J. Francis: None. J.M. Hondzinski: None.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.10/D50

Topic: C.03. Parkinson's Disease

Support: APDA P09
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Udall Parkinson's Foundation Research Center of Excellence
NIH (NINDS) T32 NS115724

Title: Dbs lead localization using dbs local evoked potentials: a deep learning approach

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Abstract: Deep Brain Stimulation (DBS) surgery is an established procedure that uses electrical stimulation via implanted electrodes in deep brain structures to alleviate symptoms of diseases such as Parkinson's (PD). While being greatly successful, a challenge in DBS surgery is precise electrode placement in the target structure, as incorrect placement of the electrodes can have adverse side effects or no therapeutic effect. Recent studies have revealed a novel biomarker known as DBS Local Evoked Potentials (DLEPs), which show strong potential for functional mapping while the patient is both asleep and under anesthesia. However, two issues persist. The first is extracting evoked potentials (in this case, DLEPs) from recorded local field potentials (LFPs) due to stimulation artifacts, and the second is effectively utilizing these DLEPs to localize electrodes. We designed two deep-learning approaches to tackle these issues. The models were trained on LFP data from 13 PD subjects undergoing bilateral STN implantation surgery, while delivering 30 bursts of 130Hz stimulation (10 pulses) at 1mA for each contact on a DBS lead. Only depth information was considered, leading to 4 depth levels for each DBS lead by averaging the LFPs recorded on directional contacts at the same depth and level. The first approach was a novel convolutional neural network (CLEARNet), which was trained on raw LFP data to predict stimulation artifacts. The cross-validation average root mean square error (RMSE) and relative RMSE of the model were 99.04 (SD=18.82) and 0.21 (SD=0.08), respectively. The second deep-learning approach (Lead Finder) is an encoder classifier, which uses convolution and LSTM layers to encode and learn spatiotemporal features. This network is trained on DLEPs extracted from LFPs to predict the voxel where the DLEP originates. The

model's average five-fold cross-validation accuracy and F1 score were 68% (SD=0.98%) and 68% (SD=1%), respectively, with random chance being 4.5%. CLEARNet shows great potential for the removal of stimulation artifacts from any recorded LFPs across patient populations and electrode geometries. Lead Finder shows promising applications in accurate intraoperative localization of electrodes, which can improve surgical implantation and prevent side effects and revision surgeries.

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Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

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Topic: C.03. Parkinson's Disease

Support: NRF grant funded by the Korean government (MIST) (No. 2021R1C1C1011822)

Title: High-intensity interval training enhances executive function and brain connectivity in early-stage Parkinson's disease patients: a preliminary intervention study

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Abstract: Parkinson's disease (PD) is characterized by motor symptoms such as tremor and rigidity. However, non-motor symptoms-including cognitive impairment-can further worsen patients' quality of life. Exercise has emerged as a promising non-pharmacological intervention to address these issues, yet the neurobiological mechanisms by which different exercise intensities impact cognitive function remain unclear. This study aimed to explore how moderate intensity continuous training (MICT) and high-intensity interval training (HIIT) influence executive function and resting-state functional connectivity in early PD, compared to usual care (UC). Thirty-three early PD patients participated in a 6-month intervention and underwent assessments of aerobic capacity (VO₂peak), executive performance (Stroop task), and high-resolution resting-state functional MRI (rs-fMRI). Both MICT and HIIT improved aerobic capacity compared to UC. Only HIIT led to significant improvements in executive function: Stroop incongruent condition reaction time significantly decreased ($p<0.01$) and error rate decreased ($p=0.02$), resulting in improved inverse efficiency scores ($p=0.04$). Rs-fMRI analysis revealed that HIIT showed significant increases in functional connectivity strength between the frontoparietal and visual networks ($t=4.5$, $p<0.05$), as well as increased participant coefficient in

the visual network ($t=4.5$, $p<0.05$), indicating heightened network integration. In conclusion, this preliminary investigation suggests that HIIT uniquely enhances executive function and promotes brain network reorganization in early PD beyond the benefits of aerobic alone. These findings suggest the potential of HIIT as a targeted approach to preserve cognitive function and improve quality of life in PD through network-level adaptations.

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PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.12/D52

Topic: C.03. Parkinson's Disease

Support: MJFF-020020
Edward and Barbara Bell Endowed Chair

Title: Characterizing the neural signature of Parkinsonian freezing of gait during an immersive virtual reality paradigm

Authors: ***M. MILLER KOOP;**
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Abstract: Freezing of gait (FOG) is among the most disabling, least understood, and poorly treated symptoms of Parkinson's disease (PD). Novel deep brain stimulation devices (adaptive-DBS, aDBS) provide new potential for effectively treating FOG as they sense neural signals in real time and provide stimulation in response to patient-specific pathological neural activity. A key barrier to using adaptive DBS for FOG treatment is the limited understanding of the underlying subthalamic nucleus (STN) activity related to FOG as acquiring neural signals during FOG events is challenging. FOGs triggers are multi-factorial, vary between individuals, and are difficult to replicate in clinical settings. The Cleveland Clinic - Virtual Home Environment (CC-VHE) Platform was developed to address these challenges by combining an omnidirectional treadmill with immersive virtual reality (VR) paradigms to induce FOG through tasks that were loaded with emotional (Anxiety), cognitive (Dual-task), and physical triggers to determine if the neural signals related to FOG varied across different triggers. In eight PD patients with the Medtronic Percept system, STN local field potential recordings (STN-LFPs) were collected during 167 FOG events with a total freeze duration of 1028 s. Combining STN-LFP data across all modules revealed that alpha-beta band power (8-30 Hz) was elevated by 28% ($p<0.05$) during FOG compared to walking. Post-hoc pairwise comparison revealed significant increases in the alpha-beta power during FOG compared to Walking in each module with the Dual-task module demonstrating the largest increase (41%, $p<0.01$) followed by the Anxiety (24%, $p<0.01$) and Physical (23%, $p<0.01$) module, resulting in a significant difference between the Dual-task and

Physical alpha-beta power ($p < 0.01$). Significant differences in the increase in alpha-beta band power between the modules during FOG suggest that the neural signature of FOG varies based on the environmental stimuli. Identifying the unique neural signatures underlying FOG will advance its treatment.

Disclosures: M. Miller Koop: None.

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PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

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Program #/Poster #: PSTR159.13/D53

Topic: C.03. Parkinson's Disease

Title: A stereotaxic brain atlas for a novel mouse model of Parkinson's disease

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Abstract: Advanced Parkinson's disease still represents a huge burden for patients, as it displays motor deficits that often lead to falls and loss of independence. Progress in the treatment of such symptoms has been hindered by the lack of preclinical mouse model that faithfully replicates these impairments and their progressive onset. Current rodent models of PD are not clinically relevant and do not adequately replicate disease progression or exhibit clear gait and balance impairments. We recently adopted a new transgenic mouse model (cNdufs2^{-/-}) that develops key features of progressive parkinsonism, including gait and balance deficits as well as freezing of gait, allowing us to investigate circuit-level dysfunctions. While using standard stereotaxic coordinates for brain surgery, we quickly realized that the skull and brain size and anatomy of these animals diverged significantly from existing mouse brain atlases. To address this, we developed a stereotaxic brain atlas tailored to this model by using high-resolution anatomical MR imaging at 9.4 Tesla with a cryoprobe, achieving 50-micron isotropic resolution, combined with microCT imaging of the skull. The datasets were co-registered and aligned to the Allen Brain Atlas. We anticipate that this new atlas will be a valuable tool for stereotactic procedures in this promising Parkinsonian mouse model. It has already enabled reliable DBS, viral injections,

and lens implantations. More importantly, it allowed us to resume the experiments we had to pause, and finally move forward in exploring the circuits we set out to study.

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Topic: C.03. Parkinson's Disease

Support: NIH 1R21NS129147-01

Title: Stn beta burst dynamics reveal neural correlates of cognitive load in parkinson's disease dual-task interference

Authors: *V. BERKI¹, S. DAVIDSON², A. BAZYK², M. MILLER KOOP², N. MALAN², J. L. ALBERTS²;

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Abstract: People with Parkinson's disease (PD) face significant motor and cognitive challenges, particularly when attempting to perform two tasks simultaneously. Despite therapies like Deep Brain Stimulation (DBS), dual-task (DT) interference often persists, highlighting the need to understand its neural basis. Pathological subthalamic nucleus (STN) beta oscillations (13-35Hz) are linked to PD motor symptoms, but how DT impacts STN beta burst dynamics, differentiating physiological from pathological patterns, is unclear. This study investigated STN beta burst modulation in unmedicated PD patients during motor single-task (ST) grip force tracking, ST cognitive N-Back, and DT motor-cognitive conditions using a combination of thresholding methods for local field potentials (LFPs).

STN LFPs from 13 PD patients OFF medication were recorded during ST and DT motor/cognitive conditions. Beta bursts were analyzed first with a physiological threshold for all beta fluctuations, then a 75th percentile threshold to define high-power, pathological bursts. We assessed beta burst duration, burst rate, burst amplitude, and their correlation with concurrent motor (force-tracking) and cognitive (N-Back accuracy) performance, focusing on changes representing DT cost.

Findings revealed neural correlates of DT interference. Greater increases in average beta burst duration from ST cognitive to DT correlated with larger cognitive performance declines in DT conditions ($r_s = -0.670$, $p=0.015$). Higher beta burst rates during ST cognitive (N-Back) were associated with poorer cognitive performance in that task ($r_s = -0.464$, $p=0.017$). Furthermore, greater beta burst rate increases from ST cognitive to DT correlated with greater cognitive DT cost ($r_s = 0.631$, $p=0.018$). However, changes in average beta burst duration from ST motor to DT

did not significantly correlate with motor DT costs ($r_s = -0.159$, $p = 0.604$), and beta burst rate within ST or DT motor tasks did not correlate with motor performance. DT in unmedicated PD patients significantly modulates STN beta burst duration and rate. These changes are associated with cognitive, but not clearly motor, performance decrements in demanding conditions. Correlations suggest beta burst duration/rate alterations during DT reflect neural processes of cognitive overload. Understanding these nuanced beta dynamics is crucial for developing targeted interventions to alleviate DT difficulties in PD.

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Poster

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Program #/Poster #: PSTR159.15/D55

Topic: C.03. Parkinson's Disease

Title: Pilot study on vibrotactile stimulation for the treatment of Parkinson's disease

Authors: *M. AL BORNO;
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Abstract: PD is characterized by excessive neuronal synchronization in the subthalamic nucleus (STN) and a cluster of motor control disorders, including rigidity, bradykinesia, tremor and postural instability. Currently, the main treatment for PD is the dopamine prodrug levodopa, which loses effectiveness over time and involves motor complications in most patients. The other common treatment is deep brain stimulation (DBS), which requires brain surgery. An alternative potential treatment, termed "peripheral vibrotactile stimulation" (PVS), entails the delivery of mechanical vibratory input via small motors on the fingertips to desynchronize pathological STN networks. Treating PD with PVS would be a breakthrough with the potential to improve the lives of millions of people for whom current treatments are ineffective or unaffordable. A cost-effective vibrotactile stimulation treatment would avoid the side effects and decreasing effectiveness of levodopa, while avoiding the risk of surgically implanting electrodes in the brain. Even merely prolonging the effectiveness of levodopa by reducing the required dosage could provide dramatic benefits. PD is characterized by the loss of dopaminergic neurons and pathological (i.e., excessive) oscillations in the beta range (~13-30 Hz) in basal ganglia cortical loops. Beta power is a proxy for neuronal synchronization and is correlated with the severity of PD motor impairments (specifically, rigidity and bradykinesia, but not tremor), and is inversely correlated with dopamine levels. We will present a study showing the effects of PVS on local field potential (LFP) recordings in the STN. Our preliminary results (9 subjects) indicate that PVS, applied for one hour for each stimulation pattern, can reduce LFP beta power in most subjects (average decrease of 20%).

Disclosures: M. Al Borno: None.

Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

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Topic: C.03. Parkinson's Disease

Support: Michael J. Fox Foundation for Parkinson's research

Title: Purpose-built spinal cord neuroprosthesis alleviates gait deficits in individuals with advanced Parkinson's disease

Authors: *C. VARESCON¹, P. SANCHEZ LOPEZ², E. MAUGUIN², C. DESCHENAUX², L. BOLE-FEYSOT², S. HERNANDEZ CHARPAK², G. CARPARELLI², A. WATRIN³, F. BECCE⁴, J. BALLY^{4,5}, V. AURELI², L. ASBOTH², J. BLOCH², E. MORAUD², G. COURTINE²;

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Abstract: Despite advances in neuromodulation therapies for Parkinson's disease (PD), a large number of patients with advanced PD develop disturbances of gait and balance, including postural instability, festination, or freezing of gait, that are often refractory to existing treatments. These deficits lead to frequent falls and increase comorbid conditions. We previously reported that epidural electrical stimulation (EES) of lumbosacral spinal cord improved gait asymmetry, shuffling steps, imbalance, and freezing of gait in one patient with advanced PD (STIMO-PARKINSON clinical trial, NCT04956770). This proof-of-concept trial used re-purposed technology that was originally developed to treat chronic pain and is therefore suboptimal for this application. To confirm our preliminary results, we are now conducting a clinical trial in 6 individuals with PD who presents severe gait and balance deficits (SparkL, NCT06295614). We also aim to resolve technological limitations of repurposed technologies with the evaluation of a purpose-built implantable platform designed for precise stimulation of the spinal cord and enhanced usability to support daily mobility. Our first participant so far demonstrated improved gait quality, extended walking capacities, decreased freezing of gait, and increased confidence during daily mobility. At-home monitoring confirmed these improvements, which translated into a reported increase in his quality of life. These results will have to be confirmed in the next participants.

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Topic: C.03. Parkinson's Disease

Support: SNSF Starting Grant (TMSGI3_218471)

Title: Adaptive DBS controlled by neural gait signatures alleviates locomotor deficits in people with Parkinson's disease

Authors: *V. DE SETA¹, S. SCAFA^{1,2}, R. WANG¹, P. SANCHEZ LOPEZ¹, C. VARESCON¹, I. ENDERLI¹, C. DESCHENAUX¹, I. SAKR¹, J. BALLY³, A. PUIATTI², H. LORACH¹, A. COLLOMB-CLERC¹, G. COURTINE¹, J. BLOCH¹, E. MORAUD¹;

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Abstract: Advanced Parkinson's disease (PD) leads to a spectrum of locomotor deficits, including heterogeneous gait abnormalities and freezing of gait (FOG) that remain poorly managed by standard treatments. Unlike cardinal motor symptoms, conventional deep brain stimulation (DBS) often displays variable and sometimes detrimental efficacy for locomotor deficits. As a result, a majority of individuals with advanced PD experience progressive loss of mobility, increased risk of falls, and long-term care dependency. Locomotor deficits exhibit episodic and context-dependent behaviors, emerging during demanding tasks or when multitasking. These deficits are further exacerbated by fatigue, stress, or unexpected attentional shifts. Continuous DBS (cDBS) protocols are thus suboptimal to address this episodic nature, which may explain their inconsistent clinical efficacy. Instead, approaches that dynamically adjust stimulation in real time, aligned with the onset of gait disturbances, may more effectively prevent FOG, imbalance, asymmetry, and initiation difficulties. Here, we present preliminary results from the ADAPGAIT clinical trial (NCT06791902), in which we evaluate the safety and preliminary efficacy of aDBS therapies aligned to locomotor states to better address gait impairments. We enrolled two participants with advanced PD, chronically implanted with a Percept PC (Medtronic, USA) in the subthalamic nucleus (STN), and exhibiting disabling gait disorders. For each participant, we used a neural decoding algorithm to identify the best personalised STN neural signatures that capture the encoding of locomotor activities - sit, stand, walk, or avoiding obstacles - across fluctuating L-DOPA dosages and changing DBS amplitudes.

We mapped how changes in DBS amplitudes influence cardinal versus locomotor deficits and identified optimal stimulation amplitudes to address each set of impairments. We finally leveraged neural biomarkers to automatically adapt the delivery of DBS in real time, based on the ongoing locomotor activity. In both participants, gait-targeted aDBS improved locomotion compared to cDBS, increased gait fluidity, and normalised kinematic and electromyographic patterns to those of healthy controls. Participants' subjective reports confirmed these quantifications. Adaptive stimulation also markedly reduced FOG episodes. Clinical evaluation (MDS UPDRS-III) confirmed that aDBS improved gait without worsening other cardinal motor symptoms. These findings demonstrate the feasibility and therapeutic potential of gait-adaptive DBS. Ongoing recruitment will assess the generalizability of these results in a larger cohort.

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Title: Personalized closed-loop adaptive deep brain stimulation targeting gait in parkinson's disease

Authors: *H. FEKRI AZGOMI¹, R. RAMESH², K. H. LOUIE¹, J. E. BATH², K. PRESBREY³, J. BALAKID², J. MARKS⁴, A. SAYASENG¹, P. A. STARR², D. D. WANG²;
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Abstract: While deep brain stimulation (DBS) effectively treats many motor symptoms of Parkinson's disease (PD), gait impairments remain challenging. This reflects the lack of standardized gait metrics, the complexity of tuning stimulation parameters, and an incomplete understanding of gait-related neurophysiology. Although low-frequency DBS may benefit gait, it can compromise control of other symptoms, highlighting the need for more advanced solutions. Leveraging bidirectional devices capable of real-time neural sensing and stimulation, we developed a closed-loop adaptive DBS (aDBS) system that identifies patient-specific gait-optimized settings and uses neural biomarkers to adjust stimulation based on movement state. Three individuals with PD implanted with a bidirectional neurostimulator (Summit RC+S,

Medtronic) performed walking tasks. Local field potentials from the globus pallidus, electrocorticography from the motor cortex, and wearable sensor data were recorded simultaneously. Walking performance was assessed using a composite index of key gait metrics. Gait-optimized DBS settings were identified using Gaussian process regression. Spectral neural features trained subject-specific linear discriminant analysis (LDA) classifiers for movement-state detection. Classifiers were validated offline, optimized, and deployed to the implant for real-time switching between gait- and clinically-optimized settings. Compared to clinical settings, gait-optimized DBS led to improvements of 2.3%-21.1% in stride velocity, 2.0%-4.7% in arm swing amplitude, and 11.2%-46.8% reductions in step time variability across participants. Refined spectral biomarkers enabled LDA classifiers to detect movement state accurately (offline AUCs: 0.67-0.98; simulated on-device AUCs up to 0.81). This performance reflects a two-stage optimization: first, selecting individualized power bands and classifier weights; second, tuning temporal parameters to ensure stable real-time performance. By studying how DBS modulates pallidal and motor cortical networks, we identified neurophysiological biomarkers associated with improved gait, offering insight into circuit dynamics and informing future designs of aDBS systems that respond to real-time brain-state fluctuations. This study shows that personalized, closed-loop aDBS can improve gait in PD by using individualized settings and real-time neural biomarkers for movement state-dependent switching. This system offers a clinically feasible solution for improving gait while preserving the therapeutic benefits of standard DBS.

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PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

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P30 AG066515 - Stanford Alzheimer's Disease Research Center
NINDS UH3NS128150

Title: A neuroimaging-guided optimisation of stimulation parameters in the nucleus basalis of meynert

Authors: ***C. E. CASSELTON**¹, **A. K. ABAY**¹, **K. B. WILKINS**¹, **T. HOWARD**¹, **R. CROCKETT**⁴, **A. NEGI**¹, **M. M. ZEINEH**², **V. BUCH**³, **J. M. HENDERSON**³, **H. BRONTE-**

STEWART¹;

²Radiology, ³Neurosurg., ¹Stanford Univ., Stanford, CA; ⁴Oxford Univ., Oxford, United Kingdom

Abstract: Degeneration of the nucleus basalis of Meynert (NBM) is a key factor in cognitive decline in Parkinson's disease (PD). Deep brain stimulation (DBS) of the NBM may stabilize cognitive symptoms present within PD. However, the lack of acute behavioural effects to guide programming of the NBM serves as a major barrier potentially contributing to suboptimal outcomes in previous studies. Advances in modelling of the DBS electric field, coupled with high-quality neuroimaging, has led to automated approaches for DBS parameter configuration based on lead placement relative to the individual's anatomy. This project implements and determines the feasibility of a novel neuroimaging-guided pipeline to guide programming the NBM in individuals with PD. Pre-operative T1 MRI scans were utilized to identify individualised regions of interest (ROIs) and regions of avoidance (ROAs) for the participant. Neurosurgeons used the anatomy to plan the trajectories of the leads. A secondary post-operative CT scan was collected a few weeks after surgery to account for potential lead rotation and resolution of transient brain shift in the immediate post-operative period; this was used to reconstruct the implanted leads to determine placement. Boston Scientific's Illumina software was then run with varying parameters to produce a DBS configuration to maximize ROI and minimize ROA overlap. The complete pipeline was successfully implemented in one participant, allowing for individualised stimulation modelling. Illumina provided a DBS configuration that maximized overlap with the NBM with minimal overlap of surrounding ROAs such as the optic tract, amygdala, and globus pallidus externus. This configuration was validated during clinical programming, where no immediate stimulation-induced adverse behavioural effects were present. The initial implementation of this neuroimaging-guided pipeline demonstrates the feasibility of a personalised, multimodal imaging pipeline for optimising NBM DBS. Further application of this pipeline in more participants will allow for evaluation of the reproducibility and effect on cognitive symptoms in PD.

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Title: Intermittent hypercapnia drives cerebrospinal fluid flow and clearance in Parkinson's disease and healthy older adults

Authors: E. ERHARDT¹, A. MAYER², H. LIN¹, S. PIRIO RICHARDSON¹, N. SHAFF², A. A. VAKHTIN², A. CAPRIHAN², H. VAN DER HORN³, N. HOFFMAN², J. P. PHILLIPS⁴, M. GRIGG-DAMBERGER¹, C.-H. WANG², J. GOUGH², S. M. HOBSON⁵, A. DELIGTISCH¹, G. SUAREZ-CEDENO¹, D. SUGAR¹, ***S. G. RYMAN**⁶;

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Abstract: A failure of the glymphatic pathway to clear brain byproducts may contribute to the pathophysiology of Parkinson's disease (PD). The glymphatic pathway relies on vasomotion (constriction and dilation of blood vessels) to drive cerebrospinal fluid (CSF) through the interstitial space and clear waste from the brain. As such, augmenting vasomotion may increase clearance of proteins implicated in neurodegeneration and serve as a disease-modifying intervention. The current study evaluated whether intermittent hypercapnia (exposure to low levels of CO₂ in ON-OFF cycles) can be used to induce vasomotion, CSF flow, and clearance of proteins implicated in PD from the brain. We first evaluated whether intermittent hypercapnia increases vasomotion-induced CSF inflow and how these mechanisms are altered in 35 patients with PD relative to 38 healthy control (HC) participants. Participants underwent clinical assessment and a ~5-minute intermittent hypercapnia paradigm (ON-OFF cycles of 35 seconds 5% CO₂, alternating with room air) during MRI blood oxygen level-dependent (BOLD) imaging. Each CO₂ exposure elicited a large-amplitude BOLD response (vasomotion). A decline in BOLD signal was coupled with large-amplitude CSF inflow signal. Patients with PD exhibited significantly reduced CSF inflow response to ETCO₂ relative to HC ($p=0.012$). We then evaluated whether an extended intermittent hypercapnia paradigm elicited cerebral clearance of proteins and peptides implicated in neurodegeneration. Five patients with PD and 5 age- and sex-matched HC underwent three consecutive sessions of intermittent hypercapnia paradigm totaling approximately 30 minutes while undergoing MRI BOLD imaging. Blood was collected at baseline (2x), 45-, 90- and 150-minutes from the start of the intervention, and analyzed for plasma biomarkers associated with cognitive impairment in PD. Linear mixed-effects analyses indicated a significant post-hypercapnia increase in plasma total α -synuclein ($p = 0.02$), NfL ($p < 0.001$), GFAP ($p < 0.001$), A β_{1-42} ($p = 0.046$), A β_{1-40} ($p = 0.035$), with a trend effect observed for pTau217 ($p = 0.097$). Together, this work indicates that intermittent hypercapnia elicited vasomotion-induced CSF inflow in both HC and patients with PD. The magnitude of the vasomotion-induced CSF inflow in patients with PD was reduced relative to HC. However, intermittent hypercapnia, increased the appearance of biomarkers of neurodegeneration in the plasma of both HC and PD participants. This suggests that intermittent hypercapnia may be used to clear toxic brain byproducts from the brain.

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Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

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Program #/Poster #: PSTR159.21/D61

Topic: C.03. Parkinson's Disease

Support: The Michael J. Fox Foundation for Parkinson's research
EuroStars SH-ARC 2262

Title: Closed-loop epidural electrical stimulation of the lumbosacral spinal cord to address gait impairments and fluctuations in advanced parkinson's disease

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Abstract: Despite significant progress in neuromodulation therapies for Parkinson's disease (PD), many patients with advanced PD continue to experience debilitating gait and balance impairments—including postural instability, festination, and freezing of gait—that remain unresponsive to existing treatments. In the STIMO-PARKINSON trial (NCT04956770), we previously demonstrated that epidural electrical stimulation (EES) of the lumbosacral spinal cord improved these symptoms in a patient with advanced PD. Building on these findings, we initiated the SparkL trial (NCT06295614), enrolling six individuals with severe gait and balance deficits. A major challenge in treating these impairments is managing the variability of motor symptoms, which fluctuate with medication, fatigue, stress, and environmental factors. To address this, we developed a wearable monitoring platform using smart sensorized shoes capable of AI-driven gait analysis. This platform enables continuous, real-time tracking of motor biomarkers in daily-life settings. By integrating EES with this wearable system, we implemented a closed-loop neuromodulation approach that dynamically adjusts stimulation parameters in response to real-time gait data. Tested in three participants, the system demonstrated strong usability outside the laboratory and effectively compensated for fatigue-related gait deterioration—leading to improved gait quality, increased walking endurance, and greater confidence in daily mobility. These findings support the potential of adaptive EES as a personalized therapy for gait and balance disorders in Parkinson's disease.

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Poster

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Topic: C.03. Parkinson's Disease

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John A. Blume Foundation
John E Cahill Family Foundation

Title: Distinct STN neural state dynamics revealed between adaptive and continuous DBS during chronic at-home monitoring in Parkinson's disease

Authors: *S. KARJAGI¹, J. CHOI¹, C. CUI¹, K. B. WILKINS², A. NEGI³, P. ACHARYYA³, K. W. DALEY⁵, H. BRONTE-STEWART⁴;

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Abstract: Background: Adaptive deep brain stimulation (aDBS) modulates stimulation based on real-time subthalamic nucleus (STN) beta oscillations, theoretically reducing pathological neural activity compared to continuous DBS (cDBS). However, at-home chronic neural recordings reveal complex dynamics requiring analytical approaches to understand stimulation effects on oscillatory patterns and their relationship to clinical outcomes. **Methods:** We analyzed 53 days of continuous beta power recordings from a Parkinson's disease patient ON bilateral STN DBS, no medication, using a Medtronic Percept PC device, targeting a 5Hz band around the 17.58Hz beta peak frequency. The study used a double-blinded crossover design: aDBS (25 days, n=3,677 samples) followed by cDBS (28 days, n=4,002 samples). Hidden Markov modeling (HMM) with state alignment and statistical corrections was applied for valid cross-condition comparisons. Neural states and beta amplitude were correlated with Quantitative Digitography (QDG) Mobility Scores during 47 matched assessments. **Results:** Six distinct neural states showed significantly different dynamics between conditions. aDBS demonstrated higher occupancy in high-amplitude beta power states, while cDBS showed higher low-

amplitude beta power state occupancy. The patient expressed blinded preference for cDBS. Objective motor performance was similar between conditions (QDG Mobility Scores: 79.9 ± 12.1 vs 75.8 ± 9.9 , $p=0.23$). Normalized beta power amplitude correlated with mobility ($r=0.352$, $p=0.015$), validating chronic at-home monitoring as clinically relevant. **Conclusions:** This analysis establishes a framework for understanding how DBS paradigms influence latent neural states. These neural states may capture distinct pathological beta oscillation patterns with characteristic temporal dynamics reflecting different degrees of motor dysfunction. Future work will examine how state transitions relate to motor fluctuations and whether stimulation adaptation influences transition probabilities between latent neural states.

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Poster

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Location: SDCC Halls B-H

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Program #/Poster #: PSTR159.23/D63

Topic: D.05. Spinal Cord Injury and Plasticity

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Title: Restoring hemodynamic stability with spinal cord stimulation in Parkinsonian syndromes

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Abstract: Individuals with Parkinsonian syndromes can suffer from orthostatic hypotension, resulting in increased risk of falls, decreased mobility, and reduced quality of life. In severe cases, hypotension can leave individuals bedridden. We recently demonstrated that epidural

electrical stimulation applied over the lower thoracic spinal cord reduces orthostatic hypotension in fourteen individuals with spinal cord injury. Although the etiology of orthostatic hypotension in Parkinsonian syndromes differs from that of spinal cord injury, both conditions disrupt descending commands from brainstem vasomotor centers that modulate sympathetic neurons in the thoracic spinal cord. We hypothesized that individuals with Parkinsonism with spared sympathetic pathways could benefit from spinal cord stimulation. To understand these mechanisms, we developed an experimental framework to induce orthostatic hypotension after neurodegeneration in non-human primates. We found that targeted, closed-loop spinal stimulation of the thoracic spinal cord can mitigate hypotension under orthostatic stress by increasing vasoconstriction and in turn, arterial pressure in three animals. In parallel, we validated this approach across multiple clinical case studies in people with varying Parkinsonian disorders who were implanted with epidural electrical stimulation. In these individuals, spinal cord stimulation reduced symptoms of hypotension, enhanced mobility, and improved quality of life.

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Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

Location: SDCC Halls B-H

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Topic: C.03. Parkinson's Disease

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PPMI - Michael J. Fox Foundation for Parkinson's Research
Robert and Ruth Halperin Foundation

John A. Blume Foundation
John E Cahill Family Foundation

Title: Leveraging transfer learning with neuroimaging to predict cognitive deterioration in Parkinson's disease: insights from motor phenotypes

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder that can be characterized into phenotypes based on dominant motor symptoms, such as tremor-dominant (TD) and akinetic-rigid (AR). Cognitive impairment is a prevalent non-motor symptom of PD, and its severity may be influenced by the underlying motor phenotype. Previous literature has shown that the AR phenotype may have worse cognitive outcomes than TD. This study aims to predict the progression of cognitive impairment over five years and to investigate the impact of motor phenotype on this progression. The dataset used in this study comprised of 259 participants from the Parkinson's Progression Markers Initiative, in which they completed a T1-weighted MRI scan, MDS-UPDRS III assessment, and a comprehensive neuropsychological battery at baseline. The neuropsychological battery was repeated annually for five years. We employed various machine learning models to predict the five-year neuropsychological scores using baseline scores as input. Additionally, a convolutional neural network (CNN) was adapted for this prediction task, utilizing T1 MRI image input through transfer learning. An existing CNN architecture was modified to suit the specific requirements of our dataset. To enhance interpretability, we applied Gradient Class Activation Maps (Grad-CAM) to visualize the salient features of the input T1 MRI images that significantly influenced the model's predictions. The performance of the machine learning models was rigorously evaluated, and the Grad-CAM visualizations revealed critical brain regions associated with cognitive impairment prediction, differentiated by motor phenotype. The various models were compared to identify the most relevant input features for prediction and how they varied for motor phenotype. In conclusion, this study provides insights into the progression of cognitive impairment in Parkinson's disease, emphasizing the role of motor phenotype.

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Poster

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Topic: C.03. Parkinson's Disease

Support:

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Robert and Ruth Halperin Foundation

John A. Blume Foundation

John E Cahill Family Foundation

Title: Upper-lower limb coordination as a potential kinematic marker of motor dysfunction in Parkinson's Disease

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Abstract: Deficits in interlimb coordination contribute to the motor impairment and functional mobility challenges observed in Parkinson's disease (PD). Previous studies have examined interlimb coordination in homologous limbs, reporting reduced coordination characterized by increased variability and altered phase relationships between limbs, reflecting impaired temporal synchronization during walking. The dynamics of upper-lower limb coordination, however, has been less explored. This study aims to quantify upper-lower limb kinematic coordination in people with Parkinson's (PwP) during free walking. Eight PwP and five healthy controls (HC) performed a cued forward walking (FW) task. Within the eight PwP, seven were right side more affected (MA) and one was left side MA. Participants were screened for absence of tremor and gait-impairing non-PD comorbidities. In the FW task, participants completed four periods of forward walking. Triaxial inertial measurement unit (IMU) sensors (Opals and Mobility Lab) that measure angular velocity were placed on the thighs and wrists of each participant. Upper-lower limb coordination was quantified using continuous relative phase (CRP) analysis, which computes the phase difference between opposing kinematic signals throughout the task. Limb pairings were considered both ipsilaterally and contralaterally: right wrist-left wrist (RWLW), right thigh-left thigh (RTLW), right wrist-right thigh (RWRT), left wrist-left thigh (LWLT), right wrist-left thigh (RWLT), and left wrist-right thigh (LWRT). CRP was calculated across the four free-walking periods within a trial, with participant-level means and standard deviations summarizing coordination and variability. Using the Unified Parkinson's Disease Rating Scale (UPDRS), PwP were classified as PD with gait impairment (GI) (gait subscore >0) or without gait impairment (gait subscore = 0). Significant differences were observed between HC and PD with GI in mean LWLT and LWRT CRP, and between HC and PD without GI in standard deviation of RWRT CRP. PD without GI demonstrated CRP values that were closer to expected phase relationships—anti-phase for homologous limb pairs (wrist-wrist and thigh-thigh) and in-phase for upper-lower limb (wrist-thigh) pairs—compared to PD with GI who showed larger deviations. These findings indicate that PwP with GI exhibit greater disruptions in upper-lower limb coordination, marked by increased variability and altered timing of gait. This preliminary evidence suggests that upper-lower limb coordination deficits are present in PD and may reflect aspects of motor impairment related to gait dysfunction.

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Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

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Robert and Ruth Halperin Foundation
John A. Blume Foundation
John E Cahill Family Foundation

Title: Linking pre-movement subthalamic beta desynchronization to motor impairment in Parkinson's disease

Authors: *G. SEO¹, K. B. WILKINS², H. BRONTE-STEWART³;
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Abstract: Exaggerated beta-band (13-30 Hz) oscillatory activity in the subthalamic nucleus (STN) is a known biomarker of motor impairment in Parkinson's disease (PD). While prior research focused on resting and movement states, STN neural activity during movement planning and initiation is underexplored. This study characterized beta-band local field potential (LFP) power in the STN during the pre-movement phase of various motor tasks and investigated its association with the severity of motor impairment in PD. Fifteen PD participants with sensing deep brain stimulation (DBS) systems (Medtronic Activa® PC+S) performed externally cued motor tasks (sit-to-stand, stand-to-walk, and repetitive wrist flexion/extension) under off medication and OFF DBS conditions. Accelerometer (Opals and Mobility Lab) and STN LFP data (DBS system) were recorded simultaneously. Pre-movement STN beta power was calculated from the LFP signal and normalized to resting beta power. Linear mixed-effects models examined associations between pre-movement beta desynchronization and clinical motor impairment (MDS-UPDRS III scores) and movement kinematics. Preliminary results showed beta desynchronization (decreased beta power compared to resting state) in one or both STNs during movement preparation across all tasks. Greater motor impairment (higher MDS-UPDRS III total score) was associated with smaller pre-movement beta desynchronization. The bradykinesia subscore exhibited a significant negative association with the desynchronization magnitude. This link was more pronounced in the complex stand-to-walk task (which involved integrating multiple body segments, anticipatory postural adjustments, and dynamic balance) but less evident in the simpler repetitive wrist flexion/extension. Lastly, pre-movement beta desynchronization was associated with average acceleration of the lumbar and shank regions during subsequent standing and walking. These findings suggest pre-movement beta desynchronization reflects neurophysiological mechanisms of motor impairment in PD. The observed association between reduced pre-movement STN beta desynchronization and greater motor impairment indicates a potential disruption in effective motor planning, delayed activation

of motor networks, and increased inhibitory control from the basal ganglia over the motor system. Together, these factors contribute to the challenges in initiating and executing movement, providing valuable insights into the neural correlates of motor dysfunction in Parkinson's disease.

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Poster

PSTR159: Parkinson's Disease Therapeutic Strategies: Clinical Trials

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Topic: C.03. Parkinson's Disease

Support: Department of Defense office of the Congressionally Directed Medical Research Programs

Title: The intersection of neuromodulation and balance impairments in Parkinson's disease

Authors: *V. AURELI¹, A. COLLOMB-CLERC³, A. PHILIPPIDES³, N. D. JAMES⁴, K. GALAN³, F. MERLOS³, Q. BARRAUD⁵, E. MARTIN MORAUD⁶, J. SQUAIR³, J. BLOCH², G. COURTINE⁷;

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Abstract: Parkinson's disease provokes severe gait and balance disorders that greatly reduce independence and significantly increase the risk of falls. While current treatments such as deep brain stimulation (DBS) of the subthalamic nucleus alleviate major motor symptoms, they are less effective to improve gait and balance—and can even aggravate the symptomatology. We recently showed that epidural electrical stimulation (EES) of the lumbosacral spinal cord improved gait and balance in one patient with advanced Parkinson's disease. However, the biological mechanisms underlying this improvement remain enigmatic. Here, we leveraged a new transgenic mouse model (cNdufs2^{-/-}) that progressively develops the hallmarks of Parkinsonism, including debilitating balance issues. To identify brain regions involved in the control of balance and responsible for deficits due to Parkinsonism, we mapped whole-brain transcriptional activity during a well-controlled task requiring complex balance maintenance in both wildtype and cNdufs2^{-/-} mice. To understand whether DBS and EES engage the neuronal architectures involved in balance, we also conducted this mapping in cNdufs2^{-/-} mice that received DBS and EES while they were performing the task. This work aims to uncover the neuronal architectures involved in balance impairments due to Parkinson's disease, and that can be targeted to alleviate these deficits in the future.

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Poster

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Topic: C.03. Parkinson's Disease

Support: SNSF Starting Grant (TMSGI3_218471).

Title: Cortico-subthalamic dynamics underlying freezing of gait in people with advanced Parkinson's Disease

Authors: *R. WANG^{1,2}, A. SÁNCHEZ LÓPEZ^{1,2}, C. KOHLER^{1,3}, V. DE SETA^{1,3}, C. VARESCON^{1,3}, C. DESCHENAUX^{1,3}, A. PHILIPPIDES^{1,2}, A. COLLOMB-CLERC^{1,2}, J. BALLY³, G. COURTINE^{1,2,3}, J. BLOCH^{1,2,3,4}, E. MARTIN MORAUD^{1,3};

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Abstract: Freezing of gait (FoG) is a debilitating locomotor symptom that severely impairs mobility, increases the risk of falls, and reduces autonomy in people with advanced Parkinson's disease (PD). While current neuromodulation therapies such as Levodopa (L-DOPA) or deep brain stimulation (DBS) of the subthalamic nucleus (STN) effectively address the cardinal motor symptoms of PD, they often fail to adequately improve FoG. Consequently, FoG remains a major therapeutic priority. The lack of a mechanistic understanding of the neural processes underlying FoG has limited the development of more targeted therapies. Growing evidence points to a complex interplay between motor, cognitive, and attentional components, suggesting a disruption across cortico-basal nuclei. Indeed, pathological neural signatures have been identified in both cortical and basal regions. However, the specific contributions and interactions between these structures during FoG remain unclear. To address this question, we established a multimodal monitoring platform incorporating mobile EEG and chronically implanted STN DBS neurostimulators with sensing capabilities to map the neural dynamics underlying FoG within cortical and subthalamic regions, aligned with leg muscle activity and whole-body kinematics. Twelve participants completed a set of locomotor and cognitive tasks designed to reliably elicit FoG. By comparing freezers versus non-freezers, as well as freezing trials versus non-freezing trials, we identified spatiotemporal patterns of altered neural modulation associated with FoG. These pathological modulations were spread throughout frontal, central, and parietal regions of the brain. The findings of this study open new avenues for uncovering the neural dynamics that

underlie FoG and for developing new targeted neuromodulation strategies operating in real-time across multiple sites to better address freezing of gait.

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Poster

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Support: Arizona Biomedical Research Commission ABRC ADHS18-198846
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R01 NS122805

Title: An acute L-DOPA injection partially reverses string-pulling deficits in a rat model of Parkinson's disease

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Abstract: Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide and is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta (SNc). The hallmark motor symptoms of PD include bradykinesia, tremor, and akinesia. In addition, PD profoundly disrupts motor learning and fine-motor control. Dopamine replacement therapy with L-DOPA is the current gold standard treatment for alleviating PD-related motor symptoms, yet its effects on fine-motor control and motor learning are less understood. To investigate the effect of PD on fine-motor control and motor learning, we utilized a toxin-based rat model of PD along with a novel behavioral task designed to assess fine-motor function that allows high precision analysis of individual paw movements and kinematics. We predicted that PD condition will lead to significant impairments in fine-motor control and that these deficits can be recovered by L-DOPA administration. Approach. Five Sprague Dawley rats underwent 10 days of training in an automated string-pulling system (Jordan et al., 2024). Rats were trained to pull a string for pre-specified lengths for a food reward after each bout. After reaching proficiency, the rats were unilaterally injected with 6-hydroxydopamine (6-OHDA) or vehicle (sham rats) in the medial forebrain bundle to degenerate dopamine fibers and mimic the parkinsonian condition. The rats recovered from surgery for 3 weeks and then were re-trained for 14 days. L-DOPA was injected the day after re-training ended, and the effects of L-DOPA were monitored for three days. Results. Dopamine depletion severely disrupted paw trajectories, reduced paw speeds, and impaired overall string-pulling performance in the 6-

OHDA rats. These deficits were partially restored with acute L-DOPA (6mg/kg) administration, which led to notable improvements in both paw movement patterns and string-pulling speeds. Interestingly, the therapeutic effects of L-DOPA were persistent, with enhanced pulling speeds observed for at least 24 hours post-injection. Taken together, these results indicate that dopamine depletion severely affects fine-motor functions and limb movements and that these deficits are partially restored by acute L-DOPA administration. Reference: Jordan GA, Vishwanath A, Holguin G, Bartlett MJ, Tapia AK, Winter GM, Sexauer MR, Stopera CJ, Falk T, Cowen SL. Automated system for training and assessing reaching and grasping behaviors in rodents. J Neurosci Methods. 2024 Jan 1;401:109990. doi: 10.1016/j.jneumeth.2023.109990. Epub 2023 Oct 20. PMID: 37866457; PMCID: PMC10731814.

Disclosures: R.A. Caprau: None. A. Aristieta: None. M.B. Schmit: None. A.J. Malik: None. A. White: None. V. Pederson: None. S.L. Cowen: None. T. Falk: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); 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 for and received travel support.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.01/E6

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Japan Society for the Promotion of Science (JSPS) Grant-in-Aid for Scientific Research no. 23H03700
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Title: Progressive Saccadic Reaction Time Impairments in Marmosets Following α -Syncline-Induced Synucleinopathy

Authors: *W. AMLY¹, C.-Y. CHEN², H. ONOE⁵, M. SAWAMURA⁶, R. TAKAHASHI³, T. ISA⁴;

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Abstract: α -Syncline (α S) pathology is central to several neurodegenerative diseases, including Lewy body disease with dementia and Parkinson's disease, where changes in motor and visual behavior are observed. Animal models with α S pathology have never investigated on their oculomotor behavioral changes. In this study, we aimed to investigate if there are any early alterations in eye movement behavior accompanying the α S pathology propagation in common marmosets. We selected a primate synucleinopathy model using marmosets established by our

collaborators (Sawamura et al., 2022). We injected α S preformed fibrils into the olfactory bulb of three marmosets trained on gap saccade task and analyzed their eye movements up to 11/12 months post-injection. Notably, saccadic reaction time (SRT) progressively increased as pathology advanced. To understand the underlying neural mechanism, we used a computational model to simulate the gradual increase in SRT associated with the disease progression. By adjusting model parameters associated with the frontal cortex and visual processing systems, simulating cortical deficits in these regions, we successfully reproduced the changes in SRT. Our results are consistent with the previously reported glucose hypometabolism in areas such as V1, the lateral geniculate nucleus (LGN), and the frontal lobe, using ^{18}F -FDG-PET. Furthermore, we found a significant increase in saccade deceleration periods with disease progress. This study provides novel insights into α S pathology's impact on oculomotor behavior in a non-human primate model, offering a potential early biomarker for neurodegenerative disease progression such as synucleinopathies.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.02/E7

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: MJFF 2013-8499
MJFF 2023-023629
PSP-France Foundation
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Fondation pour la Recherche Médicale

Title: Comparative proteomics of cerebrospinal fluid alterations in non-human primate models of synucleinopathies and tauopathies

Authors: R. KINET¹, M. BOURDENX¹, I. TRIGO-DAMAS², G. PORRAS¹, Q. LI³, M. VILA⁴, J. A. OBESO⁵, V. PLANCHE¹, E. BEZARD¹, *B. DEHAY¹;

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Abstract: Proteinopathies are diseases that share the aggregation of proteins, such as α -synuclein or tau, in brain-related structures. These pathologies are often diagnosed late, after massive degeneration of the affected cells, making it essential to identify biomarkers to detect the onset of these diseases at an early stage or enhance understanding of their mechanistic pathogenesis. To

discover potential targets, we examine the cerebrospinal fluid proteomic profiles of a longitudinal and unique cohort of 40 non-human primates (NHPs) of different ages distributed across six different experimental groups and a control group. NHPs were intracerebrally injected with brain-derived extracts from patients with multiple system atrophy, characterized in Teil et al. 2022, progressive supranuclear palsy described in Darricau et al. 2022, or Parkinson's disease - the latter including extracts containing either small or large α -synuclein positive aggregates- and analyzed at various pre-determined time points (6, 12, or 24 months after injection), detailed in Bourdenx et al. 2020 and Kinet et al. 2025. Lastly, a group having received an enteric injection of PD-derived fractions containing large aggregates was included, characterized in Arotcarena et al. 2020. The CSF of each individual NHP was analyzed using an unbiased mass spectrometry-based proteomics analysis on 7600 proteins. We uncovered distinct patterns of protein-protein interactions depending on the experimental groups and the diseases they model. Furthermore, various groups appear to share similar dysregulated proteins or biological processes, reinforcing the connection between pathologies and their genesis. These results may significantly impact the field of biomarkers in neurodegenerative diseases, enabling better anticipation of the genesis of these pathologies and earlier diagnosis, thus facilitating the development and follow-up or administration of treatments for patients.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.03/E8

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Assessing Blood-Based Biomarkers in Mouse Models of Neurodegenerative Disease: Insights from Simoa Assays

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Abstract: Phosphorylated tau at threonine 217 (pTau217), neurofilament light chain (NfL), and glial fibrillary acidic protein (GFAP) have emerged as robust blood-based biomarkers in human studies of neurodegenerative diseases. These markers are associated with hallmark features of pathology and correlate with disease severity, progression, and cognitive decline. pTau217, in particular, has shown high specificity for tau pathology, while NfL reflects neuronal injury, and GFAP is a sensitive indicator of reactive astrogliosis and neuroinflammation. Despite their clinical relevance, these biomarkers remain largely unstudied in preclinical models of neurodegeneration. This gap limits our ability to directly link molecular and cellular mechanisms observed in animal models to human disease trajectories. Establishing the utility of these

biomarkers in mouse models is critical for advancing translational research and optimizing therapeutic development. In this study, we applied Quanterix's ultra-sensitive Simoa assays to measure plasma levels of pTau217, total tau, NfL, and GFAP in mouse models of tauopathy. Our goal was to assess their performance in capturing disease-related changes and to determine whether these measures reflect underlying neuropathological processes. By validating these biomarkers in animal models, we aim to enhance their utility for monitoring disease progression and therapeutic response in preclinical studies. This approach strengthens the translational bridge between animal and human research, supporting the development of biomarker-informed strategies for early detection and intervention in neurodegenerative diseases.

Disclosures: **S. Rayaprolu:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Quanterix Corporation. **K.R. Miller:** A. Employment/Salary (full or part-time); Quanterix Corporation. **B.I. Giasson:** None.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.04/E9

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Ckd-513, a novel non-hydroxamic acid histone deacetylase 6 (hdac6) inhibitor for treatment of neurological disorders

Authors: ***J. KIM**¹, D. BAE¹, H. NAM¹, G. KWAK¹, S. YIM¹, S. LYU¹, K. LEE², K. SHIN³, H. SONG⁴, J. LEE⁴, I.-C. HWANG³, S.-M. KIM², N. HA¹;

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Abstract: Histone deacetylase 6 (HDAC6) is closely linked to neurological disorders such as Tauopathies and Charcot-Marie-Tooth disease (CMT), which are characterized by impaired axonal transport in neurons. Several groups have been currently developing HDAC6 inhibitors based on the non-hydroxamic acid (NHA) scaffold to overcome the safety risks associated with traditional hydroxamic acid-based HDAC6 inhibitors, such as genotoxicity and rapid clearance. However, NHA HDAC6 inhibitors, including those based on heteroaryl thioacetyl analogues and 1,2,4-trifluoromethyloxadiazole (1,2,4-TFMO), still face challenges due to limited selectivity and potency. Here, we report the discovery of CKD-513, a novel brain-penetrant NHA HDAC6 inhibitor characterized by exceptional selectivity and potency. CKD-513 demonstrates an IC₅₀ of <20 nM and over 500-fold selectivity for HDAC6 compared to other isoforms, with minimal genotoxic and cardiotoxic potential. Following a single oral administration, CKD-513 induced a sustained approximately 2-fold increase in acetylated α -tubulin—a pharmacodynamic biomarker of HDAC6 inhibition—in the cortex, hippocampus, sciatic nerve, and peripheral blood for up to 12 hours. In preclinical studies, CKD-513 effectively restored axonal transport across multiple disease-relevant *in vitro* and *in vivo* models. Oral administration of CKD-513 improved

hippocampal long-term potentiation, reduced tau phosphorylation, and enhanced cognitive performance in PS19 mice, a tauopathy animal model ($P < 0.05$). In the C3 mouse model of CMT1A, CKD-513 significantly restored myelination, axonal integrity, and neuromuscular junction structure, resulting in improved behavioral and electrophysiological outcomes ($P < 0.05$). These findings highlight the therapeutic potential of HDAC6 inhibition in neurodegenerative and neuromuscular disorders, supporting CKD-513 as a promising clinical candidate for treating tauopathies and CMT. Ongoing GLP toxicology studies and a planned Phase 1 clinical trial will further evaluate the clinical applicability of this compound.

Disclosures: **J. Kim:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **D. Bae:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **H. Nam:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **G. Kwak:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **S. Yim:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **S. Lyu:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **K. Lee:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **K. Shin:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **H. Song:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **J. Lee:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **I. Hwang:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **S. Kim:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp. **N. Ha:** A. Employment/Salary (full or part-time): Chong Kun Dang Pharmaceutical Corp..

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.05/E10

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Blast Induced TBI in hTau Transgenic Mice

Authors: *T. TAN¹, Z. ZHANG², R. SHI³;

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Abstract: Blast traumatic brain injuries (bTBIs) affect a significant portion of the military population and arise from a violent shockwave to the head. bTBIs present a complex and elusive medical problem and have been associated with neurodegenerative disorders, such as Alzheimer's disease. While bTBIs are the result of an environmental injury, the influence of genetic predisposition towards pathologies of neurodegenerative disorders on the severity of symptoms is not fully understood. One such pathology implicit to certain neurodegenerative disorders is the presence and accumulation of phosphorylated Tau (pTau) protein, which results in disruption of neuron structure and function. In this study, we sought to investigate the effect of

bTBIs on mice that express high levels of phosphorylated humanized Tau (hTau) compared to a control wild type (WT) line. Mice from both groups were randomly assigned to either a condition with the blast shock wave (bTBI) or a condition with only the sound and environment of the shock wave (sham). We found that the density of pTau in both sham and bTBI conditions was significantly higher in the hTau mice compared to the WT group. This coincided with the observation that mice in the hTau+bTBI group exhibited higher pTau density and lower neuronal density compared to hTau+sham conditions whereas there was no significant difference in the density of pTau between the WT+bTBI and WT+sham conditions. Taken together, these findings suggest that bTBIs can worsen neurogenerative pathologies in subjects with genetic risk factors. Knowledge from this study could possibly be used in tandem with other diagnostics tests to predict the occurrence of neurodegenerative pathologies in individuals with preexisting conditions.

Disclosures: **T. Tan:** None. **Z. Zhang:** None. **R. Shi:** 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.; Stock in a company: Neuro Vigor.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.06/E11

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIAAA R01-AA028782
NIAAA K99-AA029754

Title: Development of a Novel CTE Mouse Model via Retro-Orbital AAV Tau Delivery to Examine the Impact of Chronic Intermittent Ethanol Exposure

Authors: ***J. L. HOFFMAN**^{1,3}, B. WILLIAMS¹, E. SHANNON¹, M. KERRIGAN¹, A. KIM¹, K. SOONG¹, L. THOMPSON¹, J. E. ROBINSON⁴, S. P. FACCIDOMO^{1,2}, C. W. HODGE^{2,1}; ¹Bowles Ctr. Alcohol Studies, ²Psychiatry, Univ. of North Carolina-Chapel Hill, Chapel Hill, NC; ³Mol. Pharmacol. and Neurosci., Loyola Univ. Chicago SSOM, Maywood, IL; ⁴Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH.

Abstract: Chronic Traumatic Encephalopathy (CTE) is a frontotemporal dementia resulting from repeated concussive brain injuries throughout the course of a lifetime. It is frequently observed in professional athletes and military personnel but remains misdiagnosed and undertreated due to the absence of reliable biomarkers and inconsistent diagnostic criteria. This study aims to validate a novel preclinical mouse model of CTE. It is frequently observed in professional athletes and military personnel but remains misdiagnosed and undertreated due to the absence of reliable biomarkers and inconsistent diagnostic criteria. Male mice were injected

with huTau AAV (or saline) and given four weeks for transgene expression before undergoing rmTBI and ethanol exposure. For the next three weeks, mice received rmTBI (or sham) via a weight-drop procedure and were then exposed overnight to vaporized ethanol (or air) for four consecutive days per week (Monday-Thursday). Following these exposures, mice underwent a behavioral battery assessing sensorimotor gating, locomotion, and spatial memory.

Immunohistochemistry was performed on fixed tissue samples using antibodies for huTau (Tau13), gliosis (GFAP), and tau pathology (pTau 202/205; AT8) to confirm huTau distribution and investigate potential neurobiological mechanisms of tauopathy. Mice tolerated retro-orbital injections and rmTBI procedures well, as indicated by survival analyses. Likewise, blood alcohol concentration measurements confirmed that mice reached target ethanol exposure levels in the chronic intermittent ethanol model. These findings validate the methodological feasibility of using retro-orbital huTau AAV delivery, rmTBI, and ethanol exposure. Behavioral testing revealed notable effects of huTau AAV, rmTBI, and ethanol exposure on acoustic startle, pre-pulse inhibition, spatial memory (Morris Water Maze), and exploratory/locomotor behaviors (open field). For example, our results indicate that the interaction of huTau expression, TBI, and ethanol history led to increased time spent in the center of the open field task, potentially reflecting reduced inhibition and heightened impulsive-like exploratory behavior.

Immunohistochemical analyses confirmed widespread huTau expression throughout the brain, demonstrating that this approach effectively models tauopathy without invasive cranial surgery. These data provide preliminary evidence of behavioral symptoms associated with early-stage CTE and chronic ethanol exposure in mice. This model offers a valuable platform for mechanistic investigations of CTE pathophysiology and potential therapeutic targets in future studies.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR160.07/E12

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Michigan State University Tetrad Fund

Title: Novel zebrafish model for tauopathy utilizing cerebroventricular microinjection of hyperphosphorylated tau (p-tau)

Authors: M. FACCHINELLO¹, J. LAMP², S. SARASAMMA³, H.-T. HAGAR¹, K.-W. WANG¹, A. RIETHMILLER¹, J. KIMMEL³, I. E. VEGA⁴, W. LI³, M.-H. KUO¹, *Y.-W. CHUNG-DAVIDSON³;

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Abstract: Tau is a microtubule-associated protein that is integral for healthy neurological functions. It pathologically aggregates in tauopathies, characterized by accumulation of aberrantly phosphorylated tau. Zebrafish models have been demonstrated to provide valuable insights into human diseases. Here we investigated tau-mediated toxicity in zebrafish brain by introducing recombinant PIMAX-based hyperphosphorylated tau (p-tau) via cerebroventricular microinjection (CVMI). Untreated controls and fish receiving p-tau (30, 60, 90 ng/μL in vehicle) were evaluated for behavioral performances. Proteomics analysis was conducted on a different group of fish (6 months post-CVMI), including no treatment (control), vehicle (sham), unphosphorylated tau (15 or 30 ng/μL), or p-tau (15 or 30 ng/μL). Light/dark preference tests revealed p-tau-induced behavioral alterations: increased rotational frequency in both directions and a higher frequency in the light zone (χ^2 test, DF = 3, $p < 0.001$). Notably, 90 ng/μL p-tau significantly increased total distance moved compared to both control and p-tau 30 ng/μL groups (one-way ANOVA test, DF = 3, $p < 0.01$). These behavioral effects were largely transient, diminishing after the first week. Proteomic analysis highlighted long-term protein changes in zebrafish brain. Decreased level was observed for MAP41 in both p-tau groups. Reduced levels of CYFIP2 and GAP-43 were observed in both tau and p-tau groups compared to control while TDP-43 was found to be upregulated in tau and p-tau groups. These results highlight the feasibility of using CVMI p-tau treatment in zebrafish to model human tauopathies. Future work includes developing a p-tau CVMI transgenic zebrafish model that expresses human tau and further elucidating p-tau's transient and long-term effects post CVMI.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: CurePSP 710-2025-03-Atwood
University at Buffalo Experiential Learning Network
Collaborative Learning and Integrated Mentoring in the Biosciences
Undergraduate Program (CLIMB UP)
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NINDS R01NS117628

Title: Establishing a time course for midbrain-to-pons ratio decline and behavioral deficits in a hTau ChAT-Cre rat model of progressive supranuclear palsy-richardson's syndrome

Authors: K. GETFIELD¹, A. REDD¹, J. A. SPERNYAK², *S. D. CLARK³;

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Abstract: Progressive Supranuclear Palsy-Richardson's Syndrome (PSP-RS) is a rare neurodegenerative tauopathy often misdiagnosed as Parkinson's Disease (PD) due to overlapping symptoms such as bradykinesia, postural instability, and recurrent falls. Despite clinical similarities, PSP-RS involves more severe midbrain atrophy and cholinergic loss in the pedunculopontine nucleus (PPN), typically resulting in death within 5-8 years of diagnosis. Magnetic Resonance Imaging (MRI) can differentiate PSP-RS from PD, particularly using midbrain-to-pons volume ratios and lateral ventricle enlargement.

Previously, our lab showed that 5 months after human tau (hTau) transduction in cholinergic PPN neurons, our ChAT-Cre rat model recapitulated PSP-RS features, including cholinergic and substantia nigra neuron loss. PSP-RS-like behavioral deficits were observed, including impaired acoustic startle reflex (ASR), poor performance on the horizontal ladder, and hindlimb clasping. ASR impairment correlated with the midbrain-to-pons ratio ($r^2 = 0.5097$, $p = 0.0307$), a relationship not seen in eGFP controls. These findings led us to age the rats further. This study aims to establish a time course between declining midbrain-to-pons ratios and the development of behavioral deficits.

ChAT-Cre rats (n = 46; 21 males, 25 females) received AAV8-DIO-1N4R hTau, eGFP (control), or Null vector (non-coding control). MRI scans were acquired longitudinally at 7, 12, and 17 months, with ex vivo imaging at 23 months. ASR and motor assessments were done at 5 and 17 months. MRI data were collected on a 4.7T scanner using a 35mm RF coil and analyzed with Analyze 14.0 using rat brain atlases.

Preliminary results show ventricular enlargement beginning at 12 and 17 months in hTau rats compared to controls, supporting age-related PSP-RS pathology. Since midbrain-to-pons ratios are reduced in PSP-RS patients, we hypothesize a progressive decline in this ratio in hTau rats across 7, 12, 17, and 23 months, correlating with the onset and progression of PSP-RS-like behavioral deficits. This study design enables the tracking of structural changes from early to late stages of hTau-induced neurodegeneration and links these changes to behavioral impairments within the same animal. This model provides a valuable platform for identifying MRI biomarkers that may support early diagnosis, track disease progression, and guide the evaluation of therapeutic interventions in PSP and related tauopathies.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Program #/Poster #: PSTR160.09/E14

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: National Institutes of Health [1R01AG084552-01A1]

Title: Loss of hel-1 genes suppresses toxicity in a transgenic *Caenorhabditis elegans* model of tau

Authors: *A. SCIOCCHETTI¹, R. L. KOW², B. C. KRAEMER³, A. SAXTON⁵, A. BEALE⁶, R. ECK⁴;

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Abstract: Tau is a microtubule-stabilizing protein that accumulates pathologically in neurons when hyperphosphorylated, contributing to neurodegenerative diseases such as Alzheimer's Disease and Frontotemporal Dementia (FTD). We study the mechanisms driving tau toxicity using a transgenic *C. elegans* model in which human 1N4R tau is expressed in neurons. This expression causes the aggregation of hyperphosphorylated tau, locomotor deficits, neuron loss and shortened lifespan. We have found that mutations in hel-1, a homolog to human UAP56/DDX39B that encodes a RNA helicase critical in the regulation of mRNA export and splicing, suppresses tau-induced toxicity. This was of interest because previously loss of aly/ALYREF, a component of the transcription export (TREX) complex with UAP56, was shown to suppress tau-induced toxicity in tau transgenic *C. elegans*. We found evidence for an epistatic relationship between hel-1 and aly in tau transgenic *C. elegans*, with hel-1 and aly mutations together rescuing the locomotor phenotype exhibited by tau transgenic animals similarly to either mutation alone. To further understand the role of hel-1 in tau-induced toxicity, we have investigated the effects and mechanism of hel-1 mutations on tau-induced toxicity. We have performed immunoblot to measure variations in protein expression caused by these mutations. We have also performed RNA sequencing to both gain insight into functional conservation of hel-1 and possible molecular mechanisms relevant to tauopathy. By comparing the results of hel-1 mutations to loss of aly, we can further understand the mechanism in which the TREX complex may regulate toxic tau phenotypes.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: Grant from the National Institute on Aging (1RF1AG074256-01A1 to A.K.S.)

Title: Extracellular vesicles from Human iPSC-derived NSCs can alleviate tau phosphorylation and neurogenesis decline in PS19 mouse model of tauopathy

Authors: *R. S. BABU, V. RAO, M. KODALI, Y. SOMAYAJI, S. ATTALURI, E. NARVEKAR, L. N. MADHU, X. RAO, B. SHUAI, S. RAO, A. K. SHETTY;
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Abstract: Tauopathies are neurodegenerative diseases characterized primarily by the hyperphosphorylation of tau protein, which leads to the formation of neurofibrillary tangles within neurons. Extracellular vesicles (EVs) shed by human induced pluripotent stem cell (hiPSC)-derived neural stem cells (NSCs) carry a cargo of miRNAs and proteins capable of promoting antioxidant, anti-inflammatory, neurogenic, and neuroprotective effects, as well as inhibiting tau phosphorylation. This study investigated the efficacy of hiPSC-NSC-EVs in alleviating tau hyperphosphorylation, a hallmark of tauopathy, and hippocampal neurogenesis decline, using the PS19 mouse model. Three-month-old female PS19 mice received four intranasal doses of hiPSC-NSC-EVs (15 billion EVs per dose, administered once every two weeks over 1.5 months). After completing the treatment regimen (i.e., at 5.5 months of age), the animals were assessed for hippocampus-dependent cognitive function using an object location task (OLT) and episodic-like memory using a behavioral pattern separation task (PST). The untreated PS19 mice failed to form an object location memory in the OLT, and their pattern separation ability was impaired compared to the naïve control mice. In contrast, the PS19 mice that received hiPSC-NSC-EVs treatment demonstrated proficiency in forming object location memory formation and pattern separation, suggesting better maintenance of hippocampus-dependent cognitive function and episodic memory encoding. The improved brain function in hiPSC-NSC-EVs-treated PS19 mice was associated with a significant reduction in tau phosphorylation, as measured through AT8 immunostaining and area fraction analysis of AT8+ structures in different brain regions. The reductions in AT8+ structures in hiPSC-NSC-EVs treated PS19 mice were statistically significant in the medial prefrontal cortex (mPFC), the entorhinal cortex, and the CA3 subfield of the hippocampus, compared to untreated PS19 mice. Furthermore, analysis of hippocampal neurogenesis, measured through 5'-bromodeoxyuridine (BrdU) labeling of newly born cells and dual immunofluorescence with BrdU and neuron-specific nuclear antigen, revealed that hiPSC-NSC-EVs-treated PS19 mice displayed higher levels of neurogenesis than untreated PS19 mice, implying better preservation of hippocampal neurogenesis processes with hiPSC-NSC-EVs treatment. Thus, intermittent hiPSC-NSC-EVs treatment commencing from the early stage of tauopathy can maintain better cognitive function for extended periods, associated with significantly reduced tau phosphorylation and improved hippocampal neurogenesis.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.11/E16

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant 1R21AG085590
NIH Grant 1R21AA029784-01A1

Title: Effect of Acute Alcohol Exposure on Tauopathy Markers in Mouse Cortex

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Abstract: Background: Alzheimer's disease (AD), increasingly prevalent in aging populations, is exacerbated by alcohol consumption, which impairs brain metabolism and promotes AD risk. Alcohol may influence tau pathology via disruptions in protein acetylation—alterations in histone and tau acetylation are hallmark features of AD. While alcohol induces neurodegeneration in rodents, its role in tau-driven dementia remains unclear. **Methods and Results:** Using 9-month-old wild-type and humanized htau mice (an A β -independent tauopathy model), we combined metabolic tracing and molecular analyses to assess alcohol's impact on tau acetylation, phosphorylation, and aggregation. Acute alcohol (3 mg/kg body weight IP injection) induced time-dependent phosphorylation of tau at threonine 205 (pTauT205) and serine 396 (pTauS396, PHF-1)-key sites associated with neurofibrillary tangles formation- in the hippocampus of wild-type mice. These changes were associated with increased total tau (Tau5) accumulation. In htau mice, the same dose elevated cortical tau acetylation (acTauK174) and phosphorylation (pTauSer202/T205) and increased total tau within 4 hours. Dose-escalation studies (0-5 mg/kg) revealed that higher alcohol doses (≥ 3 mg/kg promoted high molecular weight tau phosphorylation and aggregation, correlating with elevated CBP expression—the enzyme responsible for tau acetylation. Mass spectrometry analysis of htau mice administered deuterated ethanol (EtOH-d6) showed significant [²H₃]acetyl enrichment in cortical histones, but no detectable [²H₃]acetyl incorporation into tau after short-term exposure. These results indicate that alcohol-induced epigenetic changes likely influence tau accumulation indirectly, rather than direct tau acetylation. **Conclusions:** Acute alcohol exposure disrupts tau acetylation and phosphorylation, fostering tau aggregation and potential formation of neurofibrillary tangles involved in neurodegeneration. These findings implicate epigenetic and post-translational modifications as mechanisms by which alcohol accelerates tauopathy progression, highlighting potential targets for therapeutic intervention.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Program #/Poster #: PSTR160.12/E17

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant NS088322
NIH Grant AG084497
Fulbright Scholarship FY-2024-TR-SS-13

Title: Early serotonergic alterations in a mouse model of alpha-synucleinopathy

Authors: F. WU¹, E. CINAR², Y. LIANG³, O. BOX¹, K. HOXHA¹, *K. C. LUK¹;
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Abstract: Background and Aim: Lewy body diseases (LBD) including Parkinson's disease present with both motor and non-motor symptoms. Dopaminergic dysfunction and degeneration are well-characterized in both humans and animal models, but serotonergic alterations, especially during early disease stages, remain less understood. Early serotonergic impairment may contribute to prodromal symptoms (e.g. depression and anxiety). This study aimed to assess the impact of alpha-synuclein (aSyn) pathology on serotonergic architecture and function following preformed fibril (PFF) injection into the nucleus accumbens (NAcc).

Methods: B6C3 mice were stereotactically injected with aSyn PFFs or PBS into the NAcc and sacrificed at 1- or 3-months post injection (MPI). Serotonin transporter (SERT) immunohistochemistry was used to assess serotonergic innervation in brain sections. Quantification was performed using QuPath with a custom-trained neural network-based pixel classifier to measure immunoreactivity in axons and terminals. The integrity of the Raphe nucleus, a major serotonergic center, was also assessed using tryptophan hydroxylase (TPH) staining. All procedures were approved by the University of Pennsylvania's IACUC. Behavioral studies are underway to assess associated phenotypic changes.

Results: Marked reductions (~10-fold) in SERT density were observed as early as 1 MPI in regions including the caudate-putamen, nucleus accumbens, hippocampus, amygdala, thalamus, hypothalamus, frontal cortex, substantia nigra, and ventral tegmental area. This was confirmed by bulk transcriptomics analysis. These changes persisted at 3 MPI. In contrast, minimal SERT loss was observed in the locus coeruleus and cerebellum at 1 MPI.

Conclusion:

Our findings suggest that aSyn pathology initiating from the NAcc can trigger widespread serotonergic deficits that precede dopaminergic degeneration in the PFF synucleinopathy model, and show similarities to the early patterns of degeneration and non-motor features in LBD. Although further validation in larger cohorts is necessary to confirm these observations, this model provides a promising platform for investigating early disease processes.

Disclosures: F. Wu: None. E. Cinar: None. Y. Liang: None. O. Box: None. K. Hoxha: None. K.C. Luk: None.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.13/E18

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH NS134833

Title: Impact of alpha-synuclein pathology in Locus coeruleus on cell morphology, cognition and arousal.

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Abstract: The locus coeruleus (LC) is a brainstem nucleus that plays a central role in regulating attention, arousal and the sleep-wake cycle. It is one of the earliest areas to develop alpha-synuclein aggregation and neuron loss in patients with Dementia with Lewy Body (DLB) and Parkinson's disease dementia (PDD). DLB and PDD are both associated with cognitive fluctuations, unpredictable shifts in cognitive abilities, arousal and attention, but the underlying mechanism is unknown. Given the key role of LC in attention and arousal, α -syn pathology in this region could contribute to fluctuations. However, it is not known whether LC hyperactivity or cell loss would be more likely to cause such fluctuations. We hypothesize that modest α -syn overexpression may differentially impact vulnerable LC cells and cognitive behavior compared to synuclein that's been induced to aggregate. To test this, we compared different models of LC dysfunction: 1) viral overexpression of human α -syn. 2) mouse pre-formed α -syn fibrils (PFFs). 3) viral overexpression of human α -syn + human pre-formed α -syn fibrils (PFFs). 4) IP injections DSP-4 neurotoxin, for LC cell morphology and behavior. We also compared the LC cells of these mouse models to human LC neurons from autopsy tissue with and without α -syn pathology. Our preliminary data show that human LC neurons show multiple different aggregate patterns resembling aspects of mouse models. To evaluate whether α -syn OE, aggregation or toxic cell loss in LC recapitulated aspects of cognitive fluctuations, we developed behavioral tasks to evaluate relevant aspects of cognition, attention and arousal in mouse. First, we used a spatial learning task (Barnes maze) followed by a rapid-reversal task (STARR-FIELD) to test behavioral flexibility. We speculated LC pathology would result in normal spatial learning, but impaired reversal learning. Indeed, our preliminary data showed mice with α -syn OE matched control mice in spatial learning and memory but showed more difficulty adapting to new targets. This suggests that α -syn overexpression alone in the LC may alter behavioral flexibility. We also developed an in-home cage task with an automatic tracking system (by Vulintus), to assess fluctuations across time. This tests cognition over the circadian cycle, providing repeated measurements of timing and behavioral flexibility. Finally, we evaluated sleep and novelty

evoked arousal by measuring the latency to return to sleep, via EEG, after encountering a novel object during the sleep phase.

Disclosures: **K. Gupta:** A. Employment/Salary (full or part-time): University of Iowa. **A. Bertolli:** None. **Y. Liu:** None. **R. Thangavel:** None. **G. Schoening:** None. **G.M. Aldridge:** None.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NINDS R01 NS129711
STEAD Family Scholars Program
Iowa Neuroscience Institute (INI) Research Program of Excellence

Title: Impact of alpha-synuclein aggregation in cortex and ventral tegmental area

Authors: ***S. SMADI**¹, J. RYSTED¹, K. GUPTA⁴, P. PELLATZ¹, D. LIU¹, Y. LIU¹, A. BERTOLLI², R. THANGAVEL¹, G. M. ALDRIDGE³;

¹Univ. of Iowa, Iowa City, IA; ²Univ. of Iowa, Coralville, IA; ³Neurol., Univ. of Iowa, Iowa City, IA; ⁴Systems Neurophysiol., Dept. of Neurology, Univ. of Iowa, Iowa city, IA

Abstract: Lewy body dementias (LBDs), including Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB), are characterized by the accumulation of alpha-synuclein (a-syn) protein aggregates deposited in multiple regions of the brain. Unlike PD without dementia, PDD and DLB are characterized pathologically by a-syn aggregates in regions beyond the brainstem, including the cortex. However, it remains unclear whether local cortical a-syn or worsening brainstem pathology drives disease progression to dementia. There is a pressing need to determine the regional effects of synuclein pathology, including how the aggregates in affected cells modify function and morphology, to develop targeted treatments for dementia. Previous work from our group has shown that injecting human a-syn pre-formed fibrils (PFFs) into the prefrontal cortex of mice led to cortical and subcortical a-syn aggregation associated with behavioral changes. Data published by other groups (Blumenstock 2021) suggests that introducing a-syn PFFs in mice results in increased spontaneous neuronal activity levels, enhanced response, and increased synchrony in the somatosensory cortex. However, most published studies do not distinguish between the impact of local synuclein and the remote effects of dopamine depletion. To evaluate the impact of local synuclein aggregation, we used viral vector overexpression of a-syn (AAV1-hSyn1-hSNCA-WPRE) in two applications. First, we assessed how overexpression of a-syn in the cortex affects neuronal firing during a cortical-mediated behavioral flexibility task. By employing 2-photon microscopy combined with cortical prisms and a head-fixed behavioral task, we evaluated neuronal firing and changes in

morphology across cortical layers. Our preliminary data suggest that local overexpression of a-syn modifies cortical activity during this task. Second, we targeted a-syn pathology to a separate region, the ventral tegmental area. This region projects dopaminergic fibers to the cortex, among other regions, and is hypothesized to affect cortical dysfunction as seen in LBDs. As a preliminary study, we focused on the overexpression of a-syn combined with PFFs to assess the maximum impact of pathology in this region on morphology and cell death. These parallel regional studies address our hypothesis regarding the potential contributions of a-syn pathology in different populations. Ongoing work compares vulnerable regions using parallel methods, including a-syn tagged with a fluorescent linker, which will allow evaluation of morphology in various cell types with and without the induction of aggregation.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Program #/Poster #: PSTR160.15/E20

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: 1R01AG091184
Stead Family Scholars Program for Early Career Investigator Research
Carver College of Medicine funded Research Program of Excellence:
SMASH Dementia!

Title: Exploring the burden of co-pathology in cortical synapse loss in neurodegenerative disease

Authors: *Y. LIU¹, M. BERRY-STOELZLE², R. THANGAVEL², P. ALDER³, M. HUNTER⁴, S. PIERSON⁴, K. DENIZ⁵, G. SCHOENING², M. M. HEFTI⁴, K. FIOCK⁴, G. M. ALDRIDGE²; ²Neurol., ³Med. Scientist Training Program, Carver Col. of Med., ⁴Pathology, ¹Univ. of Iowa, Iowa City, IA; ⁵Univ. of California San Francisco, San Francisco, CA

Abstract: Neurodegenerative dementias, including Alzheimer's disease dementia, Lewy body dementia, and frontotemporal dementia, are characterized by cognitive decline, neuronal loss, and changes in neuron structure and function. Pathological markers used to diagnose these diseases include the presence of mis-folded protein aggregates containing amyloid, tau, alpha-synuclein and TDP-43. Studies have shown that these proteins often co-occur in the same patients, with copathologies being a potential contributor to disease severity. Additionally, although protein aggregates and cell loss are used for clinical staging and disease diagnosis, evidence suggests cognitive decline is strongly associated with synapse loss. However, the relative influence of individual protein pathologies versus copathology on synapse loss is currently unknown. We hypothesized that regional copathological burden leads to the greatest loss of dendritic spine density in the infragranular layers of the cortex. To test this hypothesis, we

collected fresh tissue from the anterior cingulate during brain autopsy of consecutive neurodegenerative disease donors and control autopsies. Tissue was stained using the Golgi method to visualize dendritic spine morphology and changes in dendritic complexity. We analyzed post-mortem brain tissue of 10 individuals and measured dendritic spine density, morphology and neuronal complexity. We used synaptophysin and PSD-95 staining and puncta quantification as a second measure of synaptic density. Using strategic dual-immunostaining, we study the impact of regional co-pathology versus remote co-pathology in subcortical regions including the locus coeruleus, basal ganglia, hippocampus and amygdala on synapse loss. Our study presents a view of cortical synapse loss considering the impact of local and remote copathological burden in cortical and subcortical regions.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR160.16/E21

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant no.R01AI147731

Title: Comparative analysis of biochemical and behavioral alterations in mice treated with nanoformulated versus conventional antiretroviral drugs

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Abstract: Human Immunodeficiency Virus (HIV) affects approximately 39.9 million individuals globally as of 2023. While combination antiretroviral therapy (cART) has dramatically improved the life expectancy of the people with HIV (PWH), long-term use, especially in aging populations, has been associated with neuropsychiatric effects such anxiety. Therefore, there is a current need to develop HIV drug formulations that are safe for long-term use. In this regard, the study used a comparative analysis to investigate if cART drugs and their polymer based nanoformulations contribute to dopamine (DA) metabolism and respective behavioral changes in the treated mice. In this study, male BALB/c mice were treated with clinically available cART drugs such as dolutegravir (DTG), emtricitabine (FTC), tenofovir disoproxil fumarate (TDF), and their respective nanoformulated (NF) drugs (NF-DTG, NF-FTC) once a week over a 4-week period. Behavioral phenotyping via the open field test (OFT) and ANY-maze video tracking

software assessed anxiety-like behaviors through locomotor activity, center/periphery time. Biochemical tests were used to assess concentration of specific neurotransmitters to corroborate behavioral phenotypes. Overall, analysis indicated that DTG-treated mice displayed significantly increased anxiety-like behaviors, indicated by reduced center zone time and increased peripheral activity. FTC and NF-FTC groups showed similar behavioral shifts compared to non-nanoformulated counterparts. NF-DTG also elevated total locomotion. Neurochemical assays of the prefrontal cortex and striatum revealed DA depletion and altered DA metabolite ratios in NF-DTG-treated mice. Moreover, one-dose-per-week treatments significantly elevated 5-HIAA, norepinephrine (NE), epinephrine (EPI), and acetylcholine (ACh), while decreasing GABA suggested a broader monoaminergic and cholinergic disruption. Elevated 5-HIAA indicates altered serotonin metabolism in treated mice. Conversely, the reduction in GABA, the primary inhibitory neurotransmitter, removes a crucial brake on neural excitability, allowing for exaggerated or uncontrolled movements. Together, these alterations in neurotransmitter levels help explain the increased anxiety-like behaviors and abnormal movement patterns observed in treated mice. These results highlight the increased risk of neurotoxicity of antiretrovirals modulating anxiety-related behaviors and disrupting neurotransmitter systems. Overall, the study suggests that neuropsychiatric monitoring and formulation-specific safety assessments are critical in optimizing long-term cART strategies among PWH.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Program #/Poster #: PSTR160.17/E22

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NSF Cooperative Agreement #OIA-2242771
Marshall University Undergraduate Creative Discovery and Research
Scholar Award

Title: Silver nanoparticles induce p-tau aggregate formation in rat brain.

Authors: *R. SMITH¹, N. SPITZER²;
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Abstract: Silver nanoparticles (AgNPs) are incorporated in products including toys, cosmetics, and surgical tools due to their antimicrobial properties. Because of their unique physical properties, AgNPs pass through the blood-brain barrier. When animals are exposed, AgNPs bioaccumulate in the brain and persist for months with no clearance. Previously, our lab found that AgNPs inhibit neurite outgrowth and disrupt the cytoskeletal protein f-actin *in vitro*. Actin filaments and microtubules maintain a dynamic relationship to support the cytoskeleton, which is

critical to neuroplasticity. AgNPs directly induce the formation of reactive oxygen species (ROS) *in vivo*. Tau protein serves to support the structure of microtubules and becomes hyperphosphorylated (p-tau) during oxidative stress, forming aggregates that cause a loss of signaling capabilities and apoptosis. Once tau is abnormally phosphorylated, it disassociates from the cytoskeleton, contributing to the disintegration of microtubules. Aggregated p-Tau localizes to nuclei and may hinder nuclear and cytoskeletal communication. Superoxide Dismutase 1 (SOD1) breaks down toxic ROS to reduce oxidative stress in cells. SOD1 is typically located in the cytoplasm but shifts to the nucleus during times of cellular stress to protect DNA. This project aimed to determine if AgNP induce nuclear accumulation of SOD1 and p-tau in the dentate gyrus (DG) of the hippocampus. The DG is a site of active cytoskeletal remodeling that is involved with neurogenesis and memory formation with increased sensitivity to oxidative stress. After nine weekdays of treatment with control, low (25 mg/kg) or high (100 mg/kg) oral AgNPs in sucrose, brains were collected either one day after treatment to investigate acute effects or after one month to investigate the effect of bioaccumulated AgNPs. Using immunohistochemistry, we quantified p-tau aggregation and SOD1 expression localized to nuclei of the DG. p-Tau and SOD1 signals were significantly increased in brains collected immediately after AgNP exposure. Moreover, both markers remained significantly increased in DG after exposure to bioaccumulated AgNPs. These findings suggest that exposure to AgNPs induces long-term disruptions to the cytoskeletal proteins that underlie neuroplasticity and activate cellular mechanisms associated with neurodegenerative diseases. As AgNPs continue to be incorporated into everyday products, these data emphasize the importance of investigating their effect on neuroplasticity.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Program #/Poster #: PSTR160.18/E23

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant R01AG068581
NIH Grant RF1AG076122
NIH Grant R21AG085314
NIH Grant R01AG077771

Title: Profiling the Cell Type-Specific Proteomic Response to Tau Pathology in Mouse Brain

Authors: M. C. WREN¹, *D. MORDERER², C.-W. TSAI², W. QIAO³, D. W. DICKSON⁴, N. ZHAO⁵, J. PENG⁶, W. ROSSOLL³;

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Abstract: Tauopathies are a diverse group of neurodegenerative diseases characterized by the accumulation of hyperphosphorylated tau protein into insoluble aggregates in the brain. Although tau pathology is known to be accompanied by neuronal loss, inflammation and reactive gliosis, the molecular mechanisms underlying cell-type-specific responses to tau accumulation in neurons, microglia, and astrocytes remain poorly understood. To resolve the proteomic changes of defined brain cell populations in response to tau pathology in vivo, we employed neuron-specific TurboID proximity labeling and single-cell type isolation of astrocytes and microglia using magnetic-activated cell sorting (MACS). Cell-type-specific proteomes were obtained from brains of B6;Cg-Tg(Prnp-MAPT*P301S)PS19Vle/J (PS19) mice and their wild-type littermates at 6 and 11.5 months of age, representing early- and late-stage disease, respectively (n = 4 per sex/genotype/age/cell type), followed by proteomic analysis by LC-MS/MS. We confirmed the enrichment of known cell-type-specific markers within the corresponding proteomes, validating the specificity of our approach. The proteomic profiles largely mirrored established pathological features of tauopathy, such as early synaptic loss and microglial activation. Notably, early-stage changes also included downregulation of mitochondrial function and upregulation of select synaptic proteins. Among the most striking alterations was the upregulation of the homeobox protein Mohawk (Mkx), observed at both early and late stages of disease progression. Interestingly, our preliminary data suggests its co-aggregation with tau pathology in brains from PS19 mice, as well as in post-mortem frontal cortex sections from Alzheimer's disease patients. By delineating distinct proteomic responses in neurons, astrocytes, and microglia, this study identified stage- and cell-type-specific proteomic changes in tauopathies and uncovered novel tau pathology-associated proteins for further functional analysis in tauopathy disease models.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant 1R21AG085590
Kent State University-NEOMED Brain Health Research Institute

Title: Impact of high-fat diet on tau pathology in hTau mouse model.

Authors: *A. ARIAS-ALVARADO, A. GRDEN, M. AGHAYEV, B. CSUBAK, S. ILCHENKO, M. A. SMITH, C. M. DENGLER-CRISH, S. M. FLEMING, T. KASUMOV;
Pharmaceut. Sci., Northeast Ohio Med. Univ., Rootstown, OH

Abstract: Background: Alzheimer's disease (AD), one of the top ten causes of death in the United States, has no cure and is characterized by tauopathy and metabolic dysregulation. While

type 2 diabetes (T2DM) is a known risk factor for late-onset AD, its mechanistic link remains unclear. Post-translational lysine acetylation, regulated by acetyl-CoA, influences metabolism, epigenetics, and protein stability. Altered substrate metabolism in T2DM affects NAD⁺ and acetyl-CoA levels, impacting histone and tau acetylation, which are associated with age-related memory decline. To assess the impact of diet-induced diabetes on tauopathy, we fed 3-5-month-old humanized *hTau* mice with a high-fat diet (HFD) or chow for 8 months and assessed the effect of diet on tau acetylation, tauopathy markers, and cognitive functions. **Results:** HFD-fed mice developed obesity, hepatomegaly, and systemic insulin resistance, impairing glucose utilization. Behavioral tests showed an increased fear response in the elevated plus maze, which is an early sign of cognitive decline, while Y-maze and object recognition revealed working memory loss and attention deficits. Immunofluorescence detected pathological pTauSer202 and acTauK174, which co-localized but also appeared independently, indicating different tau species. In 10-12-month-old mice, pTauSer202 showed fibrillar morphology, indicative of advanced pathology. Slight increases in acTauK174 near fibrils suggest a relationship, yet they were not co-localized, implying separation of acetylated and phosphorylated tau. No pathological pTauSer202 and acTauK174 were detected in *hTau*^{-/-} mice. **Conclusion:** Our findings suggest that acetylation-driven alterations in transcription, protein degradation, and tau aggregation contribute to T2DM-associated tauopathy and cognitive decline in Alzheimer's disease. Since the inhibition of lysine acetyltransferases (KATs) alleviates tau pathology, this study may inform the development of selective, site-specific acetylation inhibitors aimed at reducing tau aggregation and neurodegeneration in T2DM-associated tauopathies.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Blueprint and BRAIN Initiative D-SPAN Award (F99/K00)

Title: Tdp43's role in synaptic metabolism in the adult mouse brain

Authors: *E. BREWER¹, R. KIMURA¹, N. G. KHOLODILOV¹, Z. LI², J. LIPPONEN¹, M. DEBNATH¹, L. STIENE¹, G. ZHANG², U. HENGST¹, T. T. SANDS¹, A. YAMAMOTO¹;
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Abstract: A growing number of studies find that the abnormal cytosolic accumulation of TDP43 is correlated with worsened cognitive decline across many neurodegenerative diseases. Although the cytosolic aggregation of TDP43 has been suggested to lead to its loss of function, the breadth

of TDP43 function is not yet fully understood. Thus, we aimed to perform an unbiased, holistic study of TDP43 function by defining its protein interaction network in the adult mouse brain. TDP43 is a DNA/RNA binding protein with an intrinsically disordered C-terminus, which partakes in dynamic and transient protein interactions. Given the presence of the intrinsically disordered domain, we hypothesized that to capture all TDP43 interactions it would be essential to use an approach that would capture interaction partners regardless of interaction strength. We therefore fused TDP43 to TurboID, a promiscuous biotin ligase that can efficiently label nearby proteins and delivered it via AAV-PHP.eB. TDP43 interactions in the brain reflected TDP43's predominantly nuclear localization. 37% of identified interactors were associated with splicing (e.g. Snrpd, Sf3b, Sfpq), many of which had not previously been identified, and 65% were known RNA binding proteins (including many Hnrnp proteins), suggesting promising specificity of this approach. Additionally, we identified numerous synaptic proteins interacting with TDP43, consistent with previous studies implicating TDP43 in activity dependent synaptic local translation. To pursue this further, we fractionated homogenates into nuclear and synaptosomal fractions to determine how the interactomes might change in response to neuronal activity. We found that whereas the nuclear TDP43 interactome remained unchanged, neuronal activity significantly altered the synaptic TDP43 interactome, especially of proteins involved in synaptic metabolism. These data suggest that TDP43 may play a key role in regulating ATP production and utilization at the synapse. To test this hypothesis, we present preliminary evidence using orthogonal validation approaches such as proximity ligation within brain tissue, as well as within primary neuronal cultures before and after 4-aminopyridine and bicuculline treatment supporting these findings. Collectively, these findings point to a novel mechanism by which TDP-43 dysfunction may impair synaptic metabolism, driving synaptic loss and accelerating cognitive decline in neurodegenerative disease.

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Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.21/E26

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH grant R21AG058080

Title: Evaluating the Effect of HDAC6 Modulation on Tau Pathology

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Abstract: Alzheimer's Disease (AD) is a neurodegenerative disease characterized by A β -plaques, neurofibrillary tangles, and chronic neuroinflammation. However, due to an incomplete understanding of disease progression, AD currently lacks many suitable treatment options. HDAC6 is a cytosolic HDAC whose expression is increased in AD patients and is involved in several processes that may contribute to disease progression, such as NLRP3 inflammasome activation, autophagosome-lysosome fusion, and regulation of microtubule dynamics. In recent years HDAC6 inhibitors have shown promise in alleviating numerous inflammatory diseases and potentially neurodegenerative diseases. This project will investigate how genetic and pharmacologic modulation of HDAC6 with an HDAC6-specific inhibitor will affect disease pathology by interrogating disease hallmarks such neuronal degeneration, tau pathology, gliosis, and cognitive and memory defects using primary mouse neurons, primary mouse microglia, and P301S tau mice aged to 7-months and up. For this study, we generated cell-type specific KOs of HDAC6 and have preliminarily characterized these mice behaviorally and pathologically compared to standard P301S mice. Additionally, after confirming the efficacy of this inhibitor on known substrates like acetyl-tubulin and tau, we exposed primary mouse neurons and primary mouse microglia up to 4uM of an HDAC6 inhibitor following either pathologic tau or A β -insults and assessed the aforementioned readouts. By doing so, this project aims to fill a void in the field by exploring the cell type specific effects of HDAC6 modulation in a neurodegenerative context in an effort to inform future treatment paradigms.

Disclosures: K. Pellegrino: None. T.J. Cohen: None.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.22/Web Only

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: (NIH) R01 AG089566
NIH R21 AG068423
23AARG-1026776
T32GM142519

Title: Altered translation in the hippocampus precedes contextual fear memory deficits in PS19 mice

Authors: *A. GRETZINGER¹, J. PARK²;
²Pharmacol., ¹Wayne State Univ., Detroit, MI

Abstract: Tau is a cytoskeletal protein that plays versatile roles in cells, including cytoskeletal organization and intracellular transport. However, its pathological contribution has been noted in several neurodegenerative disorders, including Alzheimer's disease and frontotemporal dementia. Evidence has shown several tauopathy models display a reduction in neuronal protein

synthesis in the hippocampus, prefrontal cortex, and amygdala—brain regions crucial to various forms of memory. Protein synthesis is a fundamental process that occurs in both compartment-specific and global manners and is critical for various cellular and behavioral functions, including long-term potentiation and memory. While this evidence indicates additional pathogenic pathways to be considered in tauopathies, the compartment-specific regions of this reduction in protein synthesis have not been investigated. Furthermore, the identification of susceptible protein populations altered by the reduced translation needs to be investigated to reveal molecular targets for intervention. Here, we evaluate the age-dependent, compartment-specific alterations of protein synthesis in the hippocampus of a tauopathy model, PS19, which expresses the human P301S mutant. We report that a significant reduction in protein synthesis across neuronal compartments is observed as early as 4-5 months of age, with an age-dependent decline dropping below a 50% threshold, coinciding with the first observation of contextual fear memory deficits at 9-10 months of age. Additionally, quantitative proteomics revealed that synaptic proteins were amongst the most susceptible to loss preceding memory deficits. Together, these data provide insight into molecular pathways and potential targets for therapeutic interventions in tauopathies and related dementia.

Disclosures: A. Gretzinger: None. J. Park: None.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH R01 AG061875
NIH RF1 AG070391
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SBP P30 CA030199
NIH S10 OD026929
NIH S10 OD030285

Title: Sorla upregulation suppresses global pathological effects in aged tauopathy mouse brain

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Abstract: A role for the trafficking receptor SORLA in reducing A β levels has been well-established, however, relatively little is known with respect to whether and how SORLA can potentially affect tau pathology in vivo. Here, we show that transgenic SORLA upregulation (SORLA TG) can reverse pathological effects in aged PS19 (P301S tau) mouse brain, including tau phosphorylation and seeding, ventricle dilation, synapse loss, LTP impairment and glial

hyperactivation. Proteomic analysis indicates reversion of PS19 profiles in PS19/SORLA TG hippocampus, including pathological changes in synapse-related proteins as well as key drivers of synaptic dysfunction such as Apoe and C1q. snRNA-seq analysis reveals suppression of PS19- signatures with SORLA upregulation, including proinflammatory induction in glia. Tau seeding and aggregation, neuroinflammation induction are exacerbated in PS19 hippocampus with SORLA deletion. These results implicate a global role for SORLA in neuroprotection from tau toxicity in PS19 mouse brain.

Disclosures: H. Huang: None. T.Y. Huang: None.

Poster

PSTR160: Tauopathies and Synucleinopathies: Animal Model Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant 2T32AG061892-06
Florida Department of Health Ed and Ethel Moore Alzheimer's Disease
Research Program Grant
Barbara's Dream Fund for Frontotemporal Dementia Research &
Education

Title: Identification and Functional Characterization of the Axolotl (*Ambystoma mexicanum*)
Tau Protein

Authors: *Z. STRICKLAND¹, E. D. SMITH², B. I. GIASSEN⁴, J. M. LEWIS³;
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Abstract: Tauopathies are characterized by abnormal aggregation of tau that results in neuronal dysfunction and degeneration. Developing strategies to preserve existing neuronal function, prevent neurodegeneration, or restore lost neurons may have the most potential to combat human tauopathy; however, the adult human brain possesses limited capacity to replace lost neurons. Interestingly, some vertebrate species such as axolotls (*Ambystoma mexicanum*) possess the capacity to regenerate large portions of their anatomy, including the brain and spinal cord. We previously reported that axolotls express a tau protein with high similarity to human tau in the putative microtubule binding domain and C-terminus. In humans, missense mutations of the MAPT gene at the Proline-301 residue within the microtubule binding domain to a lysine (P301L) or serine (P301S) increase the self-aggregation ability of tau and are causal for tauopathy. We previously compared the degree of homology between the human, axolotl, and mouse tau gene and protein. Using confocal immunofluorescent microscopy and proximity ligation assays, we demonstrate co-localization between axolotl tau and the microtubule subunit protein β -tubulin III. Utilizing in vitro tau self-aggregation assays and tau-microtubule binding

assays, we will determine axolotl tau's ability to aggregate and bind microtubules. As the axolotl tau microtubule binding domain possesses a Proline-301 equivalent site (Proline-387), we will also explore how P387S and P387L mutations change the aggregation potential and microtubule binding ability of axolotl tau. We will report the first ever characterization of axolotl tau's ability to bind to microtubules and potential for self-aggregation and how mutations equivalent to the human P301L and P301S tau mutants impact these abilities. Our microscopy data suggests that tau and β -tubulin III co-localize in axolotl brain tissue. These results will further elucidate our understanding of tau-microtubule interactions in the axolotl, unveil axolotl tau's capacity for aggregation, and position the axolotl as a novel model system in which to investigate how a regenerative organism might respond to an attempt to induce tauopathy.

Disclosures: **Z. Strickland:** None. **E.D. Smith:** None. **B.I. Giasson:** None. **J.M. Lewis:** None.

Poster

PSTR161: Stroke: Imaging and Assessment

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Program #/Poster #: PSTR161.01/E29

Topic: D.03. Stroke

Support: RFAG042189 to FS; AARF-21-849749

Title: Differential Effects of Intravenous and Neuron-Specific miR-20a-3p Delivery on White Matter Integrity and Cognitive Recovery After Stroke in Middle-aged Female Rats

Authors: ***Z. AKBARI**¹, D. SAMPATH², F. SOHRABJI³;

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Abstract: Our previous studies show that microRNA-20a-3p (miR-20a-3p) is a promising therapeutic candidate for ischemic stroke, but the precise mechanism and optimal delivery strategy remains unclear. Intravenous (IV) administration of miR-20a-3p in middle-aged female rats after stroke led to robust recovery, improving both acute sensorimotor outcomes and long-term cognition. This was accompanied by preservation of forebrain white matter tracts and reduced secondary neurodegeneration, as evidenced by callosal, internal capsule and anterior commissure volume and ventricular symmetry. Our previous studies also showed that IV mir20a-3p localized to neurons. In the present study, we investigated whether neuron-specific expression of miR-20a-3p would yield similar neuroprotective effects. Using a Tet-inducible AAV vector containing mir20a-3p or a scrambled oligo under the neuron-specific enolase (NSE) promoter, we delivered the construct stereotactically to the striatum. Five weeks later, stroke was induced via middle cerebral artery occlusion (MCAo) followed by ip administration of doxycycline (a Tet analog) to induce expression of the construct. Stroke impaired sensorimotor

function in the acute phase, which was attenuated by neuron-specific mir20a-3p enrichment. In the chronic phase, stroke impaired spatial learning strategies as tested with Barnes maze, which was attenuated by neuronal miR20a-3p, but did not improve recall. Histopathology showed that stroke reduced the volume of the ischemic hemisphere and enlarged ventricular volume, which was not attenuated by neuronal mir20a-3p. Anterior commissure, corpus callosum and internal capsule volumes all showed a significant reduction in the left (ischemic) hemisphere of scrambled oligo treated stroke rats, while in the miR20a-3p enriched stroke group anterior commissure volume was preserved but not corpus callosum and internal capsule. These findings suggest that broader neuroprotection from IV delivery may result from miR-20a-3p engagement with multiple cell types, including astrocytes and microglia targets, not reached by neuron-restricted expression. Overall, our results suggest systemic drug delivery maximizes neuroprotection in stroke recovery. Future studies will focus on determining the cellular target(s) necessary for therapeutic efficacy of post-stroke interventions.

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Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.02/E30

Topic: D.03. Stroke

Support: AHA Grant 25POST1356833

Title: Mapping post-stroke neuroplasticity: cortical activation and connectivity in relation to time and motor deficits.

Authors: *C. DELCAMP^{1,2}, Z. ZHOU³, R. SRINIVASAN³, S. CRAMER^{2,1};

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Abstract: Introduction: Stroke is a leading cause of disability, with post-stroke neuroplasticity a key target to improve outcomes. Electroencephalography (EEG) allows non-invasive brain monitoring of cortical activity (power) and connectivity (coherence). This study explored how stroke alters brain function over time and in relation to motor status.

Methods: Resting-state EEG (256-lead, eyes open) was recorded in 100 stroke patients and 45 controls. Partial correlations explored the links that power and coherence have with time after stroke and motor status. Permutation tests compared patients against controls according to time post-stroke time (early/late) and motor status (high/low).

Results: With greater time post-stroke, theta power decreased, and beta and gamma power increased bilaterally. In early stroke only, theta power was higher while beta and gamma power were lower vs. controls (Fig 1A). With greater time post-stroke, coherence decreased

contralesionally and increased ipsilesionally in lower frequencies, while high-frequency coherence increased bilaterally. Across all frequencies, early stroke patients showed reduced coherence vs. controls, while late patients showed greater coherence (Fig 1B). For all patients, coherence correlated negatively with motor status, with differences according to deficit severity. For beta and gamma coherence, coherence-deficit correlations were negative in patients with low motor scores and positive in those with higher motor scores.

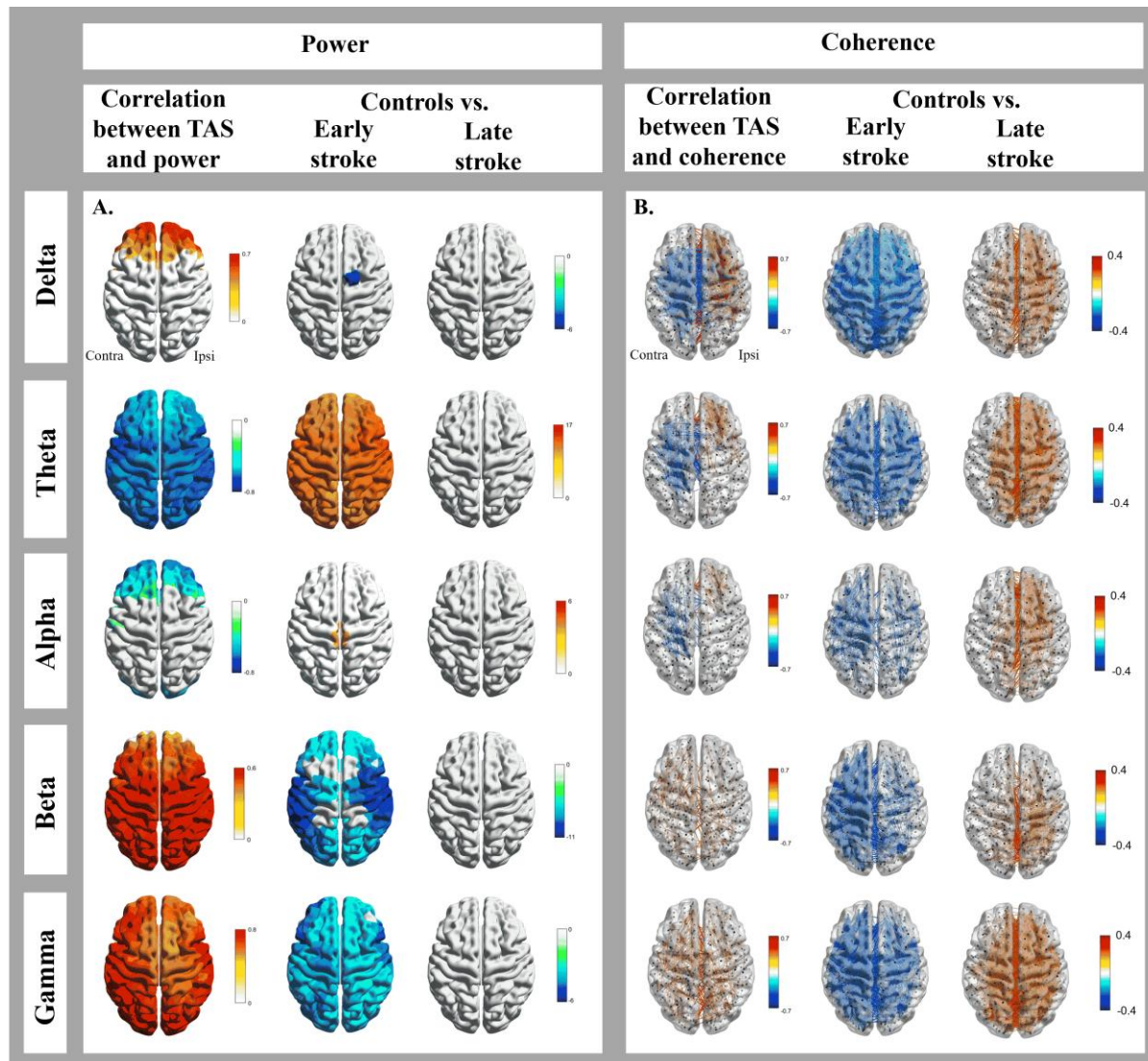


Figure 1: For each frequency band of interest: **(A)** Correlation (ρ) between cortical power and time after stroke (TAS), with age and motor status as covariates ($n=100$). $|\rho| \geq 0.3$ are presented. Also presented are significant differences in relative power between early stroke patients (<90 d post-stroke; $n=29$), late stroke patients (>90 d post-stroke; $n=29$) and healthy controls ($n=45$), after the Benjamini-Hochberg correction. A positive difference represents more power for patients compared to controls. Scales represent observed percentage differences. **(B)** Correlation (ρ) between cortical coherence and TAS, with age and motor status as covariates ($n=100$). Only the 1st percentile and 99th percentile of $|\rho| \geq 0.3$ are presented to enhance readability of results. Also presented are significant differences in cortical coherence between early stroke patients ($n=29$), late stroke patients ($n=29$) and controls ($n=45$), after the Benjamini-Hochberg correction. Scales represent differences in cortical coherence originally expressed in arbitrary units, bounded between 0 and 1.

Conclusions: EEG reveals a bidirectional post-stroke plasticity: early slowing with reduced connectivity, reflecting lesion effects, diaschisis, and enhanced inhibition; and later increased coherence and high-frequency power, reflecting normalization of inhibition and compensatory recruitment. Higher coherence in low-functioning patients may indicate maladaptive plasticity, while in high-functioning patients is beneficial. EEG-based assessment integrating time, motor status, and oscillatory dynamics may inform individualized neurorehabilitation strategies in the future.

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Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

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Program #/Poster #: PSTR161.03/E31

Topic: D.03. Stroke

Support: NIH Grant NS132533
AFOSR Grant FA9550-18-1-0051
DURIP grant 13107771
DURIP grant FA9550-23-1-0627

Title: Acute neuronal stress drives a formin-dependent pro-survival response despite severe ATP depletion

Authors: B. CALABRESE¹, H. ZHOU¹, S. SRAPYAN¹, E. GRINTSEVICH², *S. L. HALPAIN¹;

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Abstract: Neuronal “actinification” is a formin-mediated pro-survival response involving an extensive reorganization of the actin cytoskeleton within the cell body and dendrites following ischemic injury and/or hyperactivation of NMDA receptors in culture and during stroke *in vivo*. During actinification, inverted formin-2 (INF2) mediates the polymerization of highly stable F-actin throughout the somatodendritic compartment. As previously described (Calabrese et al., Nat Comm 2022), this process is initiated by the convergence of two key elements: calcium influx and cell swelling (driven by sodium and chloride influx), and is facilitated by the abrupt increase in available actin monomers that are released from depolymerizing F-actin in dendritic spines. Ordinarily, cellular F-actin polymerizes at the filament barbed end using ATP-bound G-actin in complex with profilin. This incorporated G-actin-bound ATP undergoes hydrolysis to

ADP within the growing filament, and depolymerization occurs at pointed ends, thereby releasing ADP-actin monomers. However, using the ATP sensor iATPSnFR2.A95A.A119L in cultured hippocampal neurons, together with selective ATP synthesis inhibitors, we found that actinification occurs under extremely low ATP conditions, which normally would be expected to disfavor conventional F-actin polymerization. In addition, ATP depletion always preceded actinification. Using pyrene actin assembly assays in cell-free conditions, we provide evidence that INF2 can promote F-actin polymerization using ADP-actin monomers in the absence of ATP. Together, these data suggest that INF2-driven actinification might utilize ADP-bound G-actin as a novel mode of extensive actin filament reorganization during energy stress. *In vitro*, purified ADP-actin filaments are intrinsically unstable. In contrast, however, actinified filaments in neurons are stable and highly resistant to depolymerization in the presence of the G-actin sequestering compound latrunculin-A, suggesting that one or more additional factors regulate this unusual filament stability during ongoing cellular stress.

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Poster

PSTR161: Stroke: Imaging and Assessment

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Topic: D.03. Stroke

Support: NIH Grant R01NS131227 (PI: Vahdat)
Florida Department of Health James and Esther King Biomedical Research, Award Number 23K07 (PI: Vahdat)

Title: Hyperreflexia correlates with primary motor and premotor lesion volumes in a mouse ischemic model of post stroke spasticity

Authors: *S. KAUL¹, L. LIU², E. CANDELARIO-JALIL³, S. VAHDAT⁴;
¹Univ. of California, Riverside, Riverside, CA; ³Neurosci., ²Univ. of Florida, Gainesville, FL;
⁴Bioengineering, Univ. of California Riverside, Riverside, CA

Abstract: Post-stroke spasticity (PSS), marked by hypertonia and hyperreflexia, is a common and debilitating complication of cerebrovascular accidents that hinders motor recovery. Despite its prevalence, the neurophysiological mechanisms driving PSS remain unclear, in part due to the absence of reliable animal models. One clinical correlate of spasticity is a weakened rate-dependent depression (RDD) of the Hoffman reflex (H-reflex), particularly in upper limbs of chronic stroke patients. However, the mechanistic basis of RDD impairment and its relation to brain lesion characteristics remains insufficiently defined. This study aims to characterize the progression of H-reflex RDD in a forelimb muscle over time following ischemic stroke in mice, and investigate the association between weakened RDD and lesion volume across cortical and

subcortical areas using structural MRI. Male C57BL/6J mice (n=16) received photothrombotic strokes in the sensorimotor cortex and striatum, while sham-operated controls (n=9) were used for comparison. H-reflexes were recorded from the contralateral forelimb's flexor carpi radialis (FCR) muscle using low- and high-frequency stimulation of the median nerve. RDD was measured by comparing peak-to-peak H-reflex amplitudes under both conditions at baseline and days 3, 7, 14, 21, and 30 poststroke. Based on prior research, we hypothesized maximal RDD impairment at 2-3 weeks poststroke. Lesion volumes were determined using T2-weighted MRI on day 2 poststroke, and quantified via voxel-based analysis aligned with the Allen Mouse Brain Atlas. Correlations between lesion volumes and average RDD on days 14 and 21 were calculated to localize regions contributing to hyperreflexia. RDD was significantly reduced on days 14 ($p < 0.01$) and 21 ($p < 0.05$) poststroke, reflecting increased hyperreflexia. Approximately 60% of stroke mice exhibited RDD weakening, consistent with PSS prevalence in humans. A strong positive correlation emerged between lesion volumes in contralateral M1 and M2 motor cortices and average RDD of days 14 and 21 ($r = 0.674$; $p < 0.01$), linking larger lesions with greater impairment. These results suggest damage to motor cortical areas disrupts central reflex-modulating circuits, driving post-stroke hyperreflexia and potentially spasticity. In summary, RDD in forelimb muscles becomes significantly weakened poststroke, peaking at 2-3 weeks, and correlates with lesion burden in motor cortices. These findings underscore the importance of primary motor and premotor cortices in maintaining reflex inhibition. The stroke model presented offers a valuable platform for investigating neural mechanisms underlying PSS.

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Poster

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German Research Foundation (DFG) grant HA 9566/1-1 (PH)
Wu Tsai NPIL Neuro-Imaging Pilot Grant (PH)

Title: A reproducible pipeline for longitudinal dMRI analysis detects microstructural signatures of stem cell-driven recovery after chronic stroke

Authors: *P. HABIB¹, S. EWBANK², X. LIANG¹, R. NORISTANI¹, N. JOHNSTON¹, J. KIM³, R. AIRAN², T. BLISS¹, G. K. STEINBERG¹;
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Abstract: Neurorestorative treatments remain scarce for the millions of chronically disabled patients after ischemic stroke. Intraparenchymal transplantation of human neural stem cells

(hNSCs) in chronic stroke patients has demonstrated excellent safety and feasibility, with evidence of clinical efficacy in some early phase trials. Transplanted hNSCs improve motor, sensory, and cognitive impairments implying that they modulate various neural circuits, including in regions distant from the graft site. Understanding brain-wide structural changes driving stem cell-induced recovery is critical for enhancing therapeutic efficacy.

To address this, we established a stem cell therapy paradigm after chronic stroke in adult male Sprague Dawley rats subjected to 30 minutes of transient middle cerebral artery occlusion (MCAO), followed one month later by ipsilesional striatal injection (Tx) of embryonic-derived hNSCs (NR1) or vehicle. To investigate structural brain changes associated with NR1-induced recovery, we performed longitudinal MRI (T2w, FLAIR, DWI, SWI, DTI) on a 7T Bruker BioSpec system and neurobehavior (whisker paw, cylinder, EBST, corner, and T-maze tests) over a 4-month post-stroke period. Using containerized open-source tools and high-performance computing, we developed a rigorous, generalizable pipeline for batch diffusion MRI (dMRI) model fitting, atlas registration, and statistics enabling unbiased ROI-based and voxel-wise analyses and cross-species translation. Rats exhibiting stable neurological deficits one month after stroke showed significant recovery following NR1 transplantation, with improved motor, sensorimotor, and cognitive performance compared to vehicle controls ($p < 0.01$). Unbiased ROI- and voxel-based analyses revealed widespread reductions in fractional anisotropy (FA) and quantitative anisotropy (QA) in chronic stroke-injured brains compared to sham, indicating compromised white matter integrity. Notably, FA was significantly reduced bilaterally in the corticospinal tract, striatum, corpus callosum, and hippocampus after chronic stroke ($p < 0.05$). NR1 transplantation partially reversed these stroke-induced structural deficits, increasing FA and QA in multiple brain areas compared to vehicle controls. Early (1d, 3d, and 7d post-Tx) and late (12 weeks post-Tx) variations in DTI metrics (FA, QA, and MD) correlated strongly with long-term behavioral recovery.

Our data indicate widespread NRI-induced DTI changes after chronic stroke correlating with functional recovery, suggesting that DTI metrics may serve as valuable imaging biomarkers to predict and monitor therapeutic efficacy.

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Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.06/E34

Topic: D.03. Stroke

Title: Spatiotemporal Disruption of Cerebral Vasomotion Synchrony After Middle Cerebral Artery Reperfusion Visualized by Wide-Field Two-Photon Microscopy

Authors: ***S. WAKITA**^{1,2,3}, **S. TAKEMOTO**⁴, **M. HANDA**⁴, **Y. TAJIMA**³, **H. TAKUWA**¹;

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Med. and Pharmaceut. Sciences, Chiba Univ., Chiba, Japan; ³Dept. of Neurolog. Surgery, Chiba Univ. Grad. Sch. of Med., Chiba, Japan; ⁴Grad. Sch. of Sci. and Engineering, Chiba Univ., Inage-ku, Chiba-shi, Chiba, Japan

Abstract: Reperfusion following middle cerebral artery occlusion (MCAO) frequently induces secondary complications such as hemorrhagic infarction, vasogenic edema, and microvascular damage, which significantly affect stroke outcomes. However, the underlying microcirculatory dynamics, particularly the spatiotemporal synchrony of cerebral vasomotion in vivo, remain unclear. In this study, we developed a custom in vivo imaging system using wide-field two-photon laser scanning microscopy to achieve large-scale high-resolution visualization of vascular dynamics in the living mouse brain. C57BL/6J mice (n = 10) were implanted with a cranial window and subjected to temporal craniotomy, followed by 1-hour MCA occlusion and subsequent reperfusion. Imaging was performed under wakeful conditions at three time points: pre-surgery (baseline), postoperative day 1 (POD1), and postoperative day 7 (POD7), under both resting and whisker-stimulated conditions. We analyzed the rhythmic fluctuations in vessel diameter (vasomotion) in the MCA trunk, branches, arterioles, and venules. The proximal MCA trunk segment served as a reference vessel to assess synchrony. At the baseline, vasomotion synchrony was the highest among spatially adjacent vessels. On POD1, overall synchrony was markedly reduced, and the spatial correlation between distance and synchrony was lost. By POD7, partial recovery of both synchrony and spatial organization was observed. Notably, the relationship between whisker-evoked vasodilation and vasomotion synchrony showed a dynamic shift: a positive correlation at the baseline, a reversal to a negative correlation on POD1, and a return toward a positive correlation by POD7. These findings suggest that reperfusion disrupts vascular regulatory mechanisms, likely because of endothelial damage and inflammation, transiently impairing coordinated cerebrovascular function. Our results demonstrate that wide-field two-photon microscopy enables in vivo mapping of vasomotion synchrony at a single-vessel resolution. Further, vasomotion synchrony may serve as a functional biomarker for microcirculatory integrity and vascular recovery, offering potential applications in elucidating reperfusion injury mechanisms and evaluating therapeutic interventions.

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Poster

PSTR161: Stroke: Imaging and Assessment

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.07/E35

Topic: D.03. Stroke

Title: Streamline-based corticospinal tract lesion load outperforms state-of-the-art in motor impairment prediction for stroke patients

Authors: J. STOUT¹, ***Z. HUANG**¹, L. ZHU¹, Y. WANG², J. A. FELD¹, C. C. CHARALAMBOUS¹, W. FENG¹;
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Abstract: Post-stroke prognosis on motor impairments determines the stratification of patients into different therapy regimes to maximize recovery outcomes, while traditional clinical practice in vascular neurology relies on pure lesion volume to interpret lesion severity. It has been shown that the lesion load on corticospinal tract (CST) provides better post-stroke prognosis on motor impairment than pure lesion volume, and various methods have been proposed to determine CST lesion load. **Total overlap** looks at the raw intersection of tract volume and lesion, **weighted volume** weights the total overlap by voxel-wise fiber density to obtain a rescaled volume, and **maximum slice** takes the maximum proportional overlap between tract volume and lesion across axial slices. We aimed to benchmark these existing methods and devise a method for better neuroimaging-based prognosis of post-stroke motor impairments. In doing so, the **percentage CST streamline loss** due to a stroke surfaced to be the best candidate. On a T1-weighted dataset (3-Tesla GE Signa UHP scanner, magnetization-prepared rapid acquisition gradient-echo, three-dimensional 1x1x1 mm³ voxels, sagittal acquisition, fat suppression) of eighteen stroke participants over 30 days post-stroke (9 females, 57±12 years old, mean ± standard deviation), streamline loss gives the best prediction of motor impairments (measured by the Fugl-Meyer upper-extremity score) among the four methods. For streamline loss, $R^2 = 0.2720$, $p = 0.026$; for total overlap, $R^2 = 0.1586$, $p = 0.102$; for weighted volume, $R^2 = 0.149$, $p = 0.113$; and for maximum slice, $R^2 = 0.144$, $p = 0.120$. We obtained the percentage streamline loss by 1) obtaining an initial T1-based lesion segmentation via a deep learning pipeline, 2) quality controlling the initial lesion segmentation manually, 3) extracting and transforming the brain and the lesion segmentation to a probabilistic normative map of CST streamlines created using the Human Connectome Project, and 4) intersecting the lesion segmentation to the CST streamlines in this normative streamline map. With this increased R^2 and decreased p-value in predicting motor impairments, physicians can make more informed decision on post-stroke prognosis and thus patient stratification to appropriate treatment/therapy regimes. Rehabilitation research can also benefit from this improved patient stratification when designing their clinical randomized controlled trials.

Disclosures: J. Stout: None. Z. Huang: None. L. Zhu: None. Y. Wang: None. J.A. Feld: None. C.C. Charalambous: None. W. Feng: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.08/E36

Topic: D.03. Stroke

Title: Quantitative T1 Mapping of Ferritin Phantoms Using Inversion Recovery MRI at 3 Tesla: A Preliminary Step Toward Iron Quantification in Cerebral Hemorrhage

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Abstract: Introduction: Iron accumulation after cerebral hemorrhage (CH) contributes to secondary injury, including oxidative stress and inflammation. Ferritin, the primary intracellular iron-storage protein, plays a crucial role in brain iron homeostasis, and influences Magnetic Resonance Imaging (MRI) contrast through its paramagnetic properties. Although ferritin is traditionally linked to T2 and T2* maps, its T1 relaxivity provides an alternative for iron quantification in hemorrhagic cerebrovascular diseases, offering enhanced specificity and reduced susceptibility to magnetic field inhomogeneities. This study evaluates the T1 relaxivity of ferritin at 3T to enhance MRI-based assessment of iron deposition following CH, and initiates the development of a MATLAB-based T1 mapping pipeline, that will serve as the first phase of *FerroQuant*, a proposed multimodal MRI framework for quantifying the different forms of iron in CH. **Materials & Methods:** Ferritin phantoms were prepared in 0.9% saline with serial dilutions ranging from 5mg to 0.0195mg concentrations. MRI scans were conducted on a Siemens Prisma 3T scanner using an inversion recovery (IR) spin-echo sequence with 12 inversion times (TIs), 50ms - 5000ms to achieve precise T1 mapping. Data analysis was performed using MATLAB for reproducible T1 calculation across the various regions of interest (ROIs), providing baseline data for further multimodal integration. Inter-observer variability and reproducibility were assessed between two independent analysts. **Results:** The extended range of TIs improved T1 fitting accuracy, mitigating errors seen in prior studies. Additionally, T1 measurements were reproducible across independent assessments, reinforcing the reliability of the methodology.

Conclusion: A protocol for estimating T1 relaxation in ferritin phantoms using IR MRI was successfully developed. Our results suggest T1 mapping could be a sensitive metric for detecting iron accumulation in hemorrhagic cerebrovascular conditions. As the first methodological step toward *FerroQuant*, the results of this study support the broader goal of developing a robust framework for iron quantification in cerebrovascular lesions. **Clinical Relevance Statement:** Quantitative iron mapping using standard and advanced MRI sequences can improve diagnostic accuracy, risk stratification and treatment planning in patients with various cerebral hemorrhagic conditions. *FerroQuant* offers a translational pathway for routine radiologic assessment of vascular brain lesions in research and clinical settings.

Disclosures: O. Ngwu-Hyacinth: None. M.S. Bolding: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.09/E37

Topic: D.03. Stroke

Support: NIH Grant R21NS121589

Title: Decoding Moyamoya Pathogenesis: A Spatial Transcriptomic and RNAscope Analysis of Vascular Wall Remodeling

Authors: *T. C. CHIANG^{1,3,4}, M. Y. CHENG^{2,3,4}, G. K. STEINBERG^{1,3,4},
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Abstract: Background: Moyamoya disease (MMD) is a rare, progressive cerebrovascular disease marked by the narrowing of intracranial arteries that can lead to ischemic and hemorrhagic strokes. A key pathological feature of MMD is the thickening of the innermost layer (intima), which contributes to the narrowing of arteries and impaired cerebral blood flow. Despite its clinical impact, the mechanisms driving MMD pathogenesis remain unclear. Here we investigated the transcriptomic differences in vessel tissues from MMD patients and compared them to other vascular diseases, using RNAscope in situ hybridization and the Visium HD spatial transcriptomics platform. Methods: Superficial temporal arteries (STA) and/or middle cerebral arteries (MCA) were obtained from MMD patients during surgical intervention. Other vascular tissues were collected from patients with aneurysm or cavernous malformation. Tissue sections (10µm) underwent RNAscope in situ hybridization using ACD's multiplex protocol for endothelial cells (PECAM1), vascular smooth muscle cells (ACTA2), proliferation marker (Ki67) and extracellular matrix (ECM). Imaging was performed using Zeiss laser confocal microscope (LSM800) and analyzed with ImageJ. Spatial transcriptomic profiling was performed on samples that are formalin fixed, paraffin embedded samples using the Visium HD pipeline. Results: RNAscope analysis showed mRNA expression of ACTA2 in vascular smooth muscle cells (VSMCs) and PECAM1 in endothelial cells (ECs), consistent with previous immunohistochemistry staining for vascular smooth muscle cells (α -SMA) and endothelial cells (CD31). Ki67 expression was localized in the media layer, indicating increased VSMC proliferation. Morphological analysis of VSMCs showed that while control STA mostly displays a contractile phenotype with elongated, spindle-shaped cells, MMD STAs exhibited synthetic phenotype with shorter, cobblestone appearance. Quantification of intima layer thickness showed significant increased intima thickness in MMD STA. Spatial transcriptome analysis of these vessels was processed to identify gene expression differences in these vessel layers in MMD. Conclusions: Our findings found presence of proliferation in the media layer, predominantly VSMCs, indicating a shift towards synthetic phenotype associated with increased cellular proliferation and reduced contractility, which can contribute to intimal thickening and vessel stenosis. Ongoing studies include analysis of Visium HD transcriptome changes across different layers in MMD, aneurysm, and cavernous malformation to identify key molecular changes driving these pathological features.

Disclosures: T.C. Chiang: None. M.Y. Cheng: None. G.K. Steinberg: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.10/E38

Topic: D.03. Stroke

Support: 114-OP02

Title: Integrated AI and Multidomain Behavioral Profiling Reveals Persistent Neurological Impairments in a Mouse Model of Cortical Ischemia

Authors: *Y.-Y. MEI¹, H.-M. HSU¹, S.-Y. CHENG¹, M.-J. JIANG¹, Y.-L. CHEN¹, S.-H. HUNG¹, Y.-J. CHEN^{2,1};

¹Natl. Ctr. for Biomodels, Natl. Inst. of Applied Res., Taipei, Taiwan; ²Dept. of Pharmacology, Sch. of Medicine, Univ. of California, Davis, CA

Abstract: Stroke-induced recovery of neurological and motor function is highly heterogeneous, necessitating comprehensive and multidimensional assessments for accurate characterization. In this study, we utilized a filament-induced transient middle cerebral artery occlusion (tMCAO) model in mice. Successful ischemia induction was confirmed intraoperatively using laser Doppler flowmetry, and recovery over the first three postoperative days was video-recorded to support AI-based behavioral analysis. Throughout the five-week evaluation period, tMCAO mice exhibited a consistent and robust left-turning bias in both neurological scoring and the corner turn test from postoperative day 1 through day 35, indicating prolonged impairment in proprioception and sensorimotor integration. In grip strength testing, a transient decline was observed during weeks 2 to 3, while rotarod performance deteriorated significantly from weeks 2 to 4, reflecting temporary but notable deficits in forelimb strength, coordination, and endurance. Gait analysis revealed a marked reduction in regularity index during the first postoperative week, followed by increased stance time and duty factor in the contralateral (right) hindlimb, suggestive of impaired locomotor output and compensatory weight-bearing strategies. Simultaneously, the ipsilateral (left) limbs displayed increased fore-hind pair gap and decreased base of support, indicating disrupted postural balance and interlimb coordination. Notably, open field testing showed no significant differences in total distance traveled or locomotor speed, emphasizing that gross activity measures alone fail to detect subtle yet functionally significant stroke-related impairments. These findings underscore the importance of applying high-resolution, multidimensional behavioral metrics to fully capture the complexity of post-stroke deficits. Our study establishes a temporally resolved and analytically rigorous framework for characterizing long-term motor and neurological outcomes in experimental stroke models, supporting its utility for evaluating therapeutic interventions and guiding rehabilitation strategies.

Disclosures: Y. Mei: None. H. Hsu: None. S. Cheng: None. M. Jiang: None. Y. Chen: None. S. Hung: None. Y. Chen: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.11/E39

Topic: D.03. Stroke

Title: Partitioned Perception: Navigating Neural Networks of Simultanagnosia

Authors: ***J. E. TRAN-KHANH-BICHON**¹, E. J. SOUTHAM¹, M. MARCUCCI¹, O. BENZLEY¹, M. FRIEDRICH², J. A. NIELSEN¹, M. FERGUSON³;

¹Brigham Young Univ., Provo, UT; ²Dept. of Psychiatry, Univ. Hosp. Würzburg, Würzburg, Germany; ³Harvard Med. Sch., Boston, MA

Abstract: This study aims to identify a human brain circuit directly related to simultanagnosia. First described by Rezső Bálint in 1909, simultanagnosia is a neurological condition characterized by the inability to perceive more than one object or visual element at a time, and is an associated symptom in the triad of Bálint's syndrome with optic ataxia and oculomotor apraxia. To investigate this condition, a systematic literature review was performed, with specific inclusion criteria, to find case studies of patients presenting with simultanagnosia stemming from acquired brain injury (ischemic stroke, n=50). Lesion network mapping analysis (Fox et al., 2018) was performed on 50 cases with a large cohort of healthy control resting-state scans (n=1000). This method investigates brain regions functionally connected to the lesion sites rather than the case study lesion sites exclusively. Using resting-state functional connectivity data from healthy individuals and the lesions of each patient, we identified a common brain network functionally connected to the lesion sites. We found that 90% of cases (45/50) were functionally connected to specific areas that play a role in higher visual processing and object recognition. These areas included, but are not limited to, Brodmann Areas 18 and 19, specifically in the middle to inferior occipital gyri, Brodmann Area 36 at the junction between the parahippocampal gyrus and middle portion of the lingual gyrus, Brodmann Area 20, specifically the posterior portion of the fusiform gyrus, and Brodmann Area 37 at the temporal-occipital transition zone, near the posterior end of the sylvian fissure (superior temporal sulcus). This connectivity pattern is specific to simultanagnosia compared to lesions causing other neurological conditions. This study advances the use of lesion network mapping for characterizing complex neurological conditions and provides new insight into the brain network that supports visual perception. These findings can also help clinicians more accurately understand and more effectively treat simultanagnosia. Further research is necessary to determine the mechanism of how these networks specifically interact and contribute to simultanagnosia.

Disclosures: **J.E. Tran-Khanh-Bichon:** None. **E.J. Southam:** None. **M. Marcucci:** None. **O. Benzley:** None. **M. Friedrich:** None. **J.A. Nielsen:** None. **M. Ferguson:** None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.12/E40

Topic: D.03. Stroke

Title: Hearing without understanding: a lesion network mapping analysis of auditory agnosia

Authors: *C. GARDNER¹, N. BASTIAN¹, K. BUNNELL², J. A. NIELSEN²;

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Abstract: Prior research has suggested that auditory agnosia is correlated with lesions in the bilateral temporal lobes and Wernicke's area. However, minimal research exists regarding the exact lesion networks and functionally connected areas responsible for this symptom. Our research aims to fill this gap with a detailed lesion network mapping analysis of auditory agnosia. We conducted a systematic literature review through Cadima, a software designed for comprehensive reviews, to find case studies of patients presenting with auditory agnosia following brain lesions. Each case met three criteria: (1) the case study had clear neurological imaging exhibiting brain lesions, (2) the lesions were temporally linked to auditory agnosia symptoms, (3) the case was written in the English language. We identified 64 viable cases. We subsequently performed lesion network mapping analysis on all lesions using a cohort of healthy control resting-state fMRI scans as a comparison from the Brain Genomics Superstruct Project (n=1000). Each brain scan provided in the literature was traced using Slicer 3D. These NifTI files were then analyzed using a supercomputer. As a result of the analysis, we created lesion network maps that both display lesion overlap in 56/64 cases and compare connections specific to lesions causing auditory agnosia as opposed to control lesions in any area of the brain. Analysis produced an additional map that displays functional connections between auditory agnosia and areas in the superior temporal gyrus and the amygdala. These results generally support past research which suggests that lesion activity in the bilateral temporal lobes, particularly in Heschl's Gyrus, is connected with auditory processing. In addition, the conjunction results in the amygdala point to a potential relationship between auditory processing and the limbic system. This lesion network map will be combined with other networks at the LesionBank.org website, providing a potential diagnostic tool for providers.

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Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.13/Web Only

Topic: D.03. Stroke

Support: Canadian Friends of IIT Madras

Title: Characterization of Peri-Infarct White Matter Vulnerability in Human using Multimodal Whole-brain Imaging and Histology

Authors: *A. AYYAPPAN¹, R. NANJAPPA¹, R. VERMA², J. JAYAKUMAR⁴, R. RANGASAMI^{5,6}, M. SEN⁷, R. JAMES⁷, G. M. VARGHESE^{8,9}, D. NAUEN¹⁰, R. D. FOLKERTH¹¹, M. SIVAPRAKASAM^{2,3};

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Abstract: Ischemic stroke remains a leading cause of mortality and long-term disability globally. Despite considerable research efforts dedicated to neuroprotection, the majority of these have primarily focused on the grey matter compartment of the brain. However, white matter (WM), which is crucial for interregional communication and network function, exhibits heightened vulnerability to hypoperfusion resulting from ischemic events due to its relatively sparse collateral blood supply. Animal models show that axonal regrowth can occur, but comparable human data are scarce. Mapping WM injury and intrinsic repair therefore holds major translational value. We created a human whole-brain multi-scale and multi-modal imaging pipeline that integrates pre- and post-mortem neuroimaging and histology. A proof-of-concept study was performed on the fixed brain of a 69-year-old man with COVID-19 who experienced multiple left-hemisphere strokes. Diffusion-weighted MRI obtained 20 and 15 days pre-mortem revealed multiple regions affected by stroke of different ages. Post-mortem, the brain was extracted, followed by MR imaging and cryosectioning of the whole brain into 20 micron sagittal sections. Serial sections were histochemically stained for Nissl and H&E, and immunostained for several ischemic stroke markers. Nissl and H&E stained sections corroborated with neuroimaging, and were used to guide targeted immunohistochemistry for fibrinogen, CD68, GFAP, HIF-1 α , APP and GAP-43. Subacute cores exhibited neuronal loss, astrocyte depletion and dense CD68⁺ macrophage infiltration, while peri-infarct rims showed clasmotodendrosis. Acute foci retained fragmented astrocytes and presented robust, cell-type-specific HIF-1 α up-regulation. Critically, WM adjacent to the lesions carried interleaved signatures of damage and repair: APP immunoreactivity marked axonal swellings and disconnection, whereas GAP-43 highlighted sprouting fibres at lesion margins. Our preliminary findings position WM as a dynamic substrate after ischemia, where axonal injury and regeneration coexist across a spatial gradient extending beyond the ischemic core regions. Quantifying the APP-to-GAP-43 ratio within peri-infarct and remote WM may help identify tissue that is still salvageable and direct therapies aimed at preserving network connectivity and functional recovery.

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Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.14/E41

Topic: D.03. Stroke

Title: Role of Erythrocyte Aging and F-actin Polymerization in Brain Endothelial Erythrophagocytosis

Authors: *M. RAI^{1,2}, R. CHANG^{1,2}, R. SUMBRIA^{1,2,3};

¹Biomed. and Pharmaceut. Sci., ²Dept. of Biomed. and Pharmaceut. Sci., Chapman Univ. Sch. of Pharm., Irvine, CA; ³Dept. of Neurol., Univ. of California, Irvine, CA

Abstract: Background: Brain endothelial cells (BECs) of the blood-brain barrier, conventionally considered non-phagocytic, have evolved as non-professional phagocytes, capable of erythrophagocytosis (EP). Our previous work demonstrated that oxidatively stressed red blood cells (RBCs) are phagocytosed by BECs, leading to RBC and iron deposition within the brain without disrupting BBB integrity. This suggests that BEC-EP may be a novel mechanism underlying cerebral microhemorrhage (CMH) formation. However, the precise mechanisms regulating BEC-EP remain unclear. Given the cytoskeletal constraints involved in phagosome formation and the impact of RBC aging in EP, we assessed the role of F-actin polymerization and RBC aging in BEC-EP using human cerebral microvascular endothelial cells (hCMEC/D3). **Methods:** To confirm RBC engulfment by BECs, hCMEC/D3 monolayer was incubated with human RBCs (hRBCs) that were either treated with phosphate-buffered saline (PBS) or oxidatively stressed hRBCs, using 3 mM tert-Butyl hydroperoxide (tBHP) (to mimic aged RBCs). The role of F-actin was assessed by treating the hCMEC/D3 monolayer with cytochalasin D, an F-actin polymerization inhibitor, followed by incubation with PKH26-labeled PBS-treated or tBHP-treated hRBCs. F-actin and nuclei were stained with Phalloidin 488 and DRAQ5, respectively. BEC-EP and F-actin gap length were evaluated using fluorescence staining and confocal microscopy. To mimic storage lesions in donor hRBCs during transfusions, hRBCs were aged *in vitro* by storage for 30 days at 4°C, followed by incubation with the hCMEC/D3 monolayer. BEC-EP of aged hRBCs was assessed using brightfield microscopy, and images were quantified using ImageJ. **Results:** BEC-EP did not change F-actin-density, however a redistribution of F-actin was observed such that greater RBC engulfment was associated with greater F-actin (Pearson $r=0.73$, $p<0.0001$). Further, hCMEC/D3 cells treated with cytochalasin D showed a significant ($p<0.01$) increase in F-actin gaps between adjacent endothelial cells, confirming actin depolymerization. Importantly, cytochalasin D treatment significantly reduced ($p<0.001$) BEC-EP of oxidatively-stressed (3 mM tBHP) hRBCs without affecting BEC viability. Further, hRBCs aged *in vitro* exhibited significantly higher ($p<0.05$) BEC-EP compared with freshly isolated hRBCs. **Conclusions:** These findings indicate that F-actin polymerization is important for BEC-mediated EP, providing further mechanistic insights into this understudied phenomenon. Additionally, prolonged refrigerated RBC storage increased susceptibility to BEC-EP, which implies its role in blood transfusion safety.

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Poster

PSTR161: Stroke: Imaging and Assessment

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Program #/Poster #: PSTR161.15/E42

Topic: D.03. Stroke

Support: NSF

Title: Assessing the Impact of MRI Slice Resolution on the Clinical Applicability of Lesion Mapping Models

Authors: *R. BIELSKI¹, L. L. OWEN²;

²Psychological and Brain sciences, ¹Univ. of Montana, Missoula, MT

Abstract: Ischemic stroke remains a major medical challenge , with current lesion segmentation methods often relying on time-consuming manual tracing of magnetic resonance imaging (MRI) scans. Further complicating this issue, MRI machines vary widely in spatial resolution between clinical and research settings, introducing additional complexity for deploying automated tools in real-world applications. This study investigates how MRI spatial resolution affects the performance of a custom-developed machine learning model for ischemic stroke lesion segmentation. Using the Anatomical Tracings of Lesions After Stroke (ATLAS v2.0) and the Ischemic Stroke Lesion Segmentation (ISLES) 2022 datasets with T1-weighted MRI scans and expert-annotated lesion masks, we assess the impact of differing resolutions on segmentation accuracy. The central research question explores how resolution degradation influences key metrics such as Dice Similarity Coefficient and false positive/negative rates. Preliminary findings suggest that lower-resolution inputs significantly compromise model performance. By systematically evaluating our model across a range of spatial resolutions, this research aims to inform the development of more robust, resolution-tolerant segmentation tools and reduce reliance on manual annotation in clinical workflows.

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Poster

PSTR161: Stroke: Imaging and Assessment

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Program #/Poster #: PSTR161.16/E43

Topic: D.03. Stroke

Support: NIH R01 HD58301
NIDILRR HHS Rehabilitation Engineering Research Center grant
#90RE5021

Title: Eeg-based connectivity changes in secondary motor areas are related to increased functional recovery four months post-stroke

Authors: *M. GLASSEN¹, J. PATEL², S. H. SALEH², S. V. ADAMOVICH¹, A. MERIANS², Q. Z. QIU², G. FLUET²;

¹Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ; ²Rutgers, The State Univ. of New Jersey, Newark, NJ

Abstract: This study examined how alterations in brain connectivity metrics during the first four months after a stroke relate to recovery of upper limb motor function in individuals post-stroke. Using a data-driven approach, we explored the relationship between changes in resting-state EEG-derived brain connectivity and improvements in motor function, as assessed by the Action Research Arm Test (ARAT). Resting-state EEG data were collected within the first month after stroke and again at four months post-stroke for thirty-two individuals. Connectivity metrics were analyzed across the Theta, Alpha, Beta1, and Beta2 frequency bands. Correlation analyses and modeling were employed to identify the brain networks most strongly associated with recovery. Connectivity between key motor regions was compared between participants with high and low recovery based on changes in ARAT scores. Recovery was positively associated with changes in connectivity within the affected hemisphere, especially between the dorsal premotor (PMd) and supplementary motor area (SMA) across the Theta and Beta1 frequency bands. In contrast, negative associations emerged in the unaffected hemisphere, notably between the superior parietal lobule (SPL) and precuneus (Pcun) within the Theta band. Negative coefficients were observed between the affected PMd and the unaffected SMA. These results suggest that restoring lateralized brain activity toward the affected hemisphere during the initial four months after stroke could play a key role in functional improvement. Connectivity changes in the PMd and SMA regions during the first four months after stroke show strong correlations with improvements in upper limb motor function, highlighting their potential as targets for rehabilitation. These results reinforce the value of exploring EEG-based metrics to inform individualized treatment approaches, underscoring the critical role of engaging the affected hemisphere in post-stroke recovery.

Disclosures: M. Glassen: A. Employment/Salary (full or part-time): Rutgers University. J. Patel: None. S.H. Saleh: None. S.V. Adamovich: None. A. Merians: None. Q.Z. Qiu: None. G. Fluet: None.

Poster

PSTR161: Stroke: Imaging and Assessment

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Program #/Poster #: PSTR161.17/E44

Topic: D.03. Stroke

Support: CIRM Grant TRAN1-12891
CIRM Grant DISC2-12169
CIRM Grant DISC2-15137

Title: Longitudinal Machine Learning and snRNA-Seq Reveal Stroke-Specific Behavioral and Transcriptional Signatures

Authors: ***A. PANDITRAO**¹, V. KAN², Á. M. CRUZ-LOCIEL², K. GEFEN VLASSOPOULOS², E. GONZALEZ CUBERO², I. LORENZO LLORENTE²;
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Abstract: Stroke remains a leading cause of death and long-term disability worldwide. Ischemic strokes, which account for ~87% of all cases, affect over 690,000 individuals annually in the United States. These impact both the cortical and subcortical regions of the brain. Cortical stroke (CS) typically presents with acute symptoms like unilateral weakness and dysarthria, requiring immediate intervention as neurons begin to die within minutes. In contrast, subcortical white matter stroke (WMS) progressively expands and deteriorates over time. WMS accounts for ~30% of strokes and is the leading cause of vascular dementia. With no effective therapies currently available, projected medical costs in the US are expected to exceed \$90 billion by 2030. To develop effective treatments, we must establish reliable methods integrating behavioral and molecular characterization. Traditional functional assessments like the gridwalking and cylinder tests are limited by their vulnerability to observer bias and focus on individual parameters. To address this gap, we employed Motion Sequencing (MoSeq), a machine learning pipeline, to unbiasedly characterize behavioral phenotypes in young (4-month) and aged (10-month) stroke mice during the subacute (7 days post injury) and chronic (30 days post injury) phases. MoSeq revealed that subacute CS is characterized by increased motor deficits, while subacute WMS is characterized by increased cognitive deficits. These findings remained consistent across age cohorts, with aged mice exhibiting more severe deficits. At the chronic stage, we found spontaneous motor recovery in CS mice while WMS mice experienced progressive worsening of cognitive deficits. We also identified distinct behavioral differences between male and female mice in both stroke types. We combined this behavioral phenotyping with single-nuclei RNA-sequencing for molecular characterization. This approach revealed distinct molecular signatures underlying the behavioral differences. CS exhibited robust microglial/astrocytic inflammatory responses during the subacute stage, followed by neuroplasticity-associated changes during the chronic stage, correlating with functional recovery. WMS demonstrated prolonged oligodendrocyte dysfunction and persistent vascular inflammation with progressive cell death pathway upregulation. Age-specific signatures showed enhanced inflammation and reduced neuroplasticity in aged mice, while females displayed stronger neuroprotective profiles correlating with less severe deficits. This integrated approach provides insights into stroke pathophysiology and suggests potential therapeutic targets.

Disclosures: **A. Panditrao:** A. Employment/Salary (full or part-time): Stanford University. **V. Kan:** A. Employment/Salary (full or part-time): Stanford University. **Á.M. Cruz-Lociel:** A. Employment/Salary (full or part-time): Stanford University. **K. Gefen Vlassopoulos:** A. Employment/Salary (full or part-time): Stanford University. **E. Gonzalez Cubero:** A. Employment/Salary (full or part-time): Stanford University. **I. Lorenzo Llorente:** A. Employment/Salary (full or part-time): Stanford University.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.18/E45

Topic: D.02. Ischemia

Support: NIH 5R01NS132492

Title: Casein Kinase 2 signaling differentially dictates pre- and post-ischemic protection to white matter via CDK5 and Akt pathways

Authors: *H. V. NGUYEN¹, I. HARMON¹, M. PIKE¹, S. BALTAN²;

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Abstract: White matter injury (WMI) is associated with major neurological disabilities after stroke, and the mechanisms of WMI are age- and sex- dependent and differ from gray matter. Casein Kinase 2 (CK2), a key constitutively expressed regulatory kinase, is upregulated after ischemia, leading to oligodendrocyte cell death and impaired axon function. Our previous studies showed that CK2 inhibition during oxygen-glucose deprivation (OGD) confers functional protection to axons by differentially regulating Cdk5 and Akt signaling pathways. However, whether inhibiting CK2 before or after ischemic injury exerts similar therapeutic effects has not been tested. In the present study, we investigate the effects of CK2 inhibition pre- and post-WMI and examine the underlying signaling pathways. We hypothesize that CK2 signaling differentially mediates the pre- and post-ischemic WM protection. 2-month-old C57BL/6J male mice were used in the study. For *ex vivo* experiments, isolated mouse optic nerves (MONs), pure myelinated WM tracts, were superfused with artificial cerebrospinal fluid (ACSF) at 37 °C, and saturated with 95%O₂/5%CO₂. Extracellular compound action potentials (CAPs) were evoked every 30 seconds. Axonal responses were recorded under baseline conditions for 1 hour, OGD (glucose-free ACSF saturated with 95%N₂/5%CO₂) for 1 hour, and recovery for 5 hours. CX-4945 (5 μM), a highly selective and specific CK2 inhibitor, was applied either before or after ischemia for 30 minutes. Selective inhibition of Cdk5 or Akt was achieved by using Roscovitine (5 μM) or ARQ-092 (500 nM), respectively. For *in vivo* experiments, three injections each of 200 nL of L-NIO (130μM) were deposited at previously identified coordinates. CX-4945 (75mg/kg) or vehicle was administered twice/day starting from 5 days before the injury or starting from 12 hours after WMI for 5 days. Cylinder test and longitudinal MRI were used to assess and correlate the behavioral deficits to the white matter damage at day 1,3,7 and 21 post-injury. We found that CK2 inhibition effectively preconditions and exerts post-ischemic protection of axon function, alleviates behavioral deficits, and preserves WM integrity in young males. Preconditioning with Roscovitine or ARQ-092 is equally effective, suggesting that CK2 inhibition preconditions WM by regulating both Cdk5 and Akt signaling pathways in young males. Interestingly, only post-ischemic application of ARQ-092 promotes axon recovery, suggesting that the post-ischemic protection of CK2 inhibition is mediated by the Akt signaling pathway not Cdk5. The signaling pathways underlying CK2 inhibition pre- and post-ischemia in females are being investigated.

Disclosures: H.V. Nguyen: None. I. Harmon: None. M. Pike: None. S. Baltan: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.19/E46

Topic: D.03. Stroke

Support: California Institute of Regenerative Medicine (TRAN1-12891, DISC2-12169 & DISC2-15137)

Title: Longitudinal Imaging of Circuit-Level Changes in the Motor Cortex of Freely Behaving Mice After Stroke

Authors: *V. KAN¹, A. PANDITRAO², I. L. LLORENTE³;

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Abstract: Stroke remains a leading cause of death and long-term disability worldwide. In the absence of effective therapies, patients suffer from long-term disabilities, and the projected medical costs associated with stroke are expected to exceed \$90 billion in the United States by 2030. To tackle this, we must first gather a better understanding of the circuit-level changes after stroke and during spontaneous recovery. Although limited spontaneous recovery occurs after stroke, it does not lead to meaningful repair of the damaged neural tissue. Changes in excitation/inhibition balance is one of the features during spontaneous recovery in stroke patients. The imbalance leads to impaired neuronal activity, reduced synaptic plasticity, and altered network oscillations, hindering post-stroke recovery. Studies performed in cortical stroke (CS) patients and animal models demonstrated reduced inhibition in the initial recovery phase. However, most studies were done in the intact, ipsilateral cortex of CS patients or anesthetized animal models. Here, we first characterized the activity changes in the contralateral motor cortex in freely behaving mice after stroke through a combination of genetically-encoded calcium indicators, miniature microscopy, and motion sequencing (MoSeq). We recorded both neuronal activity in the motor cortex and behavior in a rodent model of laser-induced thrombotic stroke at baseline, 1-, 7-, 14-, 21- and 30-day post injury (dpi). Our preliminary results demonstrate that stroke impacts regions beyond the primary injury site, notably affecting the contralateral cortex. Using longitudinal calcium imaging, we observed a marked reduction in overall neuronal activity from 1 to 14 dpi, followed by a gradual recovery by 30 dpi. This temporal pattern closely paralleled behavioral outcomes. MoSeq analysis identified 16 distinct behavioral patterns (syllables) and corresponding neuronal clusters with syllable-specific activity. Given that the stroke was localized to the motor cortex, and our prior work established robust motor deficits in this model, we assessed the relationship between neuronal activity and motor function. Correlation analyses revealed a shared trajectory: motor impairments were most pronounced during the period of suppressed neuronal activity (1-14 dpi) and showed functional improvement at 30 dpi, coinciding with restored cortical activity. These results indicate that stroke induces bilateral effects, with recovery patterns that parallel functional improvements. A deeper understanding of the underlying adaptive mechanisms may reveal novel therapeutic targets.

Disclosures: **V. Kan:** A. Employment/Salary (full or part-time): Stanford University. **A. Panditrao:** A. Employment/Salary (full or part-time): Stanford University. **I.L. Llorente:** A. Employment/Salary (full or part-time): Stanford University.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.20/E47

Topic: D.02. Ischemia

Support: CIHR Project Grant
HSFC Grant in Aid
NSERC Discovery Grant

Title: Reduced peri-infarct blood flow following endothelial knockdown of *Serpine1* attenuates blood brain barrier permeability and improves functional recovery after ischemic stroke

Authors: ***C. E. BROWN;**
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Abstract: Regulating blood flow within vulnerable surviving brain tissues is considered a critical component of stroke recovery. Blood coagulation and thrombolysis (clot-busting) signalling pathways are fundamental to regulating post-ischemic capillary blood flow, and thus a focus of many clinical intervention strategies. A critical component of this coagulation pathway is plasminogen activator inhibitor-1 (PAI-1; encoded by the *Serpine1* gene) which is upregulated in vascular endothelial cells after stroke, and serves to inhibit the breakdown of fibrin clots. In the present study, we hypothesized that viral knockdown of *Serpine1* in brain endothelial cells would reduce capillary clotting, thereby enhancing blood flow in peri-infarct capillaries and improve functional recovery in mice subjected to permanent focal cortical ischemia. Using longitudinal *in vivo* 2-photon imaging, we unexpectedly find that *Serpine1* knockdown leads to a long-lasting reduction in the peri-infarct capillary width, RBC velocity and flux, while having no effect on infarct volume or rates of capillary stalling. Lowered peri-infarct blood flow was associated with reduced blood brain barrier (BBB) leakage and expression of inflammation related genes. In the longer term, *Serpine1* knockdown improved recovery of cortical hemodynamic responses and performance on behavioural tests of cognitive and sensori-motor function. These findings highlight the complex and sometimes counter-intuitive relationship between coagulation signalling pathways, peri-infarct blood flow and stroke recovery. Further, our data suggest that endothelial knockdown of *Serpine1* could represent a novel therapeutic approach for improving stroke recovery without increasing the risk of micro-hemorrhage related complications.

Disclosures: **C.E. Brown:** None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.21/E48

Topic: D.02. Ischemia

Support: MOST 110-2320-B-A49A-503; 110-2320-B-A49A-504; 111-2811-B-A49A-004.

Title: Investigating the Roles of FKBP51 in Ischemic Stroke With Neuromodulation

Authors: ***C.-H. CHANG**¹, C.-W. LEE², T.-N. PENG³, T. HUNG⁴, C. LIN⁵, H.-C. LIN⁶;
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⁴Emergency department, Taipei city hospital, ZhongXing branch, Taipei, Taiwan; ⁵Dept. of Hlth. Industry Mgmt., Kainan Univ., Taoyuan City/Luzhu District, Taiwan; ⁶Physiol., Dept. and Inst. of Physiology, Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan

Abstract: Ischemic stroke is a leading cause of long-term disability, characterized by motor deficits and sustained neuroinflammation. FKBP51, encoded by the stress-inducible FKBP5 gene, regulates glucocorticoid signaling and has been implicated in inflammatory responses and synaptic plasticity. Transcranial direct current stimulation (tDCS), a non-invasive neuromodulatory technique, has shown promise in improving motor outcomes and attenuating neuroinflammation after stroke, although its underlying mechanisms remain unclear. Using a mouse model of transient middle cerebral artery occlusion (tMCAO), increased infarct volume, motor impairments, elevated FKBP51 protein levels, and upregulation of pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α were observed during the subacute phase. In *Fkbp5* knockout mice, infarct volume and sensorimotor dysfunction were ameliorated. Reduced levels of pro-inflammatory cytokines IL-1 β , IL-6, and TNF- α and increased expression of anti-inflammatory cytokines were also exhibited in *Fkbp5* knockout mice. Furthermore, motor impairments and cortical FKBP51 expression were attenuated by five consecutive days of tDCS treatment, which also suppressed IL-1 β , IL-6, and TNF- α expression while upregulating anti-inflammatory cytokines. Together, these findings identify FKBP51 as a key mediator of post-stroke inflammation and motor deficits. Both genetic deletion and tDCS intervention promoted functional recovery and reshaped immune responses, highlighting FKBP51 as a potential convergent target for post-stroke therapy.

Disclosures: C. Chang: None. C. Lee: None. T. Peng: None. H. Lin: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.22/E49

Topic: D.02. Ischemia

Support: NINDS, R01NS131484
CCDS, T32 Predoctoral Fellowship

Title: Neuroimmune signaling promotes neurogenesis and neuroplasticity following cerebral ischemia

Authors: *E. WILLIAMS¹, B. AKHTER², N. AICH², K. BROWN², M. BRADFORD², K. RODGERS²;

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Abstract: Background: Stroke-induced damage to the brain results in neuronal loss and long-term functional disabilities in millions of stroke survivors, including those in pediatric and adult/elderly populations. Following stroke in humans, robust regenerative responses have been found in the young brain, which support a greater capacity for recovery compared to adult and elderly patients. This has also been found in preclinical trials of experimental stroke using juvenile mice to model pediatric stroke (middle cerebral artery occlusion, MCAO), where plasticity and regeneration are observed in the juvenile brain along with improved functional outcomes that are not observed in adult/aged mice. Our preliminary studies have found support for stroke-induced neuroimmune responses as a possible mechanism, which promotes neuroregeneration and tissue preservation in the juvenile brain, compared with neurodegeneration and pathological damage in the adult brain. Regeneration in the young brain is coupled with improved electrophysiological outcomes, but only in MCAO-injured juvenile mice.

Methods: We utilized immunofluorescence, RNA-seq, and *in vivo* electrophysiology to explore the age-related differences in neuronal injury, regeneration, and neuroimmune responses following ischemic stroke (MCAO) in juvenile and adult mice.

Results: We found equivalent cell death, neuronal loss, and neurogenesis (newly generated immature neurons) in both juveniles and adults at acute time points post-ischemia (24hr and 7d). Remarkably, we discovered that neural regeneration only occurred in MCAO-injured juveniles at 30d, but not in MCAO-injured adults. Additionally, we found a beneficial role for microglia during the acute phase of juvenile stroke, with neural regeneration supported by anti-inflammatory signaling, while adults had proinflammatory signaling and exacerbated injury. A proteomic analysis of isolated microglia revealed homeostasis/surveillance upregulation in juveniles, which distinctly differed from the proinflammatory state found in adults. Lastly, molecular results mirrored electrophysiology data, with recovery of neuroplasticity discovered in juveniles and persistent deficits seen in adults at 30d and 60d.

Conclusions: These findings identify an important role for neuroimmune responses in post-ischemic neuronal restoration and functional recovery in juveniles, while neuroimmune responses in adults had damaging effects on the brain and functional recovery.

Disclosures: E. Williams: None. B. Akhter: None. N. Aich: None. K. Brown: None. M. Bradford: None. K. Rodgers: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.23/E50

Topic: D.02. Ischemia

Support: NIH Grant R01NS136154

Title: Endothelial cell-targeted Malat1 transgenic overexpression preserves brain structure integrity and enhances cognitive function in experimental vascular cognitive impairment and dementia

Authors: *Y. ZHANG^{1,2}, N. QIU^{1,2}, T. XIONG¹, S. LI^{1,2}, J. XUE^{1,2}, K. YIN^{1,2};

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Abstract: Vascular cognitive impairment and dementia (VCID), driven by chronic cerebral hypoperfusion (CCH), leads to progressive cognitive decline in aging populations. Although the long non-coding RNA metastasis-associated lung adenocarcinoma transcript 1 (Malat1) has been implicated in ischemic brain injury via neuronal pathways, its role and underlying molecular mechanisms in vascular brain damage associated with VCID remain unclear. To explore this, endothelial cell-targeted Malat1 transgenic mice (EC-Malat1 Tg) were generated and subjected to bilateral common carotid artery stenosis (BCAS) to induce CCH-based VCID. Cerebral blood flow (CBF) was monitored using laser speckle imaging at multiple time points post-surgery. Cognitive and sensorimotor functions were assessed using various neurobehavioral tests, while structural brain changes were evaluated at day 35 via histology, immunofluorescence, diffusion tensor imaging (DTI), and transmission electron microscopy (TEM). Compared to wild-type (WT) mice, EC-Malat1 Tg mice exhibited significantly preserved CBF, improved cognitive and sensorimotor performance, and reduced structural brain damage following VCID. Specifically, EC-Malat1 Tg mice showed shorter escape latencies and spent more time in the target quadrant during the Morris water maze, demonstrated greater spontaneous alternation in the Y-maze, and exhibited prolonged latency in the passive avoidance test, all indicating enhanced learning and memory. Sensorimotor function was also markedly improved in EC-Malat1 Tg mice after VCID, as evidenced by longer rotarod endurance, faster adhesive removal, and fewer foot faults compared to WT mice. Histological analyses revealed reduced demyelination and axonal injury in EC-Malat1 Tg mice following VCID, as evidenced by increased MBP expression, decreased SMI32 staining, and better preservation of nodes of Ranvier. Cresyl violet and NeuN staining further confirmed diminished neuronal loss in the cortex and hippocampus. DTI demonstrated higher fractional anisotropy (FA) values in key white matter tracts, while TEM corroborated enhanced myelin integrity and reduced axonal degeneration. These findings demonstrate that endothelial cell-targeted Malat1 overexpression protects against CCH-induced cognitive decline, highlighting a novel vascular-targeted therapeutic strategy for VCID and related dementias.

Disclosures: Y. Zhang: None. N. Qiu: None. T. Xiong: None. S. Li: None. J. Xue: None. K. Yin: None.

Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.24/E51

Topic: D.02. Ischemia

Support: NIH Grant R01NS131122

Title: Nitro-oleic acid ameliorates neuropathological outcomes and cognitive dysfunction in vascular cognitive impairment and dementia

Authors: *N. QIU^{1,2}, S. LI^{1,2}, T. XIONG¹, Y. ZHANG^{1,2}, J. XUE^{1,2}, K. YIN^{1,2};

¹Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; ²Veterans Affairs Pittsburgh Healthcare Syst., Pittsburgh, PA

Abstract: Vascular cognitive impairment and dementia (VCID) is the second most common cause of dementia after Alzheimer's disease, primarily resulting from chronic cerebral hypoperfusion-induced brain injury. This condition significantly impairs the daily functioning of elderly individuals. Nitro-oleic acid (OA-NO₂), a nitroalkene produced through nitric oxide-dependent oxidative reactions, has been detected in human plasma and is believed to modulate various pathophysiological processes involved in neurological disorders. Previous studies from our lab have demonstrated that intravenous infusion of OA-NO₂ preserves blood-brain barrier (BBB) integrity and provides neurovascular protection in ischemic brain injury. However, the role of OA-NO₂ in VCID remains unclear. In this study, VCID was experimentally induced in C57BL/6 mice through chronic cerebral hypoperfusion, followed by treatment with vehicle, OA, or OA-NO₂ (10 mg/kg) administered via tail vein injection one hour after VCID onset. Cognitive and sensorimotor deficits were evaluated, along with assessments of white matter injury and neuronal loss. Cognitive function was assessed using the Morris water maze (MWM) test. Mice treated with OA-NO₂ showed significantly improved cognitive performance compared to vehicle- and OA-treated groups, evidenced by shorter escape latencies during the learning phase and increased time spent in the target quadrant during the probe test. Sensorimotor function was evaluated using the rotarod test, adhesive tape removal test, and foot fault test. OA-NO₂-treated mice exhibited enhanced sensorimotor abilities, demonstrated by longer durations on the rotarod, faster removal of adhesive tape, and fewer foot faults compared to controls. Furthermore, OA-NO₂ administration markedly reduced neuronal death after VCID, with near-normal neuronal morphology observed in the cerebral cortex and hippocampus via CV staining and NeuN immunostaining 35 days post-VCID. OA-NO₂ also preserved myelin integrity, as shown by LFB staining and MBP/SMI32 double-immunofluorescence in the corpus callosum, external capsule, and striatum. Additionally, OA-NO₂ treatment mitigated the loss of nodes of Ranvier (NOR), suggesting improved NOR function. In conclusion, OA-NO₂ confers significant brain protection in VCID, highlighting its potential as a novel therapeutic strategy for this condition.

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Poster

PSTR161: Stroke: Imaging and Assessment

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.25/E52

Topic: D.02. Ischemia

Support: NIH R01 NS119166

Title: Neurodegeneration is a delayed response relative to demyelination following bilateral carotid artery stenosis in mice

Authors: S. KUNDU^{1,2}, M. HABIB¹, I. JAHAN¹, B. SARKER^{1,2}, M. RAHMAN^{1,2}, M. SULTAN¹, *M. BHUIYAN^{1,2,3};

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Abstract: Background: Vascular contributions to cognitive impairment and dementia (VCID) are among the leading causes of dementia after Alzheimer's disease (AD), particularly in the aging population, and represent a growing public health concern worldwide. The molecular and cellular mechanisms underlying VCID remain poorly understood. While glial activation, demyelination, and neurodegeneration are recognized pathological features of VCID, the temporal dynamics and interrelationships among demyelination, neurodegeneration, and cognitive deficits are not well characterized. This study aimed to elucidate the temporal progression of glial activation, blood-brain barrier (BBB) disruption, demyelination, neurodegeneration, and cognitive impairment in a mouse model of VCID. **Methods:** VCID was mimicked in young adult male mice with bilateral carotid artery stenosis (BCAS). Cerebral blood flow (CBF) was monitored using laser speckle imaging. Cognitive performance was assessed with the Morris water maze (MWM) and novel object recognition (NOR) tests. BBB integrity, glial activation, demyelination and neuronal degeneration were evaluated by immunofluorescence staining for relevant markers. **Results:** The BCAS procedure induced a rapid drop in CBF within the first 10 minutes, followed by partial recovery over 1-4 weeks. A second phase of CBF reduction was observed between 4-8 weeks post-BCAS. Increased Iba1⁺ microglia/macrophage and GFAP⁺ reactive astrocytes were evident from 3 days after BCAS, with reactive astrogliosis was sustained until 8 weeks. Significant loss of myelin basic protein (MBP) in white matter tracts was detected at 4 weeks but not at earlier time points (1-2 weeks). SMI32 immunostaining revealed no evidence of axonal degeneration throughout the 1-8 week period following BCAS. Notably, neuronal degeneration in the hippocampal CA1 region was observed at 8 weeks post-BCAS, with no significant changes detected at 1-4 weeks. BCAS mice exhibited cognitive deficits between 5-8 weeks, as demonstrated by MWM and NOR tests, which temporally aligned with white matter demyelination. **Conclusion:** These findings suggest

that glial activation is an early response to chronic cerebral hypoperfusion, followed by demyelination and subsequently delayed neurodegeneration. The temporal correlation between demyelination and cognitive impairment supports the idea that white matter damage precedes and possibly contributes to cognitive decline in VCID. *This research was supported by NIH R01 NS119166 Grant (M.I.H.B.).*

Disclosures: **S. Kundu:** None. **M. Habib:** None. **I. Jahan:** None. **B. Sarker:** None. **M. Rahman:** None. **M. Sultan:** None. **M. Bhuiyan:** None.

Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.01/E53

Topic: D.04. Brain Injury and Trauma

Support: NIH R01NS115707
NIH R01NS105691
NIH NINDS F31NS125982
NIH K00AG084261
NSF CAREER CBET 1943906

Title: Disruption of vasomotion and smooth muscle cell calcium dynamics following implantation of microelectrodes in mouse visual cortex

Authors: ***A. M. FORREST**¹, K. C. STIEGER¹, K. CHEN³, S. WELLMAN⁴, K. GOOSBY¹, A. VAZQUEZ², T. D. KOZAI¹;

¹Bioengineering, ²Radiology, Univ. of Pittsburgh, Pittsburgh, PA; ³Sunnybrook Res. Inst., Toronto, ON, Canada; ⁴Dept. of Bioengineering, Columbia Univ., New York, NY

Abstract: The cerebral vasculature plays a critical role in the delivery of metabolites to brain tissue. The brain directs blood flow to active regions with greater metabolic demand in a phenomenon known as neurovascular coupling. Following brain injury, neurovascular coupling can be impaired due to dysfunction in the smooth muscle cells (SMCs) that ensheath brain arterioles and regulate vasomotions. Vasoconstriction, defined by the reduced ability of blood vessels to respond to neural activity, is evidence of this impairment. We hypothesize that changes in SMC Ca²⁺ signaling underlie this phenomenon. Leveraging a transgenic mouse model expressing a calcium reporter in SMCs, we aimed to quantify how vessel and SMC Ca²⁺ dynamics evoked by intracortical microstimulation (ICMS) and isoflurane anesthesia change over time following injury from microelectrode implantation. For 6 weeks following implantation, evoked pial vessel diameter and SMC Ca²⁺ fluorescence were obtained using in vivo two-photon microscopy through a cranial window. Outcomes including maximum diameter and maximum change in SMC Ca²⁺ were computed for each vessel and stimulation condition. A linear mixed effects

model was generated for each outcome with days following implantation as a fixed effect and animals and vessels as random effects. An ANOVA was used to test for significance. We found that the average baseline diameter decreased slightly over days ($p=0.0001$, max on d1: $28.2 \pm 1.0 \mu\text{m}$, min on d14: $25.3 \pm 1.1 \mu\text{m}$). We also observed increased vasorigor over days, evidenced by decreases in the maximum evoked vessel diameter to 100Hz ICMS ($p<0.0001$, max on d1: $30.7 \pm 1.2 \mu\text{m}$, min on d28: $27.0 \pm 1.4 \mu\text{m}$) which corresponded to decreases in the magnitude of change in SMC Ca^{2+} ($p<0.0001$). However, while maximum diameter evoked by isoflurane anesthesia tended to increase over time (min on d0: $32.9 \pm 1.5 \mu\text{m}$, max on d28: $40.6 \pm 1.9 \mu\text{m}$) there was not a significant effect ($p=0.7128$). Thus, while the ability of the vasculature to respond to ICMS is reducing, the cellular machinery required to dilate vessels is still functioning. Interestingly, the change in SMC Ca^{2+} needed to dilate vessels under isoflurane trended to increase over days ($p=0.0678$, min on d0 at -0.26 ± 0.04 , max on d21 at -0.55 ± 0.04). This suggests that SMC Ca^{2+} sensitivity may be reduced as greater Ca^{2+} changes are required to achieve similar vasomotions. Overall, vasorigor and reduced sensitivity to SMC Ca^{2+} following electrode implantation injury can contribute to the metabolic burden in injured tissue. Developing therapies that target SMC Ca^{2+} sensitivity show promise to reduce this burden and improve tissue health following brain injury.

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Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.02/E54

Topic: D.04. Brain Injury and Trauma

Support: NIH T32 on Stroke and ADRD AG052375
NIH P20GM109098

Title: Traumatic brain injury mediates persistent capillary stalling

Authors: *M. BARBOUR¹, D. CORBIN¹, K. KARELINA², Z. M. WEIL²;
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Abstract: Epidemiological data show that traumatic brain injury (TBI) is an independent risk factor for both ischemic and hemorrhagic stroke, even after mild injuries, with vulnerability persisting for months to years. However, the mechanisms driving this long-term risk remain poorly understood. The brain is highly reliant on an intact microvascular network to maintain oxygen and nutrient delivery, and even subtle disruptions in capillary flow can impair tissue function. TBI is known to induce inflammation, coagulopathy, and endothelial dysfunction, yet the effects of these changes on capillary-scale blood flow are not well defined. Previous work in

our laboratory identified persistent capillary stalling in mice in the weeks following a moderate TBI. In healthy conditions, stalled capillaries typically clear quickly; we hypothesized that TBI promotes a pathological subset of persistent microvascular occlusions that fail to clear efficiently. These may arise from injury-induced clotting, adhesive blood cells, endothelial dysfunction, inflammatory vessel remodeling, or impaired clearance mechanisms like hemodynamic washout and angiophagy. To test this, male and female mice were injured with a moderate closed head TBI or sham injury followed by systemic injection of 4µm fluorescent microspheres into the vasculature to assess propensity for capillary stalling. Acute stalls (1-hour sphere retention) are not elevated after TBI, but older stalls (72 hours) were significantly elevated. A time course study confirmed delayed clearance of occlusions post-TBI, suggesting both increased obstruction and impaired resolution. These persistent stalls may contribute to sustained microvascular dysfunction and increased risk for tissue hypoxia and microhemorrhage, and potentially greater stroke vulnerability.

Disclosures: M. Barbour: None. K. Karelina: None. Z.M. Weil: None.

Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.03/E55

Topic: D.04. Brain Injury and Trauma

Support: American Epilepsy Society

Title: Evaluating the Activity of Dentate Gyrus Somatostatin and Parvalbumin Interneurons During Acute and Epileptic Seizures

Authors: *F. GUEVARA PANTOJA¹, E. NOZARI², N. E. ZLEBNIK⁴, V. SANTHAKUMAR³;

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Abstract: Temporal Lobe Epilepsy (TLE) is the most common seizure disorder, affecting about fifty million people worldwide. About one-third are drug-resistant, and one-fifth do not benefit from surgery. The dentate gyrus (DG), a key brain region in the hippocampus involved in memory and learning, is heavily regulated by GABAergic inhibition from diverse interneuron (IN) subtypes, including soma-targeting parvalbumin- (PV+) INs and dendrite-targeting somatostatin- (SST+) INs. Reorganization of DG circuitry in epilepsy, including loss of INs, disrupts inhibitory control and is proposed to lower the seizure threshold. Inhibitory mechanisms have also been suggested to influence seizure termination. However, there is limited data on the specific role of the major INs subtypes in the onset and termination of seizures. In order to

investigate the roles of PV+ and SST+ interneurons, we selectively expressed a fluorescent calcium-dependent protein (GCaMP) in PV+ and SST+ Cre-mice and adopted a repeated low-dose Kainic Acid (KA, 5mg/kg dose i.p) to induce status epilepticus (SE) and subsequent epilepsy. We coupled this with the development of a robust system capable of simultaneously recording EEG, photometry, and video data, enabling correlation of local IN-specific calcium activity with the EEG activity observed during seizure events. To compare calcium and electrical signals, we used the Hilbert Burst Index (HBI) to identify the point with the highest number and amplitude of EEG spikes. Our findings from in-vivo studies indicate that during KA-induced seizures in non-epileptic mice, PV+ INs exhibited increased calcium signaling near the peak activity of the HBI. In contrast, the peak of the calcium signal in SST+ INs occurred 15 seconds after the HBI, suggesting a role in seizure termination. Moreover, the intensity of the calcium peak signal in the SST+ INs during KA-evoked seizures decreases significantly in epileptic mice compared to signals observed during acute induction of SE. These data suggest that the calcium activity of PV+ INs aligns with HBI, in turn suggesting that PV+ INs remain active during the seizure. In contrast, calcium rise in SST+ INs occurs following the HBI peak, suggesting a role in seizure termination. This research is funded by NIH/NINDS R37NS069861 and R01NS097750 to VS and AES to FJGP.

Disclosures: F. Guevara Pantoja: None. E. Nozari: None. N.E. Zlebnik: None. V. Santhakumar: None.

Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.04/E56

Topic: D.04. Brain Injury and Trauma

Support: PHF 20009147
PHF 20009167

Title: Cal-dentate gyrus network dynamics dysfunction after closed head injury

Authors: *K. PHAN¹, D. BHAVSAR², L. RIGNEY³, R. NAGARAJA⁴, I. LIMVAREE³, K. M. STANDIFER⁶, A. CSISZAR³, J. BURKE³, R. PATERNO⁵;

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Abstract: Traumatic brain injury (TBI) is a leading cause of long-term cognitive impairment, often resulting in deficits in memory, attention, and executive function. Among the affected brain regions, the hippocampus is particularly vulnerable due to its critical role in learning, spatial

navigation, and memory consolidation. Here we used an established mouse animal model of closed head injury (CHI) to characterize hippocampal-dependent memory dysfunction at the anatomic, circuit and behavioral level. We quantified interneuronal density of parvalbumin (PV)- and somatostatin (SST)-expressing interneurons as well as GFAP and IBA1 at 14- and 30-days post-injury (dpi). We assessed hippocampal CA1 synaptic activity using in vitro brain slices recordings. We also investigated electrophysiological alterations in hippocampal single-unit activity and oscillatory activity in vivo, using high-density silicon probes across the CA1-dentate gyrus (DG) axis in freely moving animals performing a novel/familiar paradigm interspersed with rest sessions. We recorded the local field potentials (LTP) and single unit activity in area CA1 and DG. We further assessed hippocampal-dependent behavioral memory using a novel object location task (NLT) in addition to open field navigation. We found that TBI mice exhibit impaired spatial performance at 14-dpi without changes in exploratory activity. We also found alterations of theta-gamma oscillatory activity across hippocampal layers assessed using a cycle-by-cycle approach and change in sharp wave ripples power (SWR) after TBI. These studies highlight the potential to identify network activity contributing to cognitive dysfunction after traumatic brain injury.

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Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.05/E57

Topic: D.04. Brain Injury and Trauma

Support: U.S. Department of Veterans Affairs
Department of Defense CDMRP ERP
Virginia Commonwealth University

Title: Deterioration of CA1 inhibition over six months post-TBI

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Abstract: Post-traumatic epilepsy (PTE) is a significant long-term complication of moderate-to-severe traumatic brain injury and comprises as much as 20% of all structural epilepsies. However, there are no effective biomarkers or therapies to prevent the development of PTE in high-risk individuals, in part because the underlying mechanisms which lead to chronic seizures in the injured brain are unknown. The dentate gyrus is responsible for gating information from

the cortex as it enters the hippocampus, and damage to this network is known to occur following traumatic brain injury. In the present study, Sprague-Dawley rats were recorded bilaterally along the hippocampal CA1-dentate gyrus axis 6-8 months after lateral Fluid Percussion Injury (n= 5) or sham procedure (n= 3) using two 128-channel silicon probes and a 32-channel skull-surface EEG grid. We show preserved recruitment of dentate gyrus units during entorhinal cortex input triggered dentate spike events despite interneuron loss. However, while dentate spikes inhibit CA1 in uninjured rats, this CA1 suppression was deteriorated in late-FPI rats, and in a subset of injured rats, CA1 firing increased during dentate spikes, representing a potential mechanism contributing cognitive dysfunction and epileptogenesis after traumatic brain injury.

Disclosures: A. Gibson: None. P. Koch: None.

Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

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Program #/Poster #: PSTR162.06/E58

Topic: D.04. Brain Injury and Trauma

Title: Defining Cerebellar Dysfunction in Cortical Traumatic Brain Injuries

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Abstract: Traumatic brain injuries (TBIs) are a leading cause of death and longer-term disability¹. While most TBI research has focused on the cerebrum and hippocampus due to their well-established roles in memory and cognition², emerging evidence highlights the cerebellum as an unexplored yet critical region involved in both motor and non-motor function, including cognition, emotion, and working memory³. Notably, cerebellar involvement following non-cerebellar injuries, such as cortical TBI, remains poorly understood. Previous studies have identified Purkinje cell vulnerability and microglial activation as key pathological features of cerebellar response to cortical damage⁴, suggesting a role in excitotoxicity and secondary inflammation. Building on previous literature, we examined cerebellar histopathology and motor performance in wildtype mice subjected to a controlled cortical impact (CCI) to the right parietal cortex (n=5). At 30 days post injury, sagittal cerebellar sections were immuno-stained for calbindin to assess Purkinje cell morphology and molecular layer thickness. Compared to non-TBI controls (n=3), TBI mice exhibited significant reductions in molecular layer width across several lobular regions: between lobule 3 and lobule 4/5 (-45 μ m, p = 0.0032), lobule 8 and lobule 9 (-62 μ m, p = 0.0004), and lobule 9 and lobule 10 (-28 μ m, p = 0.031) at 0.60 mm laterality. At 1.60 mm laterality, changes between lobule 6 and lobule 7 (-30 μ m, p = 0.035) and lobule 7 and lobule 8 (-81 μ m, p = 0.012) were also observed. These lobules are implicated in higher-order processing, such as action planning and working memory. Functionally, TBI mice

demonstrated impaired motor coordination on the balance beam task, with significantly more foot-slips than controls (14.4 foot-slips vs 2.8 foot-slips, $p = 0.0045$). Lateralized analysis revealed that left foot-slips, contralateral to injury, were significantly increased (10.2 foot-slips vs 1.6 foot-slips, $p = 0.0003$), supporting cerebellar dysfunction. These preliminary findings suggest that the cerebellum exhibits structural and functional changes following cortical injury, underscoring its involvement in the broader pathophysiology of TBI. Understanding these mechanisms could enable the development of targeted therapies, such as AAV-mediated gene delivery to mitigate Purkinje cell loss and cerebellar inflammation in TBI.

Disclosures: A. LaFollette: None. S. Bouscher-Helbig: None. K. Aruljothi: None. M.S. Keiser: None.

Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.07/F1

Topic: D.04. Brain Injury and Trauma

Title: The Intersection of Sleep and Wallerian Degeneration: Exploring Neurodegeneration Mechanisms in *Drosophila melanogaster*

Authors: *H. J. WALTERS¹, R. GUERRIERO²;

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Abstract: Neurodegenerative diseases such as Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (MS) or Parkinson's Disease, have started to elevate to the top of the list for medical health concerns. This has kickstarted the demand for deeper insight into shared molecular mechanisms and finding more effective therapies. They share what is known as a protein misfolding and aggregation, which is considered to be caused by a cellular stress response. This research focuses on how Wallerian degeneration (WD) breaks down the axonal and myelin sheath when an injury or disruption to the axon occurs. WD is essential for clearing damaged neuronal debris, particularly axons and myelin, and findings suggest that sleep significantly aids in this critical cleanup process, thereby supporting neuronal health and recovery. Using *Drosophila melanogaster* as a model, we investigated how WD impacts the sleep behaviors of those that have undergone an Antenna removal assay, while comparing to those who have not. This assay is particularly useful because it causes Central Nervous System (CNS) degeneration by axotomy of the olfactory receptor neuron (ORN) axons that originate within the antenna and project into the antennal lobe of the *Drosophila*'s central brain. It is particularly important for this study of WD and the association with the glial responses in the CNS because it's a precise, non-lethal injury that is targeting a specific population of neurons with projection into the central brain. It is particularly important for this study of WD and the association with the glial

responses in the CNS because it's a precise, non-lethal injury that is targeting a specific population of neurons with projection into the central brain. The *Drosophila* are separated out by sex and genotype, with a total of 3 different genotypes (Dsarm, Axed, Nmnat), 6 crosses of those genotypes with Gal4 drivers, while using W1118 as a control that is being performed. The study leverages advanced genetic tools (UAS-Gal4 system) and behavioral monitoring (DAM2 system), to explore the link between sleep and WD. This study provides a crucial foundation for understanding the intricate relationship between neurodegeneration and sleep, offering insights into potential therapeutic avenues that leverage sleep as a protective mechanism to mitigate neuronal damage and improve outcomes in neurodegenerative diseases.

Disclosures: H.J. Walters: None. R. Guerriero: None.

Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

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Program #/Poster #: PSTR162.08/F2

Topic: D.04. Brain Injury and Trauma

Support: ONR N000142212828

Title: Identifying Secondary Injury Pathologies Following Mechanical Primary Injury in Organotypic Brain Tissue

Authors: *E. CHEN¹, A. CHEN¹, J. PARK¹, C. FRANCK², J. ZHANG¹;

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Abstract: Traumatic brain injury (TBI) remains a major public health concern and can be categorized by loading rate into blunt/inertial or blast-induced TBI (bTBI). While blunt TBI is often associated with moderate strain rates and delayed neuroinflammation, bTBI involves extremely high strain rates, resulting in immediate primary mechanical damage. However, how such mechanical injuries evolve into secondary injury cascades, such as inflammation, blood-brain barrier (BBB) disruption, and tauopathy, remains less understood. Here, we use laser-induced cavitation (LIC) to deliver high-strain-rate ($\sim 10^4 \text{ s}^{-1}$) mechanical insult to ex vivo organotypic rat brain slices. Bright-field ultra-high-speed imaging captures bubble expansion and tissue deformation. Immediately post-insult, Calcein AM live-cell imaging quantifies primary mechanical injury. Immunohistochemistry is performed at acute (0 h) and subacute (24 h) time points using markers for primary damage ($\beta 3$ -tubulin), inflammation (GFAP, IBA1), BBB integrity (CD31), and neurodegeneration (phosphorylated tau). Results show a linear correlation between the LIC bubble radius and neuronal damage zones, verified via live imaging and loss of cytoskeletal biomarkers. By 24 hours, the upregulation of GFAP and IBA1 suggests the activation of astrocytes and microglia, respectively. Detachment between GFAP-positive astrocytic endfeet and CD31-positive endothelial cells indicates BBB compromise. Total tau and

phosphorylated tau near the injury site are compared to understand the potential induction of tauopathy. This study establishes a control injury model to study how high-strain-rate mechanical loading transitions into complex secondary pathologies. By integrating mechanical characterization with biomarker analysis, our work provides insight into injury thresholds and pathways in bTBI and may inform future diagnostic or therapeutic strategies.

Disclosures: E. Chen: None. A. Chen: None. J. Park: None. C. Franck: None. J. Zhang: None.

Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

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Program #/Poster #: PSTR162.09/F3

Topic: D.04. Brain Injury and Trauma

Support: NSF 1904198

Title: High-rate mechanical insult alters oligodendrocyte precursor cell proliferation- and differentiation-related gene and protein expressions

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Abstract: Mild traumatic brain injury (mTBI) is a major health concern that can lead to psychological disorders, including post-traumatic stress disorder (PTSD), anxiety, and depression. More than 80% of military patients with traumatic brain injury (TBI) are diagnosed with mTBI. These individuals are often exposed to blast waves during daily training activities and active duty involving the use of heavy weaponry, resulting in blast-induced TBI (bTBI). bTBI can cause multiple subcellular dysfunctions in the brain, including neuroinflammation. Astrocyte and microglia reactivity following bTBI is well recognized as part of the neuroinflammatory responses. However, another glial cell type, the oligodendrocyte precursor cell (OPC), is often overlooked in bTBI studies. OPCs typically replenish myelin and generate myelinating oligodendrocyte (OL) through differentiation. In severely injured brains, OPCs can migrate to the injury site and contribute to repair by proliferating and differentiating to replace lost OLs. Although OPC-mediated tissue recovery has been observed in severe cases, their cellular and molecular responses in mTBI remain unclear. In this study, we aimed to investigate OPC proliferation and differentiation by quantifying genetic and proteomic alterations following a high-rate mechanical insult. To study OPCs' tissue recovery responses, OPCs were encapsulated in norbonene-modified hyaluronic acid (NorHA) hydrogel (2×10^5 cells per gel) and exposed to a high-rate mechanical insult at 19.08 ± 6.53 psi. RNA and proteins were

collected at 1 and 9 days post-injury for qPCR and proteomic analyses. qPCR analysis revealed a significant increase in PDGFRA gene on day 1 ($p=0.012$) and a significant decrease in GALC protein level on day 9 ($p=0.013$). Increased PDGFRA expression suggests enhanced cell proliferation, and decreased GALC expression indicates a reduction in maturing OLs. Proteomic analysis showed that CTNNB1 and HSP90AB were significantly dysregulated. A significant increase in CTNNB1 on day 1 post-injury suggests potential activation of Wnt/ β -catenin signaling pathway, which is associated with cell proliferation. A significant decrease in HSP90AB was observed in both protein and gene expression at both time points ($p=0.002$ on day 1 and $p=0.032$ on day 9), indicating enhanced cell differentiation. This study demonstrates that molecules involved in OPC proliferation and differentiation are altered following high-rate mechanical insult. Future studies are necessary to elucidate how OPC-mediated tissue recovery is influenced by other glial cell types involved in neuroinflammation.

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Poster

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Topic: D.04. Brain Injury and Trauma

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Title: Parvalbumin-mediated inhibition is selectively reduced in hippocampal dentate granule cells born after traumatic brain injury

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Abstract: The subgranular zone of the hippocampus is one of only two regions in the adult mammalian brain that undergoes adult neurogenesis, and this process is dramatically altered by brain injury. Hippocampal adult neurogenesis is modulated by inhibitory neurotransmitter signaling, and immature adult-born dentate granule cell (DGC) neurons respond to GABA released from Parvalbumin-expressing interneurons (PV-INs). Thus, changes to PV-IN function or survival after brain injury could alter the maturation of adult-born neurons and contribute to aberrant post-injury neurogenesis. To investigate this, we used Controlled Cortical Impact (CCI) to model severe brain injury in adult Parvalbumin-Cre::Channelrhodopsin-2 mice. To label adult-born DGCs, we injected retroviral vectors expressing mCherry into the hippocampus two weeks after sham or CCI injury. Three weeks later, we assessed CCI injury severity using histological

measurements and evaluated PV-IN input onto adult-born DGCs and neighboring mature granule cells using electrophysiological recordings and optogenetics. Our histological analysis revealed a 40% loss of cortical tissue overlying the hippocampus in mice that received a CCI injury compared to sham controls, as expected for this model. Despite this injury, the density of PV-IN cells and the evoked amplitude of PV-mediated inputs onto mature DGCs in CCI-injured mice was unchanged from sham controls. Surprisingly, however, the amplitude of optogenetically evoked PV-mediated inhibitory currents in adult-born DGCs was selectively reduced after CCI. Our observations highlight a selective functional change in PV-mediated inhibition onto immature DGCs that are developing within the injured hippocampal circuit. This inability to establish normal inhibitory control of newly born DGCs could contribute to their aberrant network integration and the subsequent development of seizures and post-traumatic epilepsy.

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Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

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Topic: D.04. Brain Injury and Trauma

Support: Swedish Armed Forces

Title: Subregional differences in the hippocampal transcriptomic response after penetrating TBI in rats

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Abstract: Penetrating traumatic brain injury (TBI), often caused by high-velocity projectiles like shrapnel, has become increasingly common in modern warfare, such as the conflict in Ukraine. These injuries have high mortality rates and can lead to severe, long-term neurological deficits. The hippocampus possesses a complex subregional architecture with unique transcriptomes, and multiple neurological sequelae following TBI are associated with hippocampal dysfunction. While previous research has explored general brain responses to TBI, the specific molecular changes in individual hippocampal subregions remain poorly understood. To address this, we used laser-capture microdissection, RNA-sequencing, and differential gene expression matched with gene ontology analysis to investigate transcriptional responses in hippocampal subregions (CA1, CA2, CA3, and dentate gyrus) following high-velocity penetrating TBI in a rat model. Our findings reveal distinct gene expression patterns in each region, reflecting varied pathophysiological processes. CA1 exhibited increased expression of cell-cycle and gliogenesis genes, indicating astrogliosis

and metabolic stress. CA2 showed strong immune activation, highlighting leukocyte signaling, MHC antigen processing, and complement pathways -- coupled with downregulation of oxidative phosphorylation, suggesting immune-driven metabolic dysfunction. CA3 displayed a pronounced inflammatory profile, marked by TNF-signaling and adhesion remodeling. In contrast, the dentate gyrus upregulated genes linked to tissue repair, including extracellular matrix stabilization and angiogenesis, suggesting a neuroprotective response. These results highlight the complex, subregion-specific balance between injury and repair mechanisms following TBI. Understanding these molecular dynamics is essential for developing targeted interventions aimed at mitigating damage and promoting recovery in affected individuals, especially in the context of increasing high-velocity brain injuries due to modern conflict.

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Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

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Topic: D.04. Brain Injury and Trauma

Support: AHA CDA 23CDA1055341
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Title: Dynamic Dysregulation of Hippocampal Bioenergetics and Metabolism Following Traumatic Brain Injury

Authors: Z. DI¹, M. SHI¹, M. D. KILGORE², Y. XIU¹, Y. WANG¹, T. SEIN¹, D. WANG¹, B. NING¹, X. WANG¹, J. FAN¹, *N. LIU³;

²Neurosurg., ¹Tulane Univ. Sch. of Med., New Orleans, LA; ³Tulane Univ., New Orleans, LA

Abstract: Cellular bioenergetics dysregulation in the hippocampus contributes to neurodegeneration and cognitive impairment following traumatic brain injury (TBI), yet the underlying molecular mechanisms remain unclear. Gaining deeper insights into TBI-induced metabolic disruptions could uncover novel therapeutic targets for early intervention. Using the Seahorse analyzer, we observed a significant reduction in mitochondrial oxidative phosphorylation (OXPHOS) in hippocampal dentate gyrus (DG) slices at both day 1 and day 7 post-TBI in a mouse controlled cortical impact (CCI) model. Metabolomic profiling showed marked impairments in bioenergetics involving purine nucleotides, glucose, amino acids, and fatty acid metabolism at day 1, but not day 7. Comprehensive bioinformatics analysis of spatial proteomics data further revealed persistent suppression of purine nucleotide metabolism across hippocampal subregions. Notably, fatty acid oxidation (FAO) in the DG was not markedly

impaired at day 1 and significantly increased by day 7, suggesting a compensatory role of FAO in restoring bioenergetics. Administration of sodium octanoate, a medium-chain fatty acid, at 1 hour post-TBI enhanced mitochondrial respiration at 24 hours, and reduced microglial activation and neurodegeneration at 48 hours. These findings underscore dynamic metabolic changes following TBI and suggest that promoting FAO may help restore hippocampal bioenergetics and mitigate neurodegeneration.

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Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

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Topic: D.04. Brain Injury and Trauma

Support: Project ACCESS
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Title: Blast-induced traumatic brain injury potentially destabilizes neural networks through the GABAergic pathway

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Abstract: The effects of primary blast exposure pressure waves on the brain are poorly understood, specifically on network dynamics, limiting our understanding of rehabilitation techniques. Cerebral organoids are a 3D tissue structure that replicates the architecture and physiology of human neuronal networks found in the cerebral cortex. Previously, our lab developed an in vitro blast organoid model and determined lower pressure waves induce an acute neurophysiology response that alters physiology (Silvosa). This work identified local network desynchronization following blast exposure, but did not resolve how blast alters global network organization or state transitions. To further understand blast effects on network synchrony, we have utilized optogenetic stimulation and a multi-electrode array (MEA) to characterize the changes in the network after blast. After exposure to blast overpressure, organoid networks fragment, reducing network stability while blue-light stimulation of the network increases stability. To determine the role of synaptic function on stability, we used pharmacological inhibitors to block glutamate, GABA, and action potentials. Interestingly, GABAergic signaling inhibition also increased fragmentation, suggesting its role in stabilization of the network and potentially being the target of blast. We have identified three potential areas of GABA disruption: the GABAergic interneuron, astrocytes, and the GABA_A receptor. The goal of this

study is to understand the mechanism in which blast overpressure destabilizes brain networks to eventually lead to providing rehabilitation techniques.

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Poster

PSTR162: Traumatic Brain Injury: Neural Network Dysfunction and Vascular Pathophysiology

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Topic: D.04. Brain Injury and Trauma

Support: NIH grant F31NS132447
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Title: Hippocampal circuit reorganization following traumatic brain injury

Authors: *A. TIERNO¹, R. F. HUNT^{2,3};

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Abstract: Traumatic brain injury (TBI) can lead to cognitive disabilities and epilepsy, but the circuit mechanisms are unknown. Work from our lab and others has shown the hippocampus undergoes time-dependent brain-wide synaptic reorganization after TBI. This includes initial cell loss and deafferentation shortly after a brain injury followed by a progressive increase in the number of synaptic contacts and formation of new recurrent excitatory circuits within injured areas of the brain. Inhibitory neurons are converted into hyperconnected hubs, with robust local network connections but substantially diminished long-range input (Frankowski, Tierno, 2022). However, the circuit rearrangement of excitatory neurons is not fully known. To address this, we used a combination of viral tracing and in vivo calcium imaging to produce a comprehensive map of input-output reorganization of hippocampus in a widely-used preclinical model of TBI. Initial results show the pattern of posttraumatic circuit reorganization is different for excitatory versus inhibitory neurons. We are now testing the functional consequences of these structural changes in freely behaving animals. Our findings suggest a dramatic structural and functional breakdown of hippocampal circuits after brain injury.

Disclosures: A. Tierno: None. R.F. Hunt: None.

Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Topic: D.04. Brain Injury and Trauma

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Department of Veterans Affairs Rehabilitation Research and Development
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Title: Restoration of neuroregulatory systems in the basolateral amygdala by transcranial magnetic stimulation following traumatic brain injury in rats

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Abstract: Chronic anxiety is a hallmark sequela following traumatic brain injury (TBI). While the basolateral amygdala (BLA) is known to play an important role in regulating anxiety, critical questions remain regarding TBI-induced alterations of neuroregulatory systems in the BLA and how these changes are related to anxiety disorders. Because therapeutic potential of transcranial magnetic stimulation (TMS) to treat TBI-induced anxiety has been shown in the literature, knowledge related to these questions and efficacy of this treatment are critical to develop therapeutic methods for TBI-induced anxiety disorders (including post-traumatic stress disorder). Therefore, this study was designed to determine the impacts of chronic TBI on neuroregulatory systems in the BLA and the restorative effects of TMS on them in a clinically relevant rodent model. Following an acclimatization period, rats were randomly separated into normal intact (naïve), closed-head TBI (cTBI), and cTBI with TMS (T/TMS) groups. For cTBI and T/TMS animals, mild-to-moderate cTBI was induced using a weight-drop model, and for T/TMS animals, TMS was given every other day for 4 weeks starting 1 week after injury. Twenty-one weeks following cTBI, all animals were deeply anesthetized and transcardially perfused through the left ventricle with phosphate-buffered saline followed by 4 % paraformaldehyde in phosphate buffer. Following further overnight fixation in the 4 % paraformaldehyde solution and incubation with 30 % sucrose in the phosphate buffer, brains were coronally cryosectioned to be used for immunofluorescence staining of neuroregulatory and neuroprotective molecules, such as dopamine beta-hydroxylase, glutamate decarboxylase, GABA B receptor, and brain-derived neurotrophic factor. We found that chronic cTBI significantly decreased noradrenergic and GABAergic fiber innervation of the BLA ($p < 0.01$). In addition, expressions of GABA B receptor 1 and neuroprotective molecules (e.g., brain-derived neurotrophic factor) in the BLA neurons were significantly decreased following injury ($p < 0.01$). These cTBI-induced unfavorable neurobiological events were significantly diminished by the TMS treatment ($p < 0.01$). We concluded that the TMS treatment partly restored the TBI-induced decreases in the noradrenergic and GABAergic fiber innervation as well as the expressions of GABAergic receptors and neuroprotective molecules in the BLA.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Program #/Poster #: PSTR163.02/F10

Topic: D.04. Brain Injury and Trauma

Support: Chaire Fondation Caroline Durand en traumatologie aigüe de l'UdeM

Title: Intranasal MK-801 Attenuates Acute Neurochemical Alterations Induced by Concussion in a Rotational Weight-Drop Rat Model

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Abstract: Concussion is associated with acute elevations in extracellular amino acid levels, contributing to secondary neuronal injury through overactivation of N-methyl-D-aspartate (NMDA) glutamate receptors. While NMDA receptor antagonists hold therapeutic potential, previous studies have highlighted the need for more rapid and efficient delivery methods. This study evaluated the efficacy of a novel intranasal formulation of MK-801, a non-competitive NMDA receptor antagonist, in attenuating the immediate neurochemical response to concussion. A validated rat model combining a weight-drop impact with rotational acceleration was used alongside in vivo cerebral microdialysis to continuously monitor extracellular amino acid levels in the hippocampus. Dialysate samples were collected every 10 minutes for 60 minutes before injury, during impact, and for 60 minutes post-injury. High-performance liquid chromatography was used to quantify glutamate, gamma-aminobutyric acid (GABA), taurine, glycine, glutamine, and serine. Righting time was recorded as an index of neurological recovery. Animals received either vehicle or MK-801 (10 mg/kg, intranasally) immediately following concussion or sham procedure. Vehicle-treated concussion animals exhibited significant increases in extracellular glutamate, taurine, and glycine, along with prolonged righting times, compared to sham controls. In contrast, MK-801-treated concussion animals showed amino acid levels and righting times comparable to those of sham-injured animals within the first 10 minutes post-injury. These findings suggest that intranasally administered MK-801 rapidly reaches the brain and effectively suppresses the early excitotoxic surge of neurotransmitters following concussion. Intranasal delivery of NMDA antagonists may represent a promising strategy for acute neuroprotection in traumatic brain injury.

Disclosures: I. Masse: None. C. Bouchard: None. A.P. Gratton: None. L. De Beaumont: None.

Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.03/F11

Topic: D.04. Brain Injury and Trauma

Support: The Ari and Regine Aprijaskis Fund, Grant number 347300-00;
The Dr. Miriam and Sheldon G. Adelson Center for the Biology of
Addictive Diseases, Grant number 601133461;
Sylvan Adams Sport Institute Grant number 0601133671

Title: Oral Niacin Supplementation Improves Neurobehavioral and Molecular Outcomes After Traumatic Brain Injury in Mice

Authors: M. HAR-EVEN¹, E. SHAVIT STEIN², *C. G. PICK^{3,1};

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Abstract: Traumatic brain injury remains a public health challenge with long-term cognitive and neuroinflammatory effects. Previous studies tested niacin (vitamin B3) as a therapy via intraperitoneal injection; here we explored its oral administration in water. TBI was induced in male mice using a weight drop. Mice received niacin in drinking water for up to 30 days. Cognitive performance was assessed using Novel Object Recognition, Y-Maze, and Morris Water Maze tests. Serum samples were collected at 3, 12, and 30 days post-injury to measure Neurofilament Light Chain (NfL) using Simoa technology. Immunohistochemistry for NeuN, GFAP, and Iba1 was performed in the cortex and hippocampus. Gene expression of SIRT1, PGC1 α , HCAR2, TNF α , and IL1 β was evaluated in both hippocampi. Niacin-treated mice showed improvements in several behavioural tests compared to TBI-only controls. Serum NfL levels exhibited dynamic changes, reflecting potential modulation of axonal injury. In the temporal cortex, NeuN-positive cell counts were higher in niacin-treated mice, indicating enhanced neuronal survival. GFAP and Iba1 staining showed no significant differences in the cortex. In the DGH, NeuN was higher and GFAP/Iba1 lower in niacin-treated mice, suggesting reduced glial activation. Notably, gene expression analysis revealed significant changes in the contralateral hippocampus, highlighting a complex response. Overall, oral niacin supplementation improved behavioural and molecular outcomes after TBI. These effects, while promising, were less robust than those previously observed with a ketogenic diet in our own study. This study offers a novel approach to post-TBI treatment using oral niacin, a water-soluble vitamin, which had not been tested before.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.04/F12

Topic: D.04. Brain Injury and Trauma

Support: James and Esther King Biomedical Research Program, State of Florida.
6JK08
FAU Grad Student Research Award, 2024

Title: Granulocyte colony stimulating Factor (G-CSF) gene therapy drives neuronal and glial based regenerative pathways after ischemic injury.

Authors: *G. CHAPAGAIN^{1,2}, C. FALCON³, S. CONDIKEY³, J. M. MENZIE-SUDERAM³, S. BHANDARI³, M. BEN ANDIOLO³, W. SHEN³, R. TAO³, H. PRENTICE³, J.-Y. WU³;
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Abstract: Ischemic stroke leads to a cascade of cellular and molecular events that culminates in widespread neuronal death and disruption of glial support systems. The ischemic insult initiates mitochondrial dysfunction, oxidative stress and endoplasmic reticulum stress, all of which contribute to energy failure and apoptosis within vulnerable tissue, which surrounds the ischemic core. In addition to acute tissue loss, ischemia disrupts the neurogenic niches—including subventricular zone (SVZ) and subgranular zone (SGZ)—compromising endogenous repair. Currently, tissue plasminogen activator (t-PA) is the only FDA approved treatment at restoring blood flow in ischemic stroke. However, this intervention is limited to a window of 4.5 hours post-onset, underscoring the critical need for novel therapies that extend beyond acute intervention. The human Granulocyte Colony Stimulating Factor (G-CSF) gene therapy has emerged as a promising candidate for treatment in ischemic stroke because of its pleotropic neuroprotective and neuroregenerative properties. From our previous studies, G-CSF gene therapy, mechanistically, mitigates mitochondrial and endoplasmic reticulum stress in a mouse model of global ischemia induced by Bilateral Carotid Artery Occlusion (BCAO). In this current study, we further explored the regenerative potential of G-CSF gene therapy for endogenous repair, focusing on its ability to promote neurogenesis. At 7 days post BCAO, Adeno associated virus-2 delivery of G-CSF transgene markedly promoted proliferation and differentiation of neural stem cells and progenitor cells within neurogenic niche of subgranular zone (SGZ) of dentate gyrus and subventricular zone (SVZ). This was evidenced by increase in population of quiescent stem cells (qNSCs), actively proliferating neural stem cells (aNSCs), progenitor cells, and immature neurons in these regions. Notably, human G-CSF gene therapy also appeared to support the newly formed neurons by stimulating Oligodendrogenesis, which is a critical process for myelin synthesis and repair. G-CSF may influence proliferation and survival neural precursors by modulating neurotransmission pathways critical for maintaining neural network stability and cellular homeostasis. The treated animal group continued to exhibit elevated levels of both immature and mature neurons at 14 days and 28 days indicating prolonged regenerative activity in the brain following ischemia.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Program #/Poster #: PSTR163.05/F13

Topic: D.04. Brain Injury and Trauma

Support: NIH NS084967 and NS121037 (AEK)
NIH NS110609 NINDS Landis Award supplement (COB)

Title: Acute Amantadine Enhances the Benefits of Delayed and Abbreviated Environmental Enrichment in a Pediatric Traumatic Brain Injury Model

Authors: *J. SAWHNEY, A. M. VICTORIA, H. CAPECI, R. VANGALA, P. GOYAL, P. L. RENNERFELDT, H. DONALD, J. P. CHENG, E. H. MOSCHONAS, C. O. BONDI, A. E. KLINE;
Physical Med. & Rehabil. and Safar Ctr. for Resuscitation Res., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Introduction: Environmental enrichment (EE) promotes neurobehavioral recovery after traumatic brain injury (TBI). However, most preclinical studies initiate EE immediately after injury, which contrasts with delayed rehabilitation in the clinic. To better model clinical practice, we delayed the onset of EE and administered amantadine (AMT) acutely as a therapeutic bridge. **Hypothesis:** This temporally staged combination therapy will improve neurobehavioral outcomes beyond that of either treatment alone. **Methods:** Post-natal day 21 male rats received a cortical impact or sham surgery and were housed in standard (STD) conditions. Beginning 24 h post-surgery, daily intraperitoneal injections of AMT (20 mg/kg) or saline vehicle (VEH; 1 mL/kg) were provided for 7 days (bridge phase). On post-operative day 8, a subset transitioned to abbreviated EE (6 h/day). Vestibulomotor (beam-balance), cognition (spatial learning/memory), and affect (shock probe defensive burying) were assessed on days 8-12, 14-20, and 23, respectively. Hippocampal neuron survival was quantified on day 24. **Results:** EE, regardless of AMT or VEH treatment, and AMT in STD housing, improved motor and cognitive outcomes vs. STD + VEH ($p < 0.05$). Additionally, AMT + EE outperformed VEH + EE in spatial learning and improved memory retention relative to AMT + STD ($p < 0.05$). All treatment groups engaged quicker with the shock probe and increased burying behavior compared to VEH + STD. Additionally, the AMT + EE group spent more time burying the probe than the AMT + STD and VEH + EE groups ($p < 0.05$) and did not differ from SHAM controls ($p > 0.05$). Both EE groups spared more CA₃ neurons compared to the STD-housed groups ($p < 0.05$). **Conclusions and significance:** Overall, these findings demonstrate that acute AMT treatment augments the efficacy of delayed and abbreviated EE, particularly in cognitive domains, which support the hypothesis. This temporally staged combination therapy may more accurately model clinical care and lead to greater improvement after TBI.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.06/F14

Topic: D.04. Brain Injury and Trauma

Support: NIH R01 NS 129573

Title: Chronic prazosin reduces headache symptoms through glymphatic flow enhancement

Authors: *A. DELLA PIETRA¹, A. KUBURAS², M. SEVAO³, J. D. CHO⁴, A. G. SCHINDLER⁵, J. J. ILIFF⁶, A. F. RUSSO²;

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Abstract: Mild traumatic brain injury (mTBI) is common and often leads to migraine-like post-traumatic headaches (PTH). However, the mechanisms remain unclear and effective treatments are lacking. One of the major mediators of migraine is calcitonin gene-related peptide (CGRP). Following mTBI, the glymphatic system, a brain-wide network of perivascular pathways, is impaired. This system facilitates the rapid exchange of cerebrospinal and interstitial fluid and clears interstitial solutes, including CGRP, from the brain. Whether glymphatic modulation contributes to headache is unknown. mTBI was induced in mice using a closed-head impact model via weight drop. Glymphatic function was assessed through dynamic and slice-based imaging, following the injection of a conventional fixable fluorescent tracer in the cisterna magna. Facial allodynia, a symptom of PTH and migraine, was evaluated using periorbital von Frey testing. Here we show that mTBI impairs glymphatic function and that prazosin (PZN), an $\alpha 1$ noradrenergic receptor antagonist, enhances glymphatic flow. Our preliminary results show that also CGRP induces a reduction of glymphatic function. Interestingly, PZN alleviates facial allodynia, a migraine and PTH symptom, induced by CGRP and sodium nitroprusside in mice. Instead, the β -antagonist propranolol does not treat the same symptoms. Overall, the pharmacological action of prazosin offers the chance to treat these disabling conditions.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.07/F15

Topic: D.04. Brain Injury and Trauma

Title: The Effects of Gamma Light Therapy in Fruit Fly Models of Traumatic Brain Injury (TBI)

Authors: *Z. LOPEZ, K. VU, A. OCHOA, K. MARTINEZ, G. CELAYA, R. E. HARTMAN;
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Abstract: Background: Traumatic brain injury (TBI) remains without a cure, prompting exploration of novel therapeutic approaches. *Drosophila melanogaster* offers a cost-effective, genetically tractable, and time-efficient model for studying TBI. Light-based interventions, such as gamma light, have been associated with reduced chronic TBI symptoms, enhanced neurogenesis, improved cognition, and neuroprotection. However, no studies to date have examined the effects of 40 Hz gamma flicker light on fruit fly models of TBI. This study investigates whether 40 Hz gamma flickering light can entrain gamma oscillations and ameliorate TBI-related impairments in *Drosophila*, with a focus on potential reparative and neuroprotective effects. Methods: Male *drosophila melanogaster* (N = 58) were randomly assigned to either a traumatic brain injury (TBI) or sham condition. Mild TBI was induced using a high-impact trauma (HIT) device. Within each condition, flies were further divided into two light exposure groups: gamma light (40 Hz flicker) or standard incandescent light (control). Light exposure followed a 12-hour cycle and was administered both before and after injury. Locomotor function was assessed using a negative geotaxis climbing assay (RING), conducted both prior to brain injury (pre) and following the brain injury (post). Group differences were analyzed using a repeated measures analysis of variance (ANOVA) in SPSS Version 29. Results: Flies exposed to gamma light demonstrated more stable locomotor performance over time, whereas those under incandescent light showed greater post-injury decline. Notably, differences in climbing performance emerged primarily post-injury, suggesting gamma light may support maintenance of motor function. As expected, TBI was associated with reduced climbing ability; however, this effect was less pronounced among gamma-exposed flies. Discussion: Initial findings suggest that 40 Hz gamma flicker light may help preserve locomotor function following mild TBI in *Drosophila*. The observed differences between light conditions point to gamma stimulation as a promising direction for further research. Continued work with expanded samples and additional mechanistic focus will be critical for clarifying the therapeutic potential of gamma light in post-injury neural recovery.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Topic: D.04. Brain Injury and Trauma

Support:

DOD Grant HT9425-23-1-0538

Title: Galacto-oligosaccharide, a prebiotic, selectively reduces impulsivity with minor effects on decision-making and anxiety after moderate-severe frontal TBI in rats

Authors: *A. DORINSKY¹, K. KOONTZ¹, G. BILGIN¹, L. O'CONNELL¹, J. MCCLOSKEY¹, M. E. HILT², M. T. BAILEY¹, C. VONDER HAAR¹, K. M. MARTENS¹;

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Abstract: Traumatic Brain Injury (TBI) leads to several chronic psychiatric and cognitive impairments including impulsivity and risky decision-making. However, the mechanisms underlying these deficits remain poorly understood, limiting the development of effective treatments. TBI is also associated with gut dysbiosis, or a disruption of the microbial community. Given the gut microbiome's role in modulating serotonin production via gut-derived tryptophan metabolism, such alterations in microbial composition may contribute to TBI-related behavioral deficits through disruptions in serotonin signaling. The current study assessed whether dietary supplementation with the prebiotic, galacto-oligosaccharide (GOS), could mitigate behavioral deficits following TBI and reduce the associated gut dysbiosis. Rats were administered a control diet or one supplemented with 2% GOS beginning at six weeks prior to receiving a mild or moderate-severe frontal TBI via controlled cortical impact and continued their respective diets until 60-days post injury. Behavioral function was assessed post injury and included the Rodent Gambling Task (RGT; risky decision making), the elevated plus maze (EPM; anxiety-like behavior), the forced swim test (FST; depressive-like behavior), and the Morris water maze (MWM; learning and memory). Fecal samples were collected pre-injury and at multiple post-injury time points for DNA extraction, and 16S rRNA sequencing. Brain punches were taken at the conclusion of the study to measure perilesion serotonin transporter (SERT) and receptor (5-HT1A) density via Western blot. Moderate-severe TBI increased anxiety-like behavior (EPM), decreased depressive-like behavior (FST), and impaired cognitive performance (MWM) as well as decision-making and impulsivity on the RGT. GOS (independent of injury) increased time spent in open arms on the elevated plus maze. GOS selectively reduced impulsivity in the moderate-severe TBI group on the RGT. Both moderate-severe TBI and GOS (independently) decreased alpha diversity and shifted the relative abundance of phyla in the gut microbiome across multiple time points post-injury. While GOS did not significantly influence serotonin transporter (SERT) and receptor (5-HT1A) density expression, chronic moderate-severe TBI increased both, supporting the idea of CNS serotonergic disruption but not in the anticipated direction. Together these findings highlight the therapeutic potential of targeting the gut microbiome to improve select TBI-related behavioral deficits, though further research is needed to clarify the underlying serotonergic mechanisms.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Topic: D.04. Brain Injury and Trauma

Support: NIH NS084967 and NIH NS121037 (AEK)
NIH NS110609 NINDS Landis Award supplement (COB)

Title: Brexpiprazole does not adversely impact neurobehavior following preclinical traumatic brain injury

Authors: H. E. CAPECI, P. SANTRA, R. VANGALA, P. GOYAL, J. SAWHNEY, J. P. CHENG, E. H. MOSCHONAS, C. O. BONDI, *A. E. KLINE;
Physical Med. & Rehabil. and Safar Ctr. for Resuscitation Res., Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Agitation is a common maladaptive behavioral response following traumatic brain injury (TBI) and is frequently managed with antipsychotic drugs (APDs). However, APDs that antagonize D₂ receptors hinder recovery after TBI, emphasizing the importance of exploring alternative APDs that do not cause adverse effects. Brexpiprazole, a third-generation atypical APD, exhibits partial D₂/5-HT_{1A} receptor agonism. Based on our studies, and others, showing that pharmacotherapies with D₂/5-HT_{1A} receptor actions improve function after TBI, we hypothesized that brexpiprazole would enhance neurobehavioral outcomes after TBI. Isoflurane anesthetized adult male rats received a cortical impact of moderate severity (2.8 mm at 4 m/s) or sham injury and were randomly assigned to brexpiprazole (1 mg/kg) or vehicle (saline/DMSO; 1 mL/kg) treatments administered intraperitoneally once daily on post-operative days 1-21. Motor (beam-balance/walk) and cognition (spatial learning and memory) were assessed on days 1-5 and 14-19, respectively. The data (n=10 per TBI groups; n=5 per sham groups) were analyzed by repeated measures ANOVA and the Newman-Keuls post-hoc test. No differences were found between the brexpiprazole and vehicle-treated sham groups ($p>0.05$), so the data were pooled and are presented as SHAM. As expected, the SHAM group performed better than the TBI groups ($p<0.05$). Contrary to our hypothesis, brexpiprazole did not improve outcomes relative to vehicle ($p>0.05$), but it also did not worsen. This finding suggests that brexpiprazole may be a safer option for managing TBI-induced agitation without the negative cognitive effects associated with traditional APDs with D₂ antagonist actions like haloperidol and risperidone.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Program #/Poster #: PSTR163.10/G2

Topic: D.04. Brain Injury and Trauma

Support: DoD - W81XWH2110597

Title: Low dose- interleukin-2 modulation of hypersensitivity in a stress-induced migraine model

Authors: *R. SIMOES¹, Y.-Q. CAO²;

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Abstract: Introduction: Stress is a well-established trigger for migraine attacks and a key factor in the transition from episodic to chronic migraine. It significantly increases the risk of migraine onset, with a higher prevalence in women. Migraine's complex pathophysiology involves neuroimmune dysfunction. Regulatory T cells (Tregs) and anti-inflammatory cytokines like IL-10 help control neuroinflammation and neuronal sensitization. Interleukin-2 (IL-2), with its immunomodulatory role, is a promising tool to restore immune balance. Low-dose IL-2 (LD-IL-2) has shown efficacy in reducing neuroinflammation and sensitization in immune-driven headache disorders. Methods: Male and female CD-1 mice underwent 2 h/day of restraint stress for 3 consecutive days. Sham controls remained undisturbed. Facial mechanical sensitivity was tested using von Frey filaments and the 50% withdrawal threshold was determined on days 1, 3, 5, 7, and 9. Hyperalgesic priming was assessed via i.p. sodium nitroprusside (SNP) injection, with evaluations at 3 and 24 h, and via bright light stimulation (BLS), assessed at 1 and 24 h. LD-IL-2 (1 µg in 100 µL saline) was administered i.p. for 9 days post-stress. In a separate cohort of female mice, facial expressions were scored using the Grimace Scale at baseline (day 14) and after SNP (day 15). Male mice were evaluated using the Facial Pain Score. Results: Repetitive stress induced acute mechanical hypersensitivity in the periorbital region of both sexes, persisting for one week, with hind paw hypersensitivity lasting up to 4 days. Chronic sensitization followed. BLS and SNP induced facial hyperalgesia within 1-3 h, confirming hyperalgesic priming. LD-IL-2 accelerated recovery of facial mechanical thresholds in both sexes. In females, LD-IL-2 prevented the increase in grimace scores after SNP, indicating reduced pain-related facial expressions. In males, LD-IL-2 significantly reduced facial pain scores following BLS and SNP, preventing sustained facial hypersensitivity. Conclusion: LD-IL-2 prevents the transition from acute to chronic sensitization in stress-exposed mice, supporting its potential as a therapy targeting neuroimmune dysfunction in stress-triggered migraine and chronic pain.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Program #/Poster #: PSTR163.11/Web Only

Topic: D.04. Brain Injury and Trauma

Support: A1-S-40569

Title: Antitumor effect of albendazole in combination with melatonin in a Xenograph glioma model in mouse

Authors: *M. H. CERÓN^{1,2}, M. OROZCO-MORALES³, F. PALOMARES⁴, K. DE LA CRUZ LÓPEZ⁵, H. VALENCIA-GONZALEZ⁵, A. GARCÍA-CARRANCÁ⁵, B. PINEDA OLVERA³;

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Abstract: Glioblastoma (GB) is the most aggressive brain tumor in adults. With the use of the standard pharmacologic treatment (temozolomide), the median survival time is around of 15 months. Therefore, it is required to explore more alternatives. In a previous study, it was found that the combination of albendazole (ALB)+melatonin (MLT) exerted a synergistic anticancer effect on three GB cell lines (C6, RG2, and U87), attributed to the induction of apoptosis and autophagy. Therefore, the objective of this study was to evaluate the antitumor effect of the ALB+MLT combination in an *in vivo* GB model. Methods: Male NOD-SCID mice were injected with 1.5×10^6 U87 cells by via subcutaneous. When the tumors reached a volume of 200 mm³, the animals were divided in groups: a) ALB 25 mg/kg, i.p., b) MLT 15 mg/kg, i.p., c) Combination (25 mg/kg+15 mg/kg, i.p.), d) Vehicle control (0.5% CMC, i.p.) and were administrated for 10 days. Tumor volume was measured daily, and at the end of the treatment, the animals were sacrificed to remove the tumors. Tumor weight was obtained and the percentage decreased was calculated for each treatment; the theoretical sum was obtained and was compared with the experimental tumor reduction with the combination using a Student's t-test ($p < 0.05$). Results: The combination caused a significant reduction in tumor volume compared to each drug alone and the control ($p < 0.05$) (Fig 1A). Tumor weight was also lower with the combination, which exerted a 53% reduction compared to the control ($p < 0.05$) (Fig 1B and 1C). The effect of the combination was additive, since no significant difference was observed between the theoretical reduction ($32\% \pm 23\%$) and the experimental reduction with the combination ($53\% \pm 5\%$). Conclusions: ALB in combination with MLT produced an additive antitumor effect in a Xenograph glioma model in mouse. Considering that both drugs are less toxic and cheaper than temozolomide, the combination could be an alternative for GB treatment. Further studies are required to confirm this hypothesis.

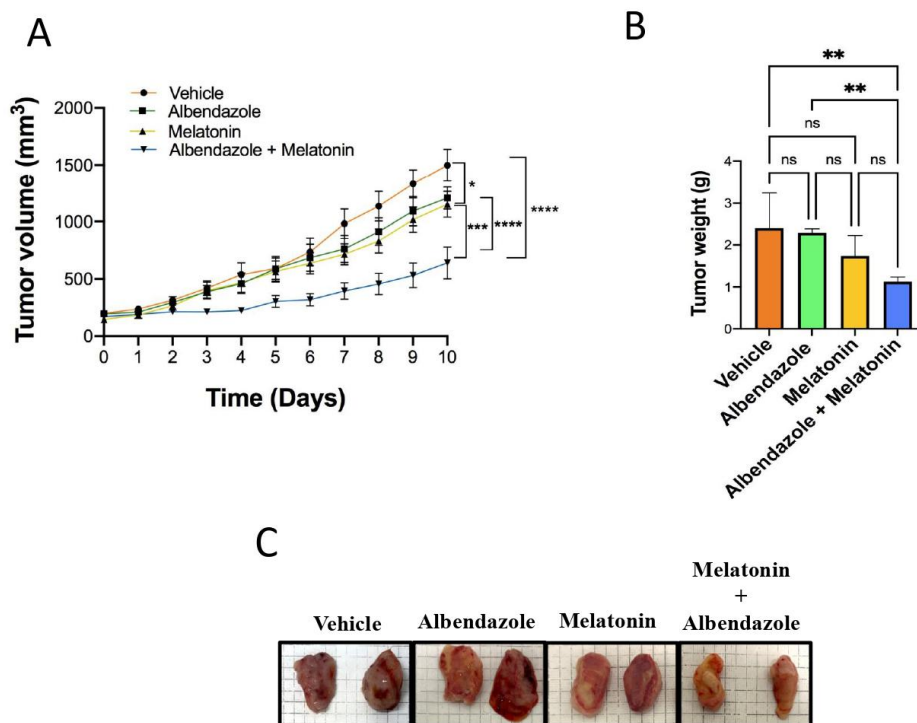


Figure 1. *In vivo* antitumor evaluation of the combination of ALB+MLT. A) Tumor growth curve (mm³). B) Tumor weight (g). C) Representative images of tumors from mice treated with ALB, MLT, the combination, or vehicle. Data are presented as mean $\pm$ standard error (SEM). Statistical analysis was performed using one-way ANOVA followed by Bonferroni's multiple comparison test. N = 5 mice per group.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

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Program #/Poster #: PSTR163.12/G3

Topic: D.04. Brain Injury and Trauma

Support: DA060139

Title: Morphine Amplifies Traumatic Brain Injury-Induced Neuroinflammation via the Kynurenine Pathway

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Abstract: Chronic pain affects over 50% of traumatic brain injury (TBI) patients, which has been strongly linked to neuroinflammation. Although opioids like morphine (MOR) are prescribed for post-TBI pain, they paradoxically worsen neuroinflammation, producing opioid-induced hyperalgesia. Therefore, identification of mechanisms underlying post-TBI pain, inflammation, and MOR action are necessary to optimize post-TBI analgesia. The kynurenine (KYN) pathway (KP) responds robustly to inflammation, producing kynurenic acid (KYNA, anti-inflammatory) and quinolinic acid (QUIN, pro-inflammatory), although their roles in TBI-induced pain, inflammation, and MOR action remain unclear. Therefore, the KP was examined after 5 days of escalating MOR treatment (1-2 days post-injury (dpi), 4 mg/kg; 3-5 dpi, 8 mg/kg) in C57Bl/6 male mice (n=4-6) following closed-skull impact. Initially, mice were secured in a stereotaxic frame and administered isoflurane to induce anesthesia. Then, a 5mm diameter metal tip was aligned along the midline suture of the intact mouse skull and driven to a 2 mm depth at 5 m/s velocity using an electronically-controlled impact device, producing a moderate, non-contusive TBI. Sham mice were surgically prepared, but not impacted. Tactile thresholds (Von Frey), inflammatory cytokines (enzyme-linked immunosorbent assays), and KP metabolites (liquid-chromatography tandem mass spectrometry) were measured by 30 dpi. Tactile threshold in TBI-saline mice was significantly reduced at 5 dpi ($p < 0.0001$ vs. sham-saline), which was reversed by MOR. However, at 30 dpi, TBI-MOR mice exhibited significantly lower tactile thresholds than TBI-saline controls ($p < 0.0001$). At 30 dpi, MOR exacerbated TBI-induced elevations in the pro-inflammatory cytokines, interleukin-1 beta and tumor necrosis factor-alpha, within the prefrontal and anterior cingulate cortices (all $p < 0.0001$ vs. TBI-saline). TBI-induced elevations in cortical QUIN were further elevated by MOR at 30 dpi ($p = 0.04$ vs. TBI-saline). These findings suggest that MOR treatment exacerbates TBI-induced elevations in chronic pain, neuroinflammation, and the central KP response, warranting future studies to explore the KP as a therapeutic target for post-TBI pain management.

Disclosures: I. Nahmoud: None. S. Lloyd: None. E.A. Woodcock: None. A. Conti: None.

Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.13/

Topic: D.04. Brain Injury and Trauma

Support: P30AG072978
R01AG090553
BX004349

Title: Repetitive head impacts induce neuronal loss and neuroinflammation in young athletes

Authors: M. BUTLER¹, K. BREEN², S. M. CALDERAZZO³, S. MAZZILLI³, Y. WANG⁴, R. NICKS³, M. M. HEFTI⁵, K. FIOCK⁶, B. R. HUBER⁷, T. D. STEIN⁸, J. CAMPBELL³, A. C. MCKEE³, *J. D. CHERRY³;

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Abstract: Repetitive head impacts (RHI) sustained from contact sports are the largest risk factor for chronic traumatic encephalopathy (CTE). Currently, CTE can only be diagnosed after death and the multicellular cascade of events that trigger initial hyperphosphorylated tau (p-tau) deposition remain unclear. Further, the symptoms endorsed by young individuals with early disease are not fully explained by the extent of p-tau deposition, severely hampering development of therapeutic interventions. Here, we show that RHI exposure associates with a multicellular response in young individuals (<51 years old) prior to the onset of CTE p-tau pathology that correlates with number of years of RHI exposure. Leveraging single nucleus RNA sequencing of tissue from 8 control, 9 RHI-exposed, and 11 low stage CTE individuals, we identify SPP1+ inflammatory microglia, angiogenic and inflamed endothelial cell profiles, reactive astrocytes, and altered synaptic gene expression in excitatory and inhibitory neurons in all individuals with exposure to RHI. Surprisingly, we also observe a significant loss of cortical sulcus layer 2/3 neurons in contact sport athletes compared to controls independent of p-tau pathology. Finally, we identify TGFB1 as a potential signal mediating microglia-endothelial cell cross talk through ligand-receptor analysis. These results provide robust evidence that multiple years of RHI exposure is sufficient to induce lasting cellular alterations that may underlie p-tau deposition and help explain the early pathogenesis in young former contact sport athletes. Furthermore, these data identify specific cellular responses to repetitive head impacts that may direct future identification of diagnostic and therapeutic strategies for CTE.

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Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.14/G5

Topic: C.01. Brain Wellness and Aging

Support: Steve and Genevieve Jurvetson
Pritzker Neuropsychiatric Disorders Research Consortium
VETS
Ambio Clinic

Title: Twelve month followup of magnesium ibogaine therapy (mistic) in special operations veterans with traumatic brain injuries

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Abstract: Study objective To evaluate the long-term durability of clinical benefits following a single administration of magnesium-ibogaine therapy (MISTIC) in Special Operations Veterans (SOVs) with traumatic brain injury (TBI). Introduction TBI often results in chronic neuropsychiatric symptoms, including posttraumatic stress disorder (PTSD), depression, anxiety, and functional disability. A prior study found that MISTIC significantly reduced symptom severity at 1-month post-treatment. We investigated whether those improvements are sustained over 12 months. Methods Thirty male SOVs with a history of TBI were assessed at baseline, immediately post-treatment, and at 1-, 3-, 6-, 9-, and 12-months post-MISTIC. Outcomes included clinician- and self-reported measures of functional disability (WHODAS-2.0), PTSD (CAPS-5), depression (MADRS), and anxiety (HAM-A). Linear mixed-effects models assessed change over time. Kaplan-Meier analyses estimated time to symptom relapse among those who achieved remission. Results Twenty-five of 30 participants completed the 12-month follow-up. Significant reductions in functional disability, PTSD, depression, and anxiety were observed at 12 months compared to baseline (all $p_{FDR} < .001$; Cohen's $d > 2.17$), with sustained improvements at interim timepoints. Among participants who achieved remission, the estimated probability of maintaining non-relapse over 12 months was 84% for PTSD, 66% for depression, and 61% for anxiety. Mean time to relapse ranged from 9.1 to 10.7 months across diagnoses. Conclusion A single MISTIC treatment was associated with large, sustained reductions in disability and psychiatric symptom severity over 12 months. These findings support the long-term durability of ibogaine-based interventions and highlight the need for controlled trials to further assess their therapeutic potential.

Disclosures: J.P. Coetzee: None. A. Faerman: None. K. Cherian: None. J.I. Lissemore: None. A. Geoly: None. C. Rolle: None. N. Williams: None.

Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.15/G6

Topic: D.04. Brain Injury and Trauma

Support: 05/IIMFAC/Pat/2024/1162

Title: Histological Estimation of Time Since Injury in Human Traumatic Brain Injury Cases

Authors: *D. K. RASTOGI¹, A. KUMAR², T. KUMAR³, R. KUMAR⁵, T. WANKHADE⁴;

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Abstract: Background:

Accurate Estimation of time since injury in cases of traumatic brain injury (TBI) presents unique forensic challenges. Histological analysis of brain tissue can provide objective and biologically consistent indicators of survival time. **Objectives:**

To investigate histopathological changes in traumatic brain injuries as potential markers for estimating Time since injury (TSI) and delineate time-dependent microscopic features correlating with known survival time. **Methods:**

Brain tissue samples were collected during medicolegal autopsies of 30 individuals with documented TBI and known survival times. Routine hematoxylin and eosin (H&E) staining, special staining (Golgi, Nissl, Masson Trichrome) and immunohistochemical markers (GFAP, CD31, etc.) were used to assess neuronal injury, glial response, axonal damage, and vascular alterations. Histological findings were categorised and correlated with clinical and postmortem timelines. **Results:**

Histological features such as early neuronal eosinophilia, microglial activation, astrocytic swelling, perivascular haemorrhage, and axonal retraction balls showed predictable temporal patterns. Acute injuries (0-6 hours) showed cytoplasmic changes and neuronal damage, while subacute phases (6-24 hours) revealed prominent glial reactions and early reparative changes. These findings were consistent across cases and correlated significantly with survival time.

Conclusion:

Immunobiological examination of brain tissue in TBI provides valuable insights for estimating survival time. When correlated with clinical and investigative data, these microscopic findings can enhance accuracy in TSI estimation. **Keywords:**

Time since injury, Traumatic Brain Injury, Histopathology, Forensic Neuropathology.

Disclosures: D.K. Rastogi: None. A. Kumar: None. T. Kumar: None. R. Kumar: None. T. Wankhade: None.

Poster

PSTR163: Traumatic Brain Injury: Therapeutic Interventions and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR163.16/G7

Topic: D.04. Brain Injury and Trauma

Title: Pediatric Repetitive Mild Traumatic Brain Injury Produces T cell-Mediated Neuroinflammation

Authors: *K. SHUMILOV BARTENEV¹, M. GARCIA BONILLA², L. ARELLANO¹, K. JACOBS¹, J. GREER³, D. LIMBRICK⁴, R. SWARUP⁴;

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Abstract: Pediatric repetitive mild traumatic brain injury (rmTBI) is a major public health concern with links to cognitive dysfunction, anxiety, and depression. The underlying mechanisms of rmTBI, especially regarding the developing brain, are not well understood. The objective of this study was to examine the impact of peripheral immune cell infiltration and the subsequent neuroinflammation on white matter (WM) disruption and neurobehavior outcomes in pediatric rmTBI. Our Central Hypothesis is that pediatric rmTBI alters brain development and long-term neurobehavior through peripheral immune cell infiltration impacting the functionality of myelinating oligodendrocyte lineage cells (OLC). Juvenile mice (n=23; postnatal day 21) were subjected to an impact acceleration TBI model with a 25g weight suspended at 50 cm for three consecutive weeks. Seven days after the last mTBI, flow cytometry of cortical tissue and blood samples was performed to quantify infiltration of peripheral immune cells, as well as immunohistochemistry of brain slices to examine gliosis and oligodendrocyte density. Thirty days after injury, Diffusion Tensor Imaging was used to analyze WM structural disruption, and light-dark box behavioral test was performed to evaluate anxiety-like behavior. One week after rmTBI, acute peripheral immune cell infiltration in the cortex, including CD4⁺ T-cells (p=0.0179) and proinflammatory M1 macrophages (p=0.0357), and increased density of astrocytes (p=0.0471) was observed in the corpus callosum (CC). The absence of T-cells reduced the infiltration of M1 macrophages and neuroinflammation in the CC. One month after rmTBI, animals exhibited anxiety-like behavior and decreased Fractional Anisotropy (FA) (p<0.05) in the CC. These findings suggest that rmTBI triggers WM disruption and neurobehavioral impairments, probably associated with the infiltration of T-cells and persistent activation of astrocytes. Our future goal is to develop an immunotherapeutic tool targeting CD4⁺ T-cells to prevent WM disruption and neurobehavioral impairments, leading to improved treatment and reducing the long-term burden of children with brain trauma.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.01/G8

Topic: D.05. Spinal Cord Injury and Plasticity

Support: DBT Grant BT2052

Title: Translating Plasticity into Recovery: Intermittent Theta Burst Stimulation Rewires Motor Circuits and Restores Function in Patients with Complete Spinal Cord Injury

Authors: *D. PATEL¹, R. BANERJEE², S. JAIN⁴, K. FAROOQUE³, H. SHARMA³, K. KOCHHAR²;

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Abstract: Complete spinal cord injury (cSCI) disrupts the corticospinal tract, leading to sensorimotor loss. However, residual CST fibers and dormant circuits can provide a substrate for neuroplasticity that may offer functional recovery. Intermittent theta burst stimulation (iTBS) induces LTP-like plasticity in motor circuits and has been shown to improve outcomes in incomplete SCI, but its capacity to reactivate dormant and spared circuits in cSCI remains a critical yet untested therapeutic target. This study investigates whether iTBS, combined with individualized rehabilitation, can re-engage spared pathways and enhance motor outcomes following cSCI. 30 AIS-A cSCI patients were randomized into 6 groups to (1) compare iTBS, rTMS, and sham effectiveness, and (2) identify optimal stimulation sites: motor cortex (MC), spinal cord (SC), or combined (MC+SC). iTBS (600 pulses at 50 Hz, 3 min/session) and rTMS (1800 pulses at 20 Hz, 15 min/session) were applied twice daily for 5 days. Outcome measures include neurological and functional scores (AIS, LEMS, WISCI), TMS parameters (MEP, MT, cSP, recruitment curve), and blood biomarkers (pNF, BDNF, GABA, and glutamate) at baseline, post-intervention, 1 and 2-month follow-ups. Both iTBS and rTMS groups showed an increase in LEMS ($p < 0.05$) and improved WISCI-II scores. LEMS strongly correlated with WISCI ($\rho = 0.72$) for iTBS, suggesting the regain of assisted ambulation by 2 months. The iTBS (MC+SC) group showed a significant increase in MEPmax and recruitment slope with reduced I50 ($p < 0.01$), indicating enhanced corticospinal excitability. Cortical silent period (CSP) was shortened post-iTBS, also demonstrating a strong correlation with GABA ($\rho = 0.69$), reinforcing the physiological link between inhibitory tone and functional recovery. Molecularly, BDNF rose significantly ($p < 0.01$) and correlated with LEMS gains ($\rho = 0.76$), while pNF-H declined ($p = 0.02$), inversely correlating with I50 ($\rho = -0.68$), suggesting reduced axonal injury. This study provides evidence that iTBS optimally reactivates dormant CST and promotes motor recovery. Enhanced corticospinal excitability, synaptic plasticity, reduced inhibition, and axonal preservation support a robust neuroplastic response. Strong correlations between physiological, functional, and molecular measures further underscore the mechanism of recovery. Compared to classical high-frequency rTMS, iTBS demonstrated superior efficacy, offered a more time-efficient and patient-friendly intervention. These findings support iTBS, combined with individualized rehabilitation, as a promising strategy to induce early motor recovery in clinically cSCI patients.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.02/G9

Topic: D.05. Spinal Cord Injury and Plasticity

Support: TIRR Mission Connect (2021-2023)

Title: Decoding the language of the spinal cord sensorimotor networks using non-invasive electrospinography

Authors: *D. DAS¹, J. A. LEMIS², Y. E. LIMA CARMONA¹, J. L. CONTRERAS-VIDAL¹;
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Abstract: Electrospinography (ESG) is an underexplored non-invasive method for assessing spinal sensorimotor networks and its applications are largely limited to evoked responses or intraoperative monitoring. Our previous study aimed to evaluate the feasibility of using ESG to characterize spatiotemporal and functional connectivity changes in spinal and cortical networks during single joint lower limb movements in ten neurologically intact subjects (Steele et al., J Neural Eng., 2024; 20(6)). In this study, we aim to replicate our previous investigation involving individuals with spinal cord injury (SCI). Two participants with SCI were recruited: a 64-year-old male with a T9-level (C) injury and a 51-year-old female with a C3-level (A) injury. Participants attempted two tasks, knee flexion and plantar flexion, while lying in the prone position, during which electroencephalography (EEG), electromyography (EMG), and ESG were recorded simultaneously. Due to the location of the injury, one participant performed the tasks while seated. A robust artifact removal strategy incorporating H ∞ filtering, artifact subspace reconstruction, and independent component analysis (ICA) was employed. EEG and ESG data were segmented by task, and independent components (ICs) were clustered across participants using k-means clustering. Functional connectivity was assessed within ICs and between ICs and ESG signals using Generalized Partial Directed Coherence (gPDC). K-means clustering of EEG ICs revealed four distinct cortical regions: Brodmann areas (BA) 8, 39, 4, and 5. Furthermore, significant bidirectional changes in functional connectivity ($p < 0.05$, adjusted for multiple comparisons) were observed within cortical ICs and between cortical and spinal (ESG) signals during movement. The gPDC model predicted a cortico-spinal delay of $33 \text{ ms} \pm 6 \text{ ms}$, which is within the theoretical delay between supraspinal and spinal networks. These results provide novel evidence that ESG can capture meaningful dynamic activity reflecting both efferent and afferent processes within the spinal cord. The findings indicate that ESG has the potential to reveal meaningful neural dynamics, paving the way for broader applications in neurophysiological research and clinical diagnostics.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.03/G10

Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH Grant HD080205

Title: Blood pressure responses to bladder and bowel distension after human spinal cord injury

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Abstract: Bladder and bowel distention are primary triggers of autonomic dysreflexia (AD) in individuals with spinal cord injury (SCI), with reports of systolic blood pressure (SBP) rising more than 20 mmHg and remaining elevated with intolerable symptoms. The goal of the current study was to quantify changes in SBP, the degree of change and extent of symptomatic indices in persons with chronic SCI in a controlled lab setting during bladder filling (urodynamics) and bowel distention (anorectal manometry; ARM). A total of 56 participants (35 males; 21 females) were enrolled in the study, with injury levels ranging from C2 to L3 and American Spinal Injury Association Impairment Scale Grade A to D. Filling cystometry and ARM were conducted on separate days using the Aquarius® LT system by Laborie Medical Technologies (Williston, VT, USA). Continuous arterial blood pressure was acquired during cystometry and ARM from a finger cuff placed around the left middle or index finger (Finapres Medical Systems). Manual arterial blood pressure measurements were taken periodically with a digital blood pressure measurement device for calibration purposes. The data (N=56) indicates 90.9% of individuals with a maximum change in SBP above 20 mmHg during filling cystometry (group mean of 45 mmHg) and 85.4% of individuals with a maximum change in SBP above 20 mmHg during ARM (group mean of 37 mmHg). One or two symptoms (goosebumps, sweating, flushing, chills tingling, headache) occurred in 43.6% of participants during cystometry and 23.6% during ARM. The maximum changes in SBP typically occurred at maximum vesicle pressure and/or at first sensation during cystometry and during balloon catheter insertion or withdrawal during the ARM procedure. Noteworthy is that 28.6% of individuals with a maximum change in SBP > 60mmHg with a full bladder had no symptoms. These data, taken together, indicate a very high prevalence of blood pressure responses triggered by both bladder and bowel distension after chronic SCI, and that a lack of symptoms is not a reliable indicator for the absence of AD.

Disclosures: C.H. Hubscher: None. S. Wang: None. S.J. Harkema: None.

Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.04/G11

Topic: D.05. Spinal Cord Injury and Plasticity

Support: 24bm1123037h0002
24bm1423002h0002

Title: Longitudinal evaluation of MRI after transplantation of iPS-derived neural progenitor cells in spinal cord injured animals.

Authors: *M. SHINOZAKI¹, H. OKANO², N. NAGOSHI³, M. NAKAMURA³;
¹Keio University, Regenerative Med. Res. Ctr., Kawasaki-shi, Kanagawa, Japan; ²Keio Univ. Sch. of Med., Kanagawa, Japan; ³Keio Univ., Tokyo, Japan

Abstract: Spinal cord injury (SCI) presents a significant clinical challenge due to its poor capacity for spontaneous recovery and the severity of sequelae that often correlate with the extent of damage. Historically, rehabilitation has been the only widely accepted treatment with proven efficacy. However, recent years have seen the emergence of novel therapeutic strategies, including clinical trials of induced pluripotent stem cell (iPSC)-derived neural progenitor cell (NPC) transplantation conducted at our institution. Transplantation of NPCs holds promise as a potentially effective treatment even for complete SCI, where no residual tissue remains, due to their high engraftment efficiency and potential to differentiate into neural tissue. Nonetheless, careful monitoring for post-transplant tumorigenesis is essential, particularly in the case of iPSC-derived NPCs. Although functional assessments, such as motor function evaluation, as well as tissue and genetic analyses are commonly used to assess treatment efficacy in research, clinical evaluation of spinal cord tissue at the histological or genetic level remains highly restricted. Magnetic resonance imaging (MRI), on the other hand, plays a critical role in clinical evaluation, not only for diagnosis but also for monitoring post-treatment outcomes. In oncology, the use of contrast agents in MRI has proven particularly valuable for obtaining detailed insights. In this study, we conducted longitudinal MRI assessments in a mouse model of SCI following transplantation of iPSC-derived NPCs. Imaging in small animals, especially in the thoracic spine, is technically challenging due to difficulties in immobilization and respiratory motion artifacts. We developed a novel fixation device that enabled repeated high-resolution imaging. Additionally, by employing contrast-enhanced MRI and subtracting pre-contrast from post-contrast images, we were able to visualize dynamic changes in contrast enhancement associated with the transplanted cells. Our findings offer valuable insights not only for spinal cord regeneration but also for a broader range of cell transplantation therapies aiming for clinical translation.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

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Program #/Poster #: PSTR164.05/G12

Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH/NINDS 1R21NS128749-01A1 (SP/HS)
P20 GM148326/GM/NIGMS NIH HHS

Title: A Novel Rodent Model to Study Sepsis-Induced Pathology Post-Spinal Cord Injury

Authors: *K. IYER^{1,1}, D. PATEL¹, J. PATEL¹, S. KAUR², D. WINCHESTER¹, T. GARG¹, M. ZAPATA-JARAMILLO¹, K. ZAMIAR¹, M. MISCIKOWSKI^{6,1}, V. KOTA³, S. RIPPY⁴, T. A. BUTTERFIELD⁵, H. SAITO⁴, S. P. PATEL¹;

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⁵Athletic Training & Clin. Nutr., Univ. of Kentucky, LEXINGTON, KY; ⁶Hampden-Sydney Col., Glen Allen, VA.

Abstract: Spinal cord injury (SCI) results in motor paralysis and significant secondary complications. Individuals with SCI have an increased susceptibility to sepsis, which exacerbates functional impairments and elevates mortality risk. This study developed a clinically relevant rodent model designed to replicate the chronic complications observed in individuals surviving sepsis following SCI. Animals were categorized into four groups: Sham, Sepsis, SCI, and SCI+Sepsis. Procedures involved T10-laminectomy and/or contusion injury (200 kDyn) administered using Infinite Horizon (IH) impactor in the Sham, SCI, and SCI+Sepsis groups. Sepsis was induced through an intraperitoneal injection of cecal slurry (3 mL) administered 15 minutes post-SCI. Fluid resuscitation and antibiotic therapy commenced 8 hours after SCI/sepsis induction, continuing twice daily for five consecutive days. Over a 12-week observation period, outcomes included bacteremia presence, survival rates, body weight changes, cytokine profiles in blood and tissues, locomotor performance (assessed by BBB and horizontal ladder tests), in vivo muscle strength, and quantitative histological analysis of spinal cord tissue. Animals in the SCI+Sepsis group exhibited significant bacteremia within 6 hours post-sepsis induction, correlating with the lowest survival rates compared to Sepsis or SCI alone. Additionally, the SCI+Sepsis group demonstrated further deterioration in hindlimb locomotor recovery and significant muscle weakness compared to the SCI-only group. No locomotor impairments were observed in Sham or Sepsis-only groups. Acute evaluations revealed splenomegaly, reduced skeletal muscle mass in the hindlimbs, and elevated cytokine levels in blood and spinal cord tissues within the SCI+Sepsis group. This model represents the first clinically relevant approach to examining acute complications of sepsis post-SCI, providing a valuable platform to explore underlying mechanisms and evaluate potential therapeutic interventions. Further studies are currently underway to investigate chronic pathophysiological consequences of sepsis following SCI.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR164.06/G13

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation 890901 to E.G.
Mary Tucker Currie Endowment to J.W.G.

Title: Sex differences in spinal cord transcriptomics following noxious stimulation and lidocaine administration in contused rats

Authors: *K. N. COLPITTS¹, K. SANCHEZ⁴, C. GIBSON⁵, T. JOHNSTON⁶, N. KOBAYASHI², A. TREVINO³, J. W. GRAU², E. GILES⁴;

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Abstract: Previously we have demonstrated that noxious stimulation following spinal cord injury (SCI) promotes disruption of the blood spinal cord barrier, increases hemorrhage, and induces deficits in locomotor function in male rats. Baine et al. (2022) observed that estrous cycle stage at the time of injury may be implicated. To elucidate the sex differences in pain-induced changes, male and female animals were subjected to a T11 moderate contusion injury. One day later, animals received 6 minutes of noxious stimulation or restraint for an equivalent duration. Animal hindlimb locomotor function was assessed before and after stimulation. Three hours following stimulation, a 1 cm section of spinal cord centered around the lesion was collected, and samples were used for bulk RNA sequencing. Principal component analysis revealed two principal components accounting for 30.92% and 14.80% of the variance, primarily driven by sex and stimulation conditions, respectively. Key pathways differentially affected by sex and/or noxious stimulation include factors involved in complement and coagulation cascades, cytokines and chemokines involved in immune response, and pathways associated with central sensitization. Another experiment with a similar design was conducted where animals received an epidural infusion of lidocaine or its vehicle immediately prior to nociceptive stimulation. This approach allows us to parse out the transcriptional changes resulting from nociceptive stimulation alone versus those associated with the pain-induced increases in hemorrhage. This large data approach provides novel insight into the mechanisms behind noxious stimulation-induced disruption of the BSCB as well as sex differences that modulate these effects.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.07/G14

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation 890901 to E.G.
Mary Tucker Currie Endowment to J.W.G.

Title: When hormones hurt: Estradiol increases mortality after pain in spinal cord injury (SCI)

Authors: *V. BALENTINE¹, K. N. COLPITTS², A. AWALT¹, J. ABRAHAM¹, E. GILES³, J. W. GRAU¹;

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Abstract: Previous work has shown that nociceptive stimulation after injury promotes the breakdown of the blood spinal cord barrier (BSCB), increases hemorrhage, and undermines locomotor performance in male rats. Baine et al. (2022) showed that estrous cycle may be implicated; long-term locomotor recovery was worse when animals were injured during the estrous stage compared to other stages. For reference, estrogen levels are quickly decreasing from their peak levels during estrous. To further elucidate the role of hormones in SCI we have tested systemic application of estradiol and progesterone prior to injury and/or prior to pain in ovariectomized rats. We found that estradiol, but not progesterone, given prior to injury attenuated the shock-induced locomotor deficit in the acute phase. To elucidate the role of these hormones on long-term recovery, ovariectomized female rats were systemically administered estradiol, progesterone, or vehicle prior to a T11 moderate contusion injury then again prior to pain, twenty-four hours later. Recovery, locomotor function, and the development of allodynia were observed over 28 days. The results suggest that neither progesterone nor estradiol attenuate the pain-induced deficit on a chronic time course but may promote recovery in animals not receiving pain. Importantly, animals receiving pain that were treated with estradiol, displayed significantly increased rates of weight loss and mortality following injury. This finding is concerning and should be considered in the development of treatment following neural injury. The results highlight the importance of considering sex differences and estrous stage in the study of secondary injury and recovery after SCI.

Disclosures: V. Balentine: None. K.N. Colpitts: None. A. Awalt: None. J. Abraham: None. E. Giles: None. J.W. Grau: None.

Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.08/G15

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Departmental pilot funds
Advancing a Healthier Wisconsin (AHW)

Title: From bad to worse: Defining the impact of concomitant spinal cord injury and traumatic brain injury

Authors: *S. KAFURA¹, A. KRONER-MILSCH²;
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Abstract: Spinal cord injury (SCI) is a devastating ailment that can cause a variety of neurological deficits including motor and sensory loss, cardiovascular complications, and respiratory dysfunction. SCI occurs in two phases: the initial primary damage caused by a mechanical insult, followed by a secondary phase marked by hemorrhage and inflammatory cascades that exacerbate the original injury and worsen the clinical prognosis. Motor vehicle accidents, falls, and combat-related traumas are the most common causes of SCI, with a high degree of polytrauma associated with these events. An estimated 60% of SCI patients also suffer from a concurrent mild traumatic brain injury (mTBI). Emerging evidence has shown even TBIs classified as mild can lead to prolonged neurological deficits. Despite the high prevalence of concurrent SCI and mTBI, there is limited knowledge regarding the biological impact of polytrauma with clinical reports being the primary source of information. Although these studies indicate worsened functional outcomes, they are limited by their retrospective nature, lack of standardization, and are inadequate for fully understanding the biological impact of TBI on SCI. Very few studies have addressed TBI/SCI in animal models, generally using severe TBI models. Therefore, our lab is generating a rodent model of the more common mild TBI combined with SCI. The goal of this study is to generate a preclinical rodent model of dual mTBI/SCI to test the hypothesis that central nervous system (CNS) polytrauma worsens functional recovery and increases tissue damage in both CNS regions beyond the effect of isolated SCI or TBI. For this, mice will be subjected to blast induced mTBI, immediately followed by thoracic SCI. This model recapitulates a combat associated polytrauma, in which mTBI is caused by a shockwave, while secondary or tertiary SCI is caused by blast-induced falls or flying objects. Our preliminary data indicate feasibility with a high survival rate of concomitant thoracic SCI and blast mTBI. Pilot studies have focused on modifying injury severities to create a behaviorally distinct phenotype and reproducible model. Currently, we are performing motor, sensory and cognitive behavioral testing to assess the functional recovery after dual injury, and various immunofluorescence techniques to evaluate the impact on tissue damage compared to single injured animal controls. A better understanding of the pathophysiologic impact of concomitant neurotrauma will provide prognostic insights and potentially elucidate novel therapeutic targets to improve the quality of life of CNS polytrauma patients, a cohort that is currently insufficiently studied.

Disclosures: S. Kafura: None. A. Kroner-Milsch: None.

Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.09/G16

Topic: D.05. Spinal Cord Injury and Plasticity

Support: R03AG073929
Lantheus Medical Imaging

Title: Differential intraspinal microvessel architecture and hemodynamics detected using contrast enhanced ultrasound with age and sex

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Abstract: Female rats have been associated with improved resistance to cerebrovascular disease and spinal cord injuries, but few studies aim to identify the key differences in intraspinal blood flow between male and female rats. Here we used b-mode, power Doppler, and contrast enhanced ultrasound (CEUS) to identify sex differences for both adult and aged rats (aged rats, 24-26 mo. male N=5, female N=6; adult rats, 4-6 mo. male N=6, female N=6). All statistics were calculated in python using a Tukey's test. Both adult and aged female rats have a markedly increased interspinal blood volume when compared to males ($p<0.01$ and $p<0.05$ respectively). We found that the resistive index, a measure of vascular resistance, was also lower in both adult and aged female rats ($p<0.01$ and $p<0.05$ respectively), suggesting better intraspinal blood flow in females compared to males. Structurally adult and aged males had larger spinal cord volumes than females ($p<0.05$ for both). Female adult and aged rats had a higher grey matter to white matter ratio than males ($p<0.001$).; this result was confirmed histologically ($p<0.001$). We also noted that the ratio of white matter in aged rats to adult rats was greater than for grey matter, in both male and female rats; this indicated white matter volume is increasing faster than the grey matter as the rats age regardless of sex. Vascular reactivity was tested by subjecting the rats to reduced oxygen for three minutes; both adult male and female rats showed an expected a hyperemic response and increased blood volume. Aged rats had a reduced response to the vascular challenge. These in vivo studies showed, for the first time, that there is a marked difference between female and male rats in interspinal blood volume, vascular resistance, and grey matter and white matter volumes; for both adult and aged groups.

Disclosures: A.A. Odarenko: None. P. P c: None. D. Jensen: None. M. Bruce: None. Z.Z. Khaing: None.

Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.10/H1

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Investigating effects of biomaterials in the sub-acute and chronic phases of spinal cord injury

Authors: *D. A. GARCIA PRADA¹, S. PRIETO³, N. J. WROBEL², B. ADAVOODY³, B. T. DAVID⁴, R. G. FESSLER³;

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Abstract: Spinal cord injury (SCI) is a devastating condition that affects over 15 million people globally with approximately 18,000 new cases occurring yearly in the United States. Most SCI cases result from trauma such as falls, accidents, and violence. These often lead to lifelong disabilities that significantly impact the quality of life. The financial burden of SCI is substantial, with lifetime costs for affected individuals ranging from \$0.7 million to \$2.5 million, depending on the severity and the age at which the injury occurs. SCI is characterized by a primary mechanical injury followed by a secondary injury cascade involving inflammation, oxidative stress, and apoptosis. Secondary damage is largely driven by overactivation of the immune system. Research into the immune profile following SCI has revealed a complex and dynamic interplay between innate and adaptive immune responses that contribute to both neurodegeneration and repair. Shortly after injury, there is an acute infiltration of neutrophils and macrophages, accompanied by activation of resident microglia, leading to the release of pro-inflammatory cytokines such as TNF- α , IL-1 β , and IL-6, which then exacerbate tissue damage. In rodent models, macrophage activity peaks at 7 and 60 days post-injury (dpi), influencing inflammation and tissue repair. Tumor necrosis factor-alpha (TNF- α), a pro-inflammatory cytokine, is a critical target in SCI therapies. Scaffolds made from poly(lactic-co-glycolic) acid (PLG), a bioresorbable polymer, have emerged as a promising strategy for promoting axonal regeneration and modulating inflammation. This study explores the effects of a highly porous form of PLG, Fluffy PLGTM (FPLG), and a TNF- α antagonist (Etanercept) to investigate their immunological effects at 14 and 60 dpi. Female wild-type Sprague Dawley rats underwent a bilateral moderate contusion at the ninth thoracic vertebral level (T9). At 1 dpi, a subset of rats underwent a myelotomy at the site of injury, followed by implantation of FPLG. At 7 dpi these rats were reopened and received injections of either etanercept or vehicle; SCI-only rats served as additional controls. All rats were sacrificed at 14 or 60 dpi. To assess inflammation at the injury site, flow cytometry was used. PLG scaffolds possibly sequester inflammatory macrophages, preserve spinal cord structure, and induce a sub-acute anti-inflammatory shift at 1wpi. Sub-acute reductions in macrophage levels were observed at 2 and 8 wpi, highlighting PLG's potential to modulate inflammation and support tissue preservation in SCI.

Disclosures: D.A. Garcia Prada: None. S. Prieto: None. N.J. Wrobel: None. B. Adavoody: None. B.T. David: None. R.G. Fessler: None.

Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR164.11/H2

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Craig H. Neilsen Foundation Grant 2401407
NIH Grant M2203367

Title: Spinal cord injury induces time-dependent alterations in hippocampal neurogenesis and astrogliosis associated with cognitive impairment

Authors: *E. C. MARKS¹, A. J. DOUTHITT², C. G. GEOFFROY³;

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Abstract: Traumatic spinal cord injury (SCI) affects over 300,000 individuals in the United States alone, with estimates as high as 15 million affected individuals worldwide. Damage to the spinal cord leads to much more than the highly visible paralysis, with countless secondary injuries occurring shortly after the original trauma. Among these secondary injuries, cognitive impairment such as early onset dementia, and executive dysfunction is shown to affect approximately 64% of patients. Also associated with SCI in rats are histological changes in the hippocampus including astrogliosis and changes in adult hippocampal neurogenesis. Here, we explore the rate and severity of cognitive impairment following SCI in male mice. Memory and learning were assessed at 3 timepoints: 3 weeks, 6 weeks, and 12 weeks post injury. We show that cognitive decline occurs in spatially targeted learning tasks, but not general memory in a time-dependent manner after injury. Additionally, analysis of hippocampal histology reveals an increase in astrogliosis and disruption of adult neurogenesis correlated with these cognitive impairments.

Disclosures: E.C. Marks: None. A.J. Douthitt: None. C.G. Geoffroy: None.

Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.12/H3

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Functional Ultrasound imaging reveals Brain and Spinal Cord signatures of bladder pressure for neural interface development

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Abstract: Neurogenic bladder dysfunction is a major concern for individuals with neurological disorders, often reported as more disruptive than impaired mobility. Yet, restoring the neural

circuits underlying micturition remains a significant clinical and technological challenge. Disruptions to these circuits, as seen in Parkinson's disease, spinal cord injury, or aging, can cause involuntary urination, leading to incontinence, retention, and renal complications. Despite advances in functional neuroimaging, the neural mechanisms underlying micturition remain poorly understood, largely due to technical challenges in capturing real-time activity from both brain and spinal cord during voiding.

This study addresses this gap by using functional ultrasound imaging (fUSI) to assess whether power Doppler (pD) signals from the brain and spinal cord can predict bladder pressure dynamics. After anesthesia, five and eight rats underwent craniotomy and laminectomy, respectively, to expose the brain and spinal cord for imaging. We simultaneously acquired fUSI images and bladder pressure recordings over 50 minutes during filling and spontaneous voiding. To assess whether distributed neural signals encode bladder dynamics in a form suitable for real-time decoding, we developed a Random Forest Regression (RFR) model to predict continuous bladder pressure from pD signals. The model was trained on baseline and the first filling-voiding cycle and tested on subsequent cycles using cross-validation. We achieved an average CV loss of 0.012 ± 0.006 and MSE of 0.042 ± 0.007 , demonstrating strong generalization and low prediction error. Predicted traces closely followed actual bladder pressure, capturing rapid filling and sharp voiding drops with high temporal precision across both brain and spinal recordings. This study demonstrates, for the first time, that pD signals from the brain and spinal cord can be used to accurately decode bladder pressure during the micturition cycle, representing a critical step toward brain-spinal cord interface technologies for neurogenic bladder dysfunction.

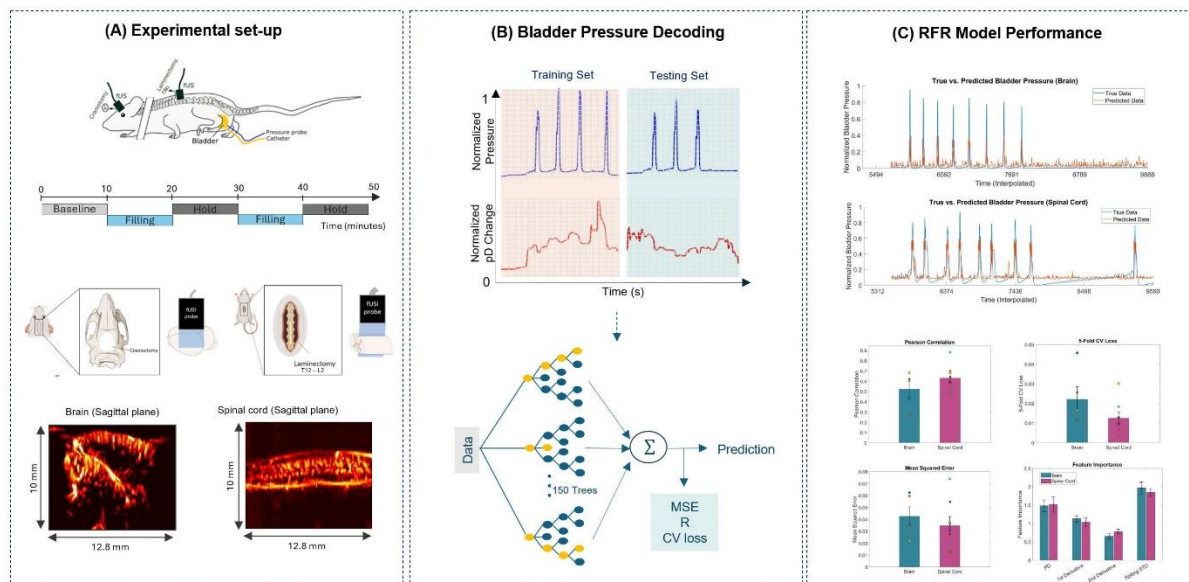


Figure 1. A) Experimental Setup. Schematic of fUSI recordings over the brain and spinal cord (in separate rats) during a bladder filling and hold protocol. Panels show the craniotomy and laminectomy sites, approximate fUSI probe placements, and representative power Doppler (pD) images of the brain and spinal cord. **B) Decoding Framework.** Both bladder pressure and power Doppler (pD) signals were preprocessed. Bladder pressure data were divided into training (baseline and first cycle) and testing (subsequent cycles) sets. A Random Forest Regression (RFR) model was trained and evaluated using mean squared error (MSE), Pearson correlation coefficient, and five-fold cross-validation (CV) loss. **C) Model Performance and Feature Importance.** Predicted (orange) and actual (blue) bladder pressure traces for representative rats show close alignment and accurate voiding detection. Bar charts summarize group-level metrics and average feature importance, with individual data points overlaid. Error bars indicate standard error of the mean.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR164.13/H4

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Use of a Porcine Model for Studying Spinal Cord Injury: A Translational Approach

Authors: *S. B. MEILIN;
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Abstract: Spinal cord injury (SCI) research predominantly relies on rodent models; however, porcine models offer significant translational advantages due to their anatomical and physiological similarities to humans. These include comparable spinal cord dimensions, the positioning of the corticospinal tract, and vascular architecture. Such features enable more clinically relevant assessments of interventions, including cellular transplantation and bioengineered therapies, which require the larger spinal cord size found in pigs to accurately reflect human therapeutic outcomes. Furthermore, pigs demonstrate nociceptive pathways and patterns of functional recovery that closely parallel human responses, making them particularly well-suited for evaluating both motor and sensory outcomes post-SCI. In this study, SCI was induced in pigs by dropping a 50 mg weight onto the exposed T10 segment of the spinal cord. The weight remained in place for five minutes, with the drop height determining injury severity. Injury quality was assessed through intraoperative electrophysiological monitoring, specifically transcranial motor evoked potentials (tcMEPs) and transcranial sensory evoked potentials (tcSEPs). Animals were monitored over a six-month period. Motor function was evaluated using a standardized scoring system alongside computerized gait analysis. Electrophysiological assessments were conducted at three time points during the study. At the conclusion, spinal cords were harvested for histopathological examination. Immediately following SCI, electrophysiological signals were markedly reduced. Within the first week, animals exhibited varying degrees of paralysis, with the majority unable to stand or walk. Gradual recovery was observed over time, though functional restoration was incomplete. Gait analysis revealed persistent abnormalities even in animals that regained the ability to walk. Notably, electrophysiological data correlated with motor outcomes, supporting its utility in assessing injury severity and recovery. These findings support the use of pigs as a viable large-animal model for SCI research, offering enhanced clinical relevance for the development and evaluation of novel therapeutic strategies.

Disclosures: S.B. Meilin: None.

Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

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Program #/Poster #: PSTR164.14/H5

Topic: D.05. Spinal Cord Injury and Plasticity

Support: SECIHT Ciencia Frontera 1311312
SECIHT a ZFL (808827)

Title: A plasma-synthesized polypyrrole/iodine implant in motor recovery after ventral root avulsion in a rabbit model

Authors: Z. FLORES LOZADA¹, A. FLORES HERNANDEZ³, C. PEDRAZA¹, Z. RENE², I. JIMÉNEZ ESTRADA⁴, J. MORALES CORONA⁵, J. MORALES-MEDINA⁶, ***D. L. CORONA QUINTANILLA**¹;

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Abstract: Locomotion is a fundamental behavior that allows animals to move in different environments and directions. This process is regulated by sensorimotor circuits located in the lumbar region. One of the most common injuries affecting this function is ventral root avulsion (VRA). In particular, VRA in lumbar region 6 (VRA L6) causes a decrease in nerve fibers, thereby reducing the information transmitted by the nerve due to axonal damage. Without a repair strategy, restoration of motor functions is minimal. The use of polymeric implants, such as polypyrrole (PPy), is relevant for the treatment of damage caused by VRA L6 due to its biocompatibility and electrically conductive properties. The objective of this project was to determine whether implanting iodine-doped PPy after VRA L6 can restore locomotion parameters in rabbits. For this purpose, Chinchilla rabbits were divided into three groups (n=7 per group): a) SHAM, b) ARV L6, and c) ARV L6 + PPy/I. The animals were anesthetized with isoflurane and underwent unilateral right avulsion surgery of the L6 ventral root. Three days later, behavioral tests were performed: 1) observation of displacement in a ring for 30 minutes, and 2) evaluation of the extension reflex of the phalanges of the lower limb by photographic recording. The results show that L6 ARV causes alterations in locomotion and postural parameters, generating paralysis and deviation of the right hindlimb in animals in the L6 ARV group. In contrast, animals in the L6 ARV + PPy/I group showed a gradual recovery of walking patterns. These results suggest that the use of the PPy/I implant after ARV contributes to maintaining communication between the spinal cord and peripheral effectors, since, at day 30 post-avulsion, a significant recovery of locomotor parameters was observed.

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Poster

PSTR164: Spinal Cord Injury: Animal Models and Human Studies

Location: SDCC Halls B-H

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Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH Grant 2R15GM124595
NIH-RISE 5R25GM061151-22
NSF LSAMP HRD-2008186
HHMI Gilliam Fellowship (#GT17115)

Title: Hnf4 modulation alters cell proliferation and tissue morphology during neural and intestinal regeneration in the sea cucumber *Holothuria glaberrima*

Authors: *J. TORRES RODRIGUEZ;
Univ. of Puerto Rico, Rio Piedras, San Juan, Puerto Rico

Abstract: Understanding how transcription factors (TFs) regulate tissue regeneration is crucial. The highly conserved hepatocyte nuclear factor 4 (HNF4) is critical for proliferation, dedifferentiation, homeostasis, and lipid metabolism in the gastrointestinal tract, yet its function in the central nervous system (CNS) and post-traumatic regeneration remains largely unexplored. In this study, we use the small-molecule agonist NCT and antagonist BIM5078 to investigate HNF4's function in CNS and intestinal regeneration in the sea cucumber *Holothuria glaberrima*, a novel model system. We induce evisceration and injury to the radial nerve cord and study the subsequent regeneration of the organs. Our observations reveal that NCT-induced HNF4 overexpression alters tissue morphology in both tissues, consistent with delayed regeneration, while BIM5078 seems to promote regeneration. Additionally, NCT treatment decreases cell proliferation in both tissues at 8 days post-injury, typically the peak period of proliferation. These findings suggest that HNF4 regulates key aspects of regeneration in echinoderms. Given its conserved function, HNF4 may play a broader role in regenerative processes across species. Further studies are needed to fully elucidate the mechanisms by which HNF4 influences regeneration in sea cucumbers and to explore its potential as a target for therapeutic interventions in regenerative medicine.

Disclosures: J. Torres Rodriguez: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.01/H7

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Cuprizone Administered Via Oral Gavage Versus in Food. A Better Way to Model Acute Demyelination in Mice. A Translational Tool for Early-Stage Multiple Sclerosis Drug Development

Authors: *K. RADHAKRISHANAN, H. LEE, J. LEE, K. PARK, S.-Y. NA, P. J. SWEENEY, L. PARK;
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Abstract: The cuprizone (CPZ) model is a well-established non-immune-mediated model of central nervous system demyelination, commonly used to study multiple sclerosis (MS). The model usually involves cuprizone administered via diet, oral gavage offers a better controlled and more reproducible alternative for inducing demyelination. We aimed to assess whether an acute demyelination model using oral gavage of CPZ in C57BL/6 male mice had better reproducibility and similar pathological features than the traditional method of inducing demyelination by having CPZ in mouse chow.

Mice were administered CPZ via oral gavage, 200 mg/kg (BID) for 7 weeks. Functional performance was conducted using the rotarod test. Brain tissues, including the corpus callosum and hippocampus, were collected for histological and immunohistochemical analyses. Markers of demyelination (MBP), astrocytosis (GFAP), microgliosis (Iba1), and oligodendrocyte lineage (Olig2) were evaluated. A treatment group receiving dimethyl fumarate (DMF, 15 mg/kg BID) was included as reference. Our findings show that CPZ administration via oral gavage, successfully induced significant motor deficits and robust demyelination in the corpus callosum, accompanied by increased astrocytic and microglial activation. The model demonstrated consistent and salient pathological features in all members of the cohort. This internal validation study establishes a more reliable and reproducible oral gavage-based CPZ model for acute demyelination in mice. The model effectively recapitulates key pathological features of MS as a result of CPZ administration via other means and provides a practical platform for evaluating demyelination and neuroinflammation, independent of dietary variability.

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Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.02/H8

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: The impact of low-intensity physical exercise on myelination and microglial activation in a cuprizone model

Authors: *K.-R. HAHN^{1,2}, I. HWANG¹, T.-W. HAHN³, D. YOO¹;

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Abstract: Demyelinating diseases, such as multiple sclerosis, damage the myelin sheath, leading to neurological deficits. Although the exact causes of MS are unknown, inflammation and inadequate remyelination are major factors in disease progression. Exercise is a promising non-drug approach for MS, with reported advantages for mobility, mood, and potential neuroprotection. Nevertheless, the specific ways exercise affects remyelination and neuroinflammation in demyelinating conditions are not entirely clear. This research explores the effects of low-intensity exercise on myelination, neuroinflammation, and neurogenesis using a cuprizone-induced demyelination mouse model, concentrating on the hippocampus, a brain region essential for cognitive function and interhemispheric communication. Mice given cuprizone underwent low-intensity forced wheel running. The results showed that exercise substantially increased myelin basic protein expression in the stratum lacunosum-moleculare of the hippocampus and the corpus callosum, indicating improved remyelination. Cuprizone-induced demyelination also led to microglial activation in the hippocampus. Importantly, exercise reduced this activation, suggesting a modulation of the neuroinflammatory response. However, TNF- α levels remained high in the exercise group, implying a complex interplay between microglial activation and cytokine production. Consequently, low-intensity exercise may not fully suppress the pro-inflammatory potential of microglia. Moreover, the exercise program did not reverse the decrease in proliferating cells or immature neurons in the subgranular zone of the dentate gyrus, showing a limited impact on neurogenesis. This study emphasizes the region-specific effects of low-intensity exercise on remyelination and neuroinflammation, particularly within the hippocampus, a region often overlooked in demyelination research. The findings support the potential of exercise as a rehabilitation strategy for demyelinating disorders and offer insights into its underlying neuroprotective mechanisms.

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Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

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Program #/Poster #: PSTR165.03/H9

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Department of Defense CDRMP MS220005

Title: Investigating the role of neuronal sulfatases following cuprizone induced demyelination and remyelination

Authors: *R. PODDETI¹, A. SHAH², R. RAVICHANDAR³, R. MUTHAIAH², F. J. SIM^{2,3};
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Abstract: Multiple inhibitory pathways converge to prevent efficient remyelination in multiple sclerosis (MS). Among these, the accumulation of inhibitory extracellular matrix components such as heparan sulfate proteoglycans is known to impair remyelination. HS glycosaminoglycan side chains undergo editing by endosulfatases, Sulf1 and Sulf2. Oligodendrocyte progenitor cells (OPCs) express sulfatases at high levels following demyelination in the adult human and mouse brain. Genetic deletion of OPC-expressed sulfatases accelerates OPC recruitment, oligodendrocyte (OL) differentiation, and remyelination in a mouse model of spinal cord demyelination (Saraswat et al., 2021; Nat. Commun.). In the brain, specific cortical neuronal populations express sulfatases, suggesting that the cortical heparanome may differ substantially from the spinal cord, and that neuronally expressed sulfatases may contribute to failed myelin repair in subcortical white matter. In this study, we investigated the role of neuronal sulfatase in oligodendrocyte fate following demyelination. To induce demyelination in subcortical white matter tracts adjacent to sulfatase-expressing neurons, we exposed adult male and female mice to cuprizone (CPZ). Following tamoxifen-induced conditional knockout (cKO) of Sulf1/2 in Thy1-expressing neurons, we observed a significant increase in the density of both OPCs and OLs after five weeks of CPZ treatment. Using lineage tracing of proliferating cells, we found that the increase in OL density was not associated with increased generation of new OLs. Furthermore, OPC proliferation was not increased at five weeks in Sulf1/2 cKO mice. To model spontaneous remyelination, CPZ was removed, and animals were allowed to recover for two weeks. Both wild-type and neuronal sulfatase cKO mice exhibited a decrease in precursor density and a corresponding increase in mature OL density. The density of OLs in neuronal Sulf1/2 cKO mice remained significantly greater than in wild-type mice during recovery. Both groups exhibited similar levels of oligodendrogenesis during the recovery phase, suggesting that the overall increase in OL density following Sulf1/2 cKO was again driven by alternative mechanisms. Together, these data suggest that the increased density of both OPCs and OL was not the result of enhanced cell generation and that neuronal sulfatase expression contributes to OL cell injury and death in the cuprizone model. Thus, targeting neuronal sulfatase may offer a novel neuronal- and oligodendrocyte-protective therapeutic approach to modulate oligodendrocyte dynamics and protect white matter integrity in demyelinating disease.

Disclosures: R. Poddeti: None. A. Shah: None. R. Ravichandar: None. R. Muthaiah: None. F.J. Sim: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.04/H10

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Maresin 1 Ameliorates Cuprizone-induced Depression-Like Behavior and Reprograms Oligodendrocyte Metabolism via Mitochondrial Restoration

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Abstract: Background: Multiple sclerosis (MS) is a chronic, progressive neurological disorder that frequently results in a broad spectrum of physical, cognitive, and psychological impairments. Among these, depression is a particularly common and impactful comorbidity, often appearing early, sometimes even before the onset of overt physical symptom and affecting up to 50% of individuals with MS. Despite the high prevalence of depressive symptoms in MS, the underlying mechanisms remain poorly understood, and effective treatment strategies are still lacking. Antidepressants, especially selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), have shown promise in improving mood and cognitive function, with some evidence suggesting potential modulation of immune system responses. However, challenges such as side effects, drug interactions, and the multifaceted nature of MS complicate treatment options. This highlights the urgent need for a deeper understanding of the neural circuits and molecular pathways linking depression and MS.

Objective: This study investigates the potential of maresin 1 (MaR1), a lipid mediator with anti-inflammatory and pro-resolving properties, in alleviating cuprizone induced depressive-like behaviors. **Methods:** We subjected mice to six weeks of cuprizone-induced demyelination followed by alternate-day treatment with MaR1 (300ng/mouse) during the remyelination phase. We did a series of extensive behavioral testing for anxiety-like & depressive-like behaviors. We did electron microscopy (EM) to evaluate myelin ultrastructure. To elucidate the molecular mechanism associated with behavioral changes, we did RNA-seq of nucleus accumbens, a region strongly implicated in depression as well as multiple sclerosis, and performed electron microscopy (EM), IHC along with some metabolic assays. **Results:** Our findings reveal that MaR1 treatment not only reduces neuroinflammation, but also significantly improved depressive-like behavior observed in cuprizone-fed mice. Further mechanistic studies revealed that MaR1 treatment enhanced myelination in the nucleus accumbens as well as in promoting oligodendrocyte mitochondrial health. **Conclusion:** Overall, this study underscores the therapeutic potential of MaR1 as an antidepressant for MS patients, highlighting its role in reducing inflammation, improving myelination and mitochondrial health which help restore neural circuitry associated with mood regulation.

Disclosures: M. Fatma: None. M. Nematullah: None. A.S. Ahmad: None. S. Giri: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

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Program #/Poster #: PSTR165.06/H11

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH P30GM15449
NIH P20GM109095
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Title: Environmental temperature Influences Disease Outcomes in a Mouse Model of Experimental Autoimmune Encephalomyelitis

Authors: ***K. J. JOHNSON**¹, J. CAVARETTA², C. KNUEVEN², B. A. HOETTELS³, B. C. JOHNSON², R. S. BEARD, Jr.²;

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Abstract: Environmental temperature remains an understudied experimental variable despite its known impact on murine models of human disease. Conventional mouse housing temperature (TC; 22°C) is substantially below the murine thermoneutral zone (TN; 29-33°C), inducing chronic cold stress that activates thermogenesis and drives systemic physiological and immunological dysregulation. Here, we investigated the contribution of ambient housing temperature to experimental autoimmune encephalomyelitis (EAE), a murine multiple sclerosis model. Female C57BL/6 mice were randomly assigned to TC or TN housing (n=10/group), induced with the MOG₃₅₋₅₅ peptide model, monitored for weight loss and disease progression using standard scoring rubrics, and then sacrificed. Compared to their TC counterparts, mice housed at TN lost significantly less weight and had significantly lower clinical scores (unpaired t-test, p<0.05 and p<0.01, respectively). Together, our preliminary findings show that environmental temperature can have a profound impact on disease outcomes in the MOG35-55 model and, in turn, suggest that it is a confounding variable that must be controlled for. As such, future studies on the intersection between environmental temperature and neuroinflammation are warranted to define the cellular and molecular mechanisms responsible. Additionally, researchers are encouraged to more stringently monitor and report housing conditions when publishing their works.

Disclosures: **K.J. Johnson:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Hooke Laboratories. **J. Cavaretta:** None. **B.A. Hoettels:** None. **B.C. Johnson:** None. **R.S. Beard:** None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

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Program #/Poster #: PSTR165.07/H12

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH-NINDS Grant 2R56NS107523-06
NIH Grant TL1TR001431

Title: Comparative single-cell transcriptomic analysis of preclinical mouse models of Multiple Sclerosis and MS tissue

Authors: *M. R. BULLARD, G. S. MELCHOR, Jr., J. K. HUANG;
Biol. Dept., Georgetown Univ., Washington, DC

Abstract: Multiple sclerosis (MS) is a chronic, demyelinating disease of the central nervous system (CNS) that affects over 2.8 million people worldwide. Although the etiology of MS is unknown, demyelinated lesions represent the fundamental pathological feature of the disease. During initial stages of the disease, remyelination within lesions occurs, though this process eventually fails. This failure to remyelinate is thought to be due to changes in the transcriptional state of the lesion's cellular architecture, although the exact mechanisms of how this contributes to demyelination and remyelination remain poorly understood. Cell types thought to contribute to remyelination failure are immune cells such as microglia that exhibit diverse activation states ranging from pro-inflammatory to pro-regenerative phenotypes, and oligodendrocyte lineage cells that show stage-specific transcriptional profiles that reflect their capacity for proliferation and myelination. To better understand the molecular pathways that govern the demyelinating vs. a remyelinating environment across models, we performed a comparative analysis of multiple publicly available single-nucleus RNA sequencing (snRNA-seq) datasets from preclinical mouse models of MS and from MS post-mortem brain tissue. Bioinformatic analysis revealed conserved and model-specific gene expression associated with oligodendrocyte loss and immune activation during demyelination and remyelination. Notably, we observed the upregulation of pathways associated with phagocytosis and ferroptosis within the demyelinating environment in all three datasets. We also observed homologous expression of genes related to certain pathways associated with an inflammatory response in each of the models that was present in the MS lesions but not the other model. These findings suggest the need for careful consideration of the experimental model and the potential use of scRNA-seq datasets in the determination of the optimal model for experimental design. The results of this comparative study will aid in the identification of novel therapeutic strategies aimed at preventing demyelination, promoting remyelination, and ultimately protecting the CNS from progressive degeneration in MS.

Disclosures: M.R. Bullard: None. G.S. Melchor: None. J.K. Huang: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

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Program #/Poster #: PSTR165.08/H13

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: DoD CDMRP W81XWH-22-1-0757

Title: Neuronal NF- κ B activation attenuates neurodegeneration during experimental autoimmune encephalomyelitis

Authors: *W. LIN;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: Multiple sclerosis (MS) is chronic inflammatory demyelinating and neurodegenerative diseases of the CNS. Neurodegeneration is considered the primary driver of chronic disability in MS; however, the underlying mechanisms of neurodegeneration remain poorly understood. Data indicate that NF- κ B participates in regulating the viability and function of neurons under normal and disease conditions. Although it is well documented that NF- κ B is activated in neurons by inflammation in MS and its animal model experimental autoimmune encephalomyelitis (EAE), the cell-autonomous role of NF- κ B activation in neurons in these diseases remains controversial and poorly defined. In this study, we showed that selective enhancement of NF- κ B activation in neurons attenuated EAE disease severity and mitigates EAE-induced axonal degeneration, neuronal loss, and demyelination. Conversely, blockage of neuronal NF- κ B activation exacerbates disease severity and promotes neurodegeneration in EAE. These findings indicate that neuronal NF- κ B activation plays a protective role in MS and EAE by promoting neuronal and axonal resilience in the face of inflammatory injury.

Disclosures: W. Lin: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

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Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NMSS grant FG-2407-43793
NIH grant 2R01NS110859

Title: Astrocytic TRIM9 suppresses STING/TBK1/NF- κ B-mediated neuroinflammation in Multiple Sclerosis

Authors: *J. ZHAN^{1,2}, R. AILANI^{3,1}, H. LEE^{1,3,2};

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Abstract: The tripartite motif (TRIM) protein family is critical for development and innate immunity in vertebrates. Among its family members, TRIM9 is highly enriched in the brain and is well-characterized for directing axon guidance during neuronal development. However, its role in glial cells remains poorly understood. Here, we show that TRIM9 is abundantly expressed in astrocytes during brain development. Using astrocyte-specific *Trim9* knockout mice, we found

that postnatal depletion of *Trim9* in astrocytes induces both astroglia and microglial activation. Since reactive gliosis is a key feature of autoimmune neuroinflammation such as multiple sclerosis (MS), we investigated TRIM9's potential role under inflammatory conditions. We found that astrocytic TRIM9 expression is markedly reduced in both human postmortem active MS lesions and in the murine MS model, experimental autoimmune encephalomyelitis (EAE). Moreover, astrocyte-specific *Trim9* knockout mice exhibited significantly exacerbated EAE severity at both behavioral and pathological levels. To investigate the mechanisms underlying *Trim9*-mediated CNS neuroinflammation, we performed astrocyte-specific multi-omic profiling from *Trim9*-depleted mouse brains *in vivo* and astrocyte cultures *in vitro*, and discovered that astrocytic *Trim9* loss triggers mitochondrial dysregulation and induces activation of STING/TBK1/NF- κ B signaling cascade by antagonizing GSK3 β . Together, these studies provide evidence that TRIM9 as an essential endogenous suppressor of MS-related neuroinflammation and reveals a new role for TRIM9 in glial biology.

Disclosures: J. Zhan: None. R. Ailani: None. H. Lee: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

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Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NS31857-01A1
5U54MD013376
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Title: Mitochondrial dysfunction is associated with the neurological deficits in an inflammatory mouse model of multiple sclerosis

Authors: *F. J. DENARO¹, T. A. MAKAR^{3,7}, S. A. MAKAR^{4,5}, M. D. WORTHINGTON¹, S. WILLIAMS², I. J. MERCHENTHALER⁶, J. BRYANT⁸;

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Abstract: Multiple sclerosis (MS) is an inflammatory demyelinating disease of the central nervous system (CNS). Evidence from experimental autoimmune encephalomyelitis (EAE) models strongly suggests that mitochondrial dysfunction presents throughout the disease course. We hypothesized that this mitochondrial dysfunction can be pharmacologically minimized. Such a change can be measured by the variations in the level of molecules relevant to mitochondrial

function. To test this hypothesis, we used 7,8-dihydroxyflavone (DHF) a small molecule that acts as a TrkB agonist, mimicking the effects of brain-derived neurotrophic factor (BDNF). DHF has been shown to reduce the neurological dysfunction and histopathology in EAE mice (Makar et.al. Neuroimmunol2016 Mar 15:292:9-20). The aim of this study was to determine if DHF can protect mitochondria as measured by relevant markers of mitochondrial function. In order to investigate this possibility a histochemical analysis was undertaken by using a battery of labels for molecules that have been shown to be associated with the development of EAE in both the human and the animal model. Labels for the following included: 1. SIRT1, may have neuroprotective therapeutic effects in EAE. SIRT1 reduces neuronal loss in this chronic demyelinating disease model 2. SIRT3 has been substantiated to be involved in almost all aspects of mitochondrial metabolism 3. PGC-1 α is described as the master regulator of mitochondrial biogenesis and function. With NAMPT it modulates SIRT1 activity. 4. NAMPT, is also involved in regulating SIRT1 activity. Sirtuin 3 (SIRT3), is a possible mitochondrial tumor suppressor 5. PINK1 has been shown to protect against neuronal cell death induced by oxidative stress. Analysis proceeded by inducing EAE in female C57B/L6 mice and treating one group with DHF (dose 5 mg/kg, Ip every day after EAE induction) and continuing the DHF till 28 days. Then mice were euthanized and spinal cords were isolated. Paraffin embedded sections were prepared for immunohistochemical staining of the above listed molecules. Intensity of staining and number of labeled cells were recorded. Interestingly, we found that in untreated EAE mice all markers were significantly downregulated. Supporting the hypothesis that DHF treatment increased mitochondrial biogenesis, homeostasis, metabolism and suppressed oxidative stress in regulating neurological deficit associated with EAE. Further studies of this drug and model may reveal significant mechanisms for EAE suppression.

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Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

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Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NMSS grant FG-2407-43793
NIH grant 2R01NS110859

Title: Loss of astrocytic Slc4a4 drives multiple sclerosis pathology via endothelin-1-mediated blood-brain barrier dysfunction

Authors: *R. AILANI;
Neurosci., Baylor Col. of Med., Houston, TX

Abstract: Multiple Sclerosis (MS) is a common autoimmune disease affecting the central nervous system (CNS), characterized by bloodborne immune cell-mediated inflammatory demyelination. Blood-brain barrier (BBB) disruption represents a critical early pathological feature in MS pathogenesis and is linked to astrocytic dysfunction. We previously identified Slc4a4, an astrocyte-enriched gene, as a key regulator of BBB integrity following CNS injury; however, its role in MS pathology remains undefined. Here, we demonstrate that Slc4a4 is significantly downregulated in human MS lesions compared to healthy control tissue. To investigate the functional consequences of Slc4a4 loss in MS progression, we utilized an astrocyte-specific Slc4a4 conditional knockout (Slc4a4-cKO) mice in the experimental autoimmune encephalomyelitis (EAE) model, which recapitulates key clinical and pathological features of human MS. Slc4a4-cKO mice exhibited significantly severe clinical symptoms and pathology during EAE, including increased demyelination, immune cell infiltration, axonal damage and heightened BBB permeability. Transcriptomic profiling of CNS tissue from these Slc4a4-cKO mice with EAE revealed dysregulation of endothelial-associated genes, most notably a marked upregulation of endothelin-1 (Edn1)—a vasoactive peptide previously implicated in promoting BBB disruption. We confirmed elevated Edn1 protein level in the spinal cord, optic nerve and cerebellum of Slc4a4-cKO mice during EAE as well as in human MS brain lesions. To establish the functional significance of Edn1 upregulation, we treated Slc4a4-cKO mice with an Edn receptor antagonist during EAE induction. This intervention significantly ameliorated clinical disease severity and restored BBB integrity in the Slc4a4-cKO mice. Take together, these studies provide evidence that Slc4a4 acts as a critical regulator of BBB integrity in MS and suggest that its loss drives pathological Edn1 upregulation, contributing to BBB breakdown and disease progression.

Disclosures: R. Ailani: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

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Program #/Poster #: PSTR165.12/I1

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Neuroinflammation imaging in vivo in the EAE mouse model using ¹⁸F-FEMPA PET

Authors: *J. TOIVANEN, J. ROKKA, J. RYTKÖNEN, S. BÄCK;
Charles River Discovery Res. Services, Kuopio, Finland

Abstract: ¹⁸F-FEMPA is a second-generation radioligand to target the 18-kDa translocator protein (TSPO). TSPO is a biomarker of microglial activation in rodents, and elevated levels are linked to increased microglial density in multiple sclerosis (MS) patients. Our aim was to assess the feasibility of ¹⁸F-FEMPA positron emission tomography (PET) imaging in experimental autoimmune encephalomyelitis (EAE) mouse model that was induced by inoculation of MOG₃₅.

55 in complete Freund's adjuvant (CFA). EAE replicates some key characteristics of MS disease, namely T cell activation, neuroinflammation, demyelination and axonal damage. Ten C57Bl/6J mice were immunized s.c. against MOG₃₅₋₅₅ in CFA at 8 weeks of age. Pertussis toxin was injected i.p. to enhance disease induction. Twenty mice were sham-immunized using PBS instead of MOG₃₅₋₅₅ and CFA. 28 days after immunization, the mice were subjected to ¹⁸F-FEMPA PET imaging under isoflurane anesthesia using a small animal PET/CT scanner (BioPET/CT, Sedecal, Spain). Approximately 10-20 MBq of ¹⁸F-FEMPA was injected i.v. A 0-60 min dynamic list mode PET scan was performed. Images were reconstructed with 2DOSEM algorithm with CT-based attenuation correction into several time frames. ¹⁸F-FEMPA uptake in the brain, spinal cord C, T and L segments and heart was determined as standardized uptake value (SUV). Brain and spinal cord SUVs were normalized against the heart SUV. The animals were weighed and weakness symptoms were scored once per day on a scale from 0 to 5. EAE mice showed increased ¹⁸F-FEMPA uptake levels throughout the central nervous system suggesting increased microglial density and neuroinflammation. The whole brain had the strongest increase relative to heart: EAE mice had 37.0% more activity as compared to the sham controls (p < 0.0001). Brain stem and cerebellum were the most frequent locations of elevated uptake. Activities in the three spinal cord segments were elevated as follows in comparison to the sham group: C-segment: 24.6% (p=0.0058); T-segment: 32.5% (p=0.0031) and L-segment: 23.3% (p=0.0130). The symptom scores on day 28 varied between 1-2 reflecting a state of complete tail paralysis to tail paralysis accompanied by moderate hind leg weakness. The mean weight change was -2.0% compared to day 0 weight. In conclusion, ¹⁸F-FEMPA PET is a noninvasive in vivo measure of neuroinflammation in the EAE mouse model that can be used to assess the efficacy of therapy interventions and may be used repeatedly to monitor disease progression.

Disclosures: **J. Toivanen:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **J. Rokka:** A. Employment/Salary (full or part-time): Charles River Discovery Research Services. **J. Rytönen:** 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

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

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Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: German Research Foundation (SFB/CRC-TR128)
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Title: Maladaptive neuronal state shifts in remission stage of a mouse model of relapse-remitting EAE extend to hippocampal circuits and are accompanied by hyperactivity-induced cortical increase of apoptosis

Authors: *A. STROH¹, K. ENGEROFF^{1,2}, T. FU^{4,3}, W. FAN⁴, B. STEFAN², F. W. OHL⁵, T. DE SCHULTZ⁵, F. ZIPP²;

¹Univ. Hosp. Muenster, Muenster, Germany; ²Univ. Med. Ctr. of the Johannes Gutenberg Univ. Mainz, Mainz, Germany; ³Univ. Med. Ctr. of the Johannes Gutenberg Univ. Mainz, Mainz, Afghanistan; ⁴Leibniz Inst. for Resilience Res., Mainz, Germany; ⁵Systems Physiol. of Learning, Leibniz-Institute for Neurobio., Magdeburg, Germany

Abstract: Maladaptive neuronal network dysregulations in remission stage have emerged as a putative novel pathological mechanism in Multiple Sclerosis (MS). Previous studies in an EAE mouse model of relapse-remitting MS discovered increased neuronal excitability in the visual cortex, prefrontal cortex, and thalamus of EAE mice. Intriguingly, grey matter atrophy in MS does not consistently correlate with white matter lesions, suggesting that alternative mechanisms—such as region-specific altered activity patterns—may play a crucial role in disease pathophysiology and progression. Here, we explore, whether maladaptive neuronal state shifts in remission of EAE mice extend to hippocampal circuits and aim to investigate the link between the network dysregulation and neurodegeneration. We performed *in vivo* multi-electrode recordings in mouse hippocampus. Female EAE mice in remission revealed an altered spike rate in the hippocampus in comparison to nonimmunized controls. While cortical neurons in EAE mice displayed a shift towards hyperactivity in the hippocampus, we observed an increased fraction of neurons with medium activity in the network spike rate in EAE mice, in comparison to nonimmunized controls. We now asked, in a comparative experimental design, whether neuronal hyperactivity is linked to subsequent neurodegeneration. In remission, we did not identify a higher rate of neuronal cell death. Consequently, we needed to explore a marker involved in the early signaling leading to subsequent cell death. Using RNAscope, we discovered changes in mRNA levels of the cell death regulator Receptor-interacting serine/threonine protein kinase 1 (RIPK1). Notably, RIPK1 levels were elevated in the visual cortex, but not in the hippocampus. Consequently, an increase of neuronal hyperactivity in the cortex was accompanied by increased cell death signaling, indicated by increased RIPK1 levels, while in the hippocampus, a shift towards medium activity levels was not associated with changes in RIPK1 transcription. These findings suggest an extended shift in network activity in EAE remission well beyond thalamo-cortical regions, and a specific role of neuronal hyperactivity in MS progression.

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Poster

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CNPq N° 26/2021 [process# 401653/2022-6].

Title: Trpv4 contributes to clinical severity, neuroinflammation, and nociception in a relapsing-remitting experimental autoimmune encephalomyelitis (rr-eae) mice model.

Authors: *P. RODRIGUES¹, J. FRARE², D. SPAT², N. RUVIARO², P. GEPPETTI³, R. NASSINI⁴, G. BOCHI², G. TREVISAN²;

¹Physiol. and pharmacology, Federal Univ. of Santa Maria, Santa maria, Brazil; ²Federal Univ. of Santa Maria, Santa Maria, Brazil; ³Univ. of Florence, Florence, Italy; ⁴Univ. of Florence, Firenze, Italy

Abstract: Relapsing-remitting multiple sclerosis (RRMS) causes neuropathic pain in 28% of patients. Although treatments exist, most patients respond poorly to available pain medications. We therefore highlight the transient receptor potential vanilloid 4 (TRPV4), previously studied in neuropathic pain-associated pathologies. TRPV4 expression increases in the presence of inflammatory cytokines, suggesting a potential link between TRPV4 and neuroinflammation. However, this relationship has not yet been studied in the relapsing-remitting experimental autoimmune encephalomyelitis (RR-EAE) model. This study aimed to clarify TRPV4's role in RR-EAE-related nociception and neuroinflammation using both pharmacological modulation and genetic deletion of TRPV4 (*Trpv4*^{-/-}). To induce RR-EAE, female C57BL/6 mice (#6202220119 and #1194/2015-PR) were immunized with 200 µg MOG₃₅₋₅₅, 45 µg QuilA (subcutaneously), and two doses of 1 ng/µl pertussis toxin (intraperitoneally). First, we administered a single dose of the TRPV4 antagonist HC-067047 (10 mg/kg, i.p.) 35 days post-induction. Next, we assessed whether repeated HC-067047 treatment (1 mg/kg, i.p., for 15 days starting on day 20) or *Trpv4*^{-/-} mice reduces neuropathic-like symptoms and neuroinflammation. In all protocols, we evaluated clinical score, mechanical and cold allodynia, thermal hypersensitivity, grip strength, and motor coordination (rotarod) from days 7 to 35 post-induction. Open field and nest building tests were conducted on days 34 and 34-35, respectively. We measured hydrogen peroxide (H₂O₂), Mog, Iba-1, Gfap, Olig-2, Par2, Trpv4, and PLA via PCR and/or immunofluorescence in the spinal cord. Demyelination in the brain and spinal cord was assessed with luxol fast blue in *Trpv4*^{+/+} and *Trpv4*^{-/-} mice. A single HC-067047 dose reversed mechanical and thermal hypersensitivity, without affecting cold allodynia or locomotion. Repeated HC-067047 treatment improved clinical score, mechanical and thermal hypersensitivity, and paw strength, with no effects on weight or locomotion. TRPV4 genetic deletion prevented RR-EAE symptom development, without altering cold allodynia. H₂O₂, a TRPV4 agonist, was elevated in *Trpv4*^{+/+} mice and reduced in HC-067047-treated or *Trpv4*^{-/-} mice. TRPV4 deletion reduced demyelination, astrocyte and microglial activation, and oligodendrocyte dysregulation. These findings indicate TRPV4 involvement in RR-EAE clinical features, suggesting that TRPV4 antagonists hold therapeutic potential for RRMS.

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Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

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Program #/Poster #: PSTR165.15/I4

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Ministry of Innovation, Science & Technology (no. – 0008147)

Title: Gut Microbiome After Exercise Training Reduces Experimental Autoimmune Encephalomyelitis

Authors: L. HAMDI¹, O. AGRANYONI², Y. GOLDBERG¹, N. ZARKA¹, N. FAINSTEIN³, P. THEOTOKIS⁴, N. GRIGORIADIS⁴, A. KATZ⁵, T. BEN-HUR³, S. NAVON-VENEZIA², *O. EINSTEIN¹;

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Abstract: Background: Exercise training (ET) benefits a range of autoimmune and neurological disorders, particularly Multiple Sclerosis (MS) and its animal model, experimental autoimmune encephalomyelitis (EAE). Previously, we demonstrated that high-intensity continuous training (HICT) mitigates EAE severity through both immunomodulatory and neuroprotective mechanisms. ET also alters gut microbiota, which influences brain and immune function through the microbiota-gut-brain and microbiota-gut-immune axes. However, the link between ET-induced changes in the gut microbiome and the progression of autoimmune neuroinflammation remains poorly understood. **Objective:** This study examined whether and how the gut microbiome mediates the protective effects of HICT on EAE. **Methods:** Healthy mice underwent HICT using a treadmill running protocol. Fecal microbiota transplantation (FMT) from HICT or sedentary (SED) donors was performed in naïve recipient mice, followed by proteolipid protein (PLP) immunization to induce EAE. Clinical and pathological outcomes were assessed. Fecal and sera were collected post-training and post-FMT to analyze gut microbiota composition (via 16S rRNA sequencing) and serum short-chain fatty acid (SCFA) concentrations (using targeted metabolomics). Additionally, the encephalitogenic potential of PLP-reactive lymph node cells (LNCs) from recipient mice was evaluated in vitro. **Results:** Mice receiving HICT-derived FMT exhibited attenuated EAE clinical course, evidenced by delayed onset, reduced maximal clinical scores, and a significantly reduced overall burden of disease. Neuropathological analysis revealed reduced central nervous system (CNS) inflammation, demyelination, and axonal injury. Gut microbiome profiling identified distinct microbial signatures, including lower relative abundance of *Bacteroides uniformis*, *Clostridiales*, and

Anaeroplasma in HICT mice. SCFA levels (butyrate, propionate, acetate) were lower in HICT mice. Furthermore, LNCs from HICT-FMT recipients showed reduced proliferation upon PLP stimulation *in vitro*. **Conclusions:** These findings demonstrate that HICT- derived gut microbiome exerts a protective effect against EAE, which is mediated, at least partially, through systemic suppression of autoreactive LNC proliferation. HICT induces compositional and functional shifts in the gut microbiota, potentially altering host-microbe metabolic interactions that contribute to immunomodulation in autoimmune neuroinflammation.

Disclosures: L. Hamdi: None. O. Agranyoni: None. Y. Goldberg: None. N. Zarka: None. N. Fainstein: None. P. Theotokis: None. N. Grigoriadis: None. A. Katz: None. T. Ben-Hur: None. S. Navon-Venezia: None. O. Einstein: None.

Poster

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Program #/Poster #: PSTR165.16/I5

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: National Institutes of Health R01 NS120877
National Institutes of Health R01 NS107946
National Multiple Sclerosis Society, RG1901-33209
Mayo Clinic Center for Regenerative Biotherapeutics

Title: Immunomodulatory and pro-regenerative effects of therapeutic PAR1 inhibition in experimental autoimmune encephalomyelitis

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Abstract: Demyelinating diseases such as multiple sclerosis involve chronic neuroinflammation and impaired myelin repair, for which current therapeutic options remain limited. Protease-activated receptor 1 (PAR1), the thrombin receptor, modulates myelin preservation and inflammatory responses in the central nervous system (CNS). Our prior work demonstrates that genetic deletion of PAR1 promotes myelin preservation and remyelination in lyssolecithin and cuprizone-induced models of demyelination. Building on this, we hypothesized that pharmacologic inhibition of PAR1 would reduce disease severity and enhance repair in the highly inflammatory experimental autoimmune encephalomyelitis (EAE) demyelination model. EAE was induced in adult male and female C57BL/6J mice (n = 5 males, 10 females) via MOG₃₅₋₅₅ peptide immunization. Mice received daily intraperitoneal injections of the FDA-approved PAR1 inhibitor vorapaxar, or vehicle, from the onset of EAE clinical scores (Day 10 post-immunization) through the experimental endpoint (Day 30). Significant functional

improvement by inclined plane test and EAE clinical scores occurred at several timepoints in male vorapaxar versus vehicle recipients. Spinal cords were analyzed histologically for myelin and inflammatory markers. A MOG₃₅₋₅₅ splenocyte recall assay assessed peripheral immune responses. In a complementary experiment, Ribotag::PDGFR α -Cre mice were likewise treated with vorapaxar or vehicle and spinal cord analyzed for histology and RNA sequencing of bulk and PDGFR α ⁺ (oligodendrocyte-enriched) cells was performed. In spinal cords, vorapaxar treatment significantly reduced demyelinated lesions, IBA1⁺ microglia/macrophages, and CD3⁺ T cells in male mice, while increasing myelin basic protein (MBP) expression ($p = 0.004, 0.004, 0.008, 0.01$, respectively, Student's t-test), consistent with preserved myelin and a reduced inflammatory environment. Both sexes exhibited elevated numbers of mature GST3⁺ oligodendrocytes ($p = 0.009$ (males), 0.05 (females), Student's t-test). Transcriptomic analysis revealed altered expression of genes regulating inflammation, lipid metabolism, extracellular matrix remodeling, and cellular signaling in a direction conducive for a pro-repair environment. Splenocyte recall responses further supported PAR1's immunomodulatory role. These data demonstrate that pharmacological inhibition of PAR1 fosters a CNS environment conducive to myelin preservation and repair, underscoring PAR1 as a promising therapeutic target for demyelinating and potentially broader neurodegenerative conditions.

Disclosures: W.L. Simon: None. H. Yoon: None. M.R. Langley: None. I.A. Scarisbrick: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.17/I6

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Improving Phagocytic Clearance of Apoptotic Cells as a Treatment Strategy to Reduce Disease Progression in Preclinical Model of Multiple Sclerosis.

Authors: *M. NEMATULLAH¹, M. FATMA², S. GIRI³;

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Abstract: Efferocytosis is the process of clearing cellular debris by professional phagocytes such as macrophages and microglia. This process helps in maintaining tissue homeostasis. Altered efferocytosis is implicated in chronic inflammatory disorders, including Multiple Sclerosis (MS), an autoimmune disease marked by the accumulation of myelin debris and dead cells in the central nervous system (CNS). To elucidate the role of efferocytosis in MS, we utilized the experimental autoimmune encephalomyelitis (EAE) mouse model. Our data revealed that macrophages and microglia in EAE mice displayed markedly reduced efferocytic activity compared to CFA controls, correlating with decreased expression of critical efferocytosis

receptors such as Mertk, Axl, and ELMO. To assess the therapeutic potential of modulating efferocytosis, we administered apoptotic cell-primed macrophages to EAE mice, which led to delayed disease onset, attenuated clinical symptoms, and reduced CNS infiltration by pathogenic CD4⁺ T cells. Furthermore, metabolic analyses using Seahorse and SCENITH assays showed that efferocytotic macrophages shifted toward oxidative phosphorylation, indicating enhanced mitochondrial efficiency. These results underscore the pivotal role of efferocytosis in modulating immune responses and disease progression in EAE, suggesting that boosting efferocytosis could offer a promising therapeutic avenue for MS and related inflammatory conditions.

Disclosures: M. Nematullah: None. M. Fatma: None. S. Giri: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.18/I7

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Betaine-induced Neuroprotection and Remyelination in Multiple Sclerosis: Robust Remyelination in Cuprizone and Inflammation-Dependent Outcomes in EAE Mouse Model

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Abstract: Multiple sclerosis (MS) is a progressive neurodegenerative disorder characterized by oligodendrocyte (OL) loss and demyelination, driven by the impaired differentiation of oligodendrocyte precursor cells (OPCs) into myelin-producing OLs, particularly under oxidative stress. This differentiation block disrupts one-carbon metabolism, reducing key metabolites like S-adenosylmethionine (SAM) and betaine, critical metabolites for epigenetic regulation via DNA and histone methylation. In MS postmortem brain tissue, diminished one-carbon metabolites and enzymes impair methylation capacity, dysregulating genes critical for energy metabolism and OL function. We investigated betaine's therapeutic potential in two preclinical MS models: the non-inflammatory cuprizone model and the inflammatory experimental autoimmune encephalomyelitis (EAE) model. In the cuprizone model, betaine supplementation restored SAM levels via the BHMT-betaine methylation pathway, significantly mitigating demyelination and promoting remyelination evidenced by challenging beam, Rotarod and MRI confirming improved motor function and myelin integrity. in 36 male WT C57BL6/J mice (8 weeks old, n=8/group: control, cuprizone 0.3% w/w for 6 weeks, cuprizone + betaine) at two time points: peak demyelination (6 weeks, cuprizone) and remyelination (7 weeks, post-cuprizone). Single-nucleus RNA-sequencing (snRNA-seq) of corpus callosum and cortex nuclei (10x Genomics Chromium, 10,000 nuclei/sample, Illumina NovaSeq 6000, 100 million reads/sample) at peak

demyelination (6 weeks) and remyelination (7 weeks post-cuprizone) revealed betaine-driven transcriptional changes promoting OPC maturation and survival. Quantitative RT-PCR and immunohistochemistry validated these candidates. Conversely, in the EAE model, betaine's neuroprotective and remyelinating effects were restricted to low-inflammatory phases, with clinical disability scores and immunofluorescence assay demonstrating that high immune infiltration correlated with reduced efficacy. These findings highlight betaine's robust efficacy in non-inflammatory contexts and its inflammation-dependent limitations. Our results identify key molecular targets, including antioxidant and differentiation pathways, for enhancing remyelination and neuroprotection. Moreover, they underscore the need for combination therapies integrating anti-inflammatory agents with betaine's neuroprotective and myelination-promoting properties to address the complex pathology of MS, paving the way for targeted therapeutic strategies in this devastating disease.

Disclosures: M. Shalih Maraicar: None. B. Nelson: None. E. Lesco: None. K. Knies: None. T.G. Bottiglieri: None. R. Clements: None. J. McDonough: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.19/I8

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: National Institutes of Health AI052463
Canadian Institutes of Health Research
Multiple Sclerosis Society of Canada
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National Institutes of Health NS082902

Title: Nicotinic acetylcholine receptor subtypes involved in causation of and in protection and recovery from an experimental model of multiple sclerosis

Authors: *R. J. LUKAS;
Ronald J Lukas, Phoenix, AZ

Abstract: Multiple sclerosis (MS) is a complex and often progressively debilitating, neuroinflammatory disorder involving nerve, glial and immune cells. Treatment options and preventive strategies are limited. Our previous work employing the experimental autoimmune encephalomyelitis (EAE) model of MS revealed involvement of specific members of the diverse family of nicotinic acetylcholine receptor (nAChR) subtypes in onset of and recovery from disease symptoms. EAE is seen in saline-treated C57BL/6J mice, whether actively induced by

injection of murine myelin oligodendrocyte glycoprotein peptide³⁵⁻⁵⁵, or triggered via adoptive transfer of T cells from immunized donor animals. However, actively-induced or adoptive transfer EAE is delayed and attenuated in severity in animals if they are instead treated on the day of immunization or a week before with nicotine (minipump delivery to plasma levels of about 300 nM). The rate of recovery from EAE severity also is accelerated and more complete in nicotine-treated animals. Those effects of nicotine (on actively-induced EAE) are absent in nAChR alpha7 subunit knockout (KO) animals. By contrast, those effects of nicotine are fully mimicked in nAChR alpha9 subunit KO mice (but not additively with nicotine's). There is no difference in effects on EAE relative to those in nAChR alpha9 subunit KO mouse also lacking via KO their typical partnering nAChR alpha10 subunits. Interestingly, there is no recovery from EAE symptoms in nAChR beta2 subunit KO mice whether treated with saline or nicotine. Remarkably, EAE severity is exacerbated in nAChR alpha/alpha9 subunit double (D) KO mice receiving saline, but nicotine treatment effects in DKO mice were like those in wild-type animals. Collectively, these findings suggest hypotheses: (1) that nicotine exposure protects against onset and magnitude of EAE, (2) that nAChR containing alpha9 +/- alpha10 subunits (alpha9*-nAChR), and found prominently in immune system cells, are involved in EAE onset or exacerbation, (3) that alpha7*-nAChR have protective actions, and (4) that remyelination necessary for recovery from EAE involves beta2*-nAChR. Whereas other studies using additional models of demyelination and/or MS should further illuminate processes involved, important roles for nAChR in causes of MS and in its treatment and perhaps prevention are suggested and warrant further investigation.

Disclosures: R.J. Lukas: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.20/I9

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NMSS Postdoctoral Fellowship FG-2307-42219

Title: The role of endothelial Stra6 in modulating the neuroinflammation

Authors: *S. AYDIN;
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Abstract: Multiple sclerosis (MS) is a neuroinflammatory disease of the central nervous system (CNS), characterized by blood-brain barrier (BBB) breakdown, immune cell infiltration across the CNS barriers, and demyelination. The orchestrated immune response in MS involves the activation and differentiation of immune cells into pro- or anti-inflammatory phenotypes, modulating inflammation. Stra6 is a known regulator of retinol transport, the downstream active

metabolite of vitamin A, and a precursor of the active signaling molecule retinoic acid (RA). RA has been demonstrated to induce a regulatory T-cell response and suppress the pathogenic response in steady-state. However, in an ongoing inflammation, RA has been shown to promote T-cell activation and enhance the pathogenic T helper cell response in a dose-dependent manner. While most studies have primarily explored the peripheral role of Vitamin A, its common form retinol, and its downstream product RA, our understanding of the immunomodulatory effects of these molecules within the CNS compartment remains rudimentary. In our preliminary efforts, we found that Stra6 is upregulated in the CNS endothelial cells in neuroinflammation, losing its region-specific endothelial expression and gaining a global expression profile, potentially allowing an increase in the influx of Vitamin A metabolites in the CNS parenchyma. Moreover, we show that the absence of Stra6 ameliorates the experimental autoimmune encephalomyelitis (EAE), a mouse model for MS. Our preliminary findings suggest that the absence of Stra6 in endothelial cells, hence, the altered concentrations of RA in the CNS parenchyma modulate the CNS-compartment specific immune response in an anti-inflammatory fashion. Our results shed light on the precise role of Vitamin A and its derivatives, their transport across cerebral endothelial cells, and their role in modulating the local CNS immune response in neuroinflammation.

Disclosures: S. Aydin: 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.; NMSS.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.21/I10

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: ERC Consolidator Grant 101044180

Title: MRI detection of myelin loosening and remyelination dynamics via the Structural Myelin Integrity metric

Authors: *J. LIMA¹, M. CORRAL-BOLAÑOS^{2,1}, H. VILA-MERKLE¹, M. PIZZOLATO², T. B. DYRBY^{1,2};

¹Danish Res. Ctr. for Magnetic Resonance (DRCMR), Dept. of Radiology and Nuclear Medicine, Copenhagen Univ. Hosp., Hvidovre, Denmark; ²Dept. of Applied Mathematics and Computer Sci., Tech. Univ. of Denmark (DTU), Kongens Lyngby, Denmark

Abstract: Demyelinating diseases feature not only macrostructural alterations in myelin content (e.g. its quantity) but also microstructural abnormalities. These include myelin loosening and suboptimal remyelination, which hinder axonal conduction velocity and thereby impair sensory,

motor, and cognitive functions. Despite their relevance, microstructural changes are usually overlooked in magnetic resonance imaging (MRI) studies in favour of changes in myelin quantity. Hypothesising that myelin loosening and remyelination alter the relationship between myelin quantity and layer organisation, we conducted confirmatory research to test this and evaluate whether combining quantitative MRI (qMRI) methods improves the characterisation of myelin structure. Accordingly, we developed the Structural Myelin Integrity (SMI) metric, which combines two qMRI-derived metrics: myelin water fraction (MWF), sensitive to both myelin quantity and layer organisation, and bound pool fraction (BPF), which reflects macromolecular content (i.e. myelin quantity) without microstructure assumptions. Next, we investigated the sensitivity of MWF, BPF, and SMI in rodent models of myelin loosening (Studies 1 and 2) and de/remyelination (Study 3). In Study 1, rats were culled and scanned longitudinally at different post-mortem intervals. In Study 2, analyses of MRI scans from mice exhibiting ‘normal’ myelin were compared to those from proteolipid protein (PLP)-null mice, which exhibit abnormally increased interlamellar spacing (i.e. ‘looser’ myelin). In Study 3, four groups of rats underwent focal demyelination via a lyssolecithin injection into the corpus callosum and were perfusion-fixed at 7, 14, 21, and 28 days post-injection (dpi), respectively. Comparisons of ex vivo imaging analyses were then made between the lesioned region and an unaffected callosal region. Our results show that MWF and BPF are indeed sensitive to specific changes: MWF to both myelin quantity and organisation, while BPF reflects only the amount of myelin. The SMI disentangles these changes and can thus be used to quantify myelin loosening. Moreover, during remyelination, SMI in the lesioned region progressively returned to normal levels by 21 dpi and subsequently stabilised, whereas MWF and BPF continued to increase. Notably, remyelination trends detected with SMI align more closely with known patterns of signal conduction velocity recovery. Overall, our results suggest SMI may serve as a proxy for myelin integrity and, thus, conduction velocity, which could yield clinically relevant insights into brain function changes associated with both progression and recovery in demyelinating diseases.

Disclosures: J. Lima: None. M. Corral-Bolaños: None. H. Vila-Merkle: None. M. Pizzolato: None. T.B. Dyrby: None.

Poster

PSTR165: Multiple Sclerosis and Neurodegeneration: Experimental Models of Demyelinating Diseases

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR165.22/Web Only

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: the Judith Jane Mason and Harold Stannett Williams Memorial Foundation National Medical Program

Title: Targeting lipid metabolic enzyme to hamper central demyelination

Authors: *J. XIAO, P. TEDDU, N. GEORGE;
Swinburne Univ. of Technol., Hawthorn, Australia

Abstract: Multiple Sclerosis (MS) is a progressive neurodegenerative disease resulting from an autoimmune attack on myelin, leading to myelin loss, axon damage and neurological deficits. No proven therapy is available for MS to stall demyelination and promote repair. Current treatments are immunomodulators that suppress autoimmunity and inflammation but do not address the primary neuropathology. This presents an urgent and clear need for new therapeutics focusing on protecting the myelin-forming oligodendrocyte and promoting myelin repair. Myelin is mostly composed (70%) of lipid, yet little research has been done on lipid metabolic molecules in myelin production and protection. Genetic evidence indicates that restoring the synthesis of S1P, a bioactive lipid, in the central nervous system (CNS) is myelin-protective in lesions and promotes remyelination after injury. However, pharmacological approaches that can directly regulate S1P synthesis in the CNS have not been identified. We bring a new strategy to harness endogenous S1P via inhibiting its degradation. Our preliminary data suggest that inhibiting S1P lipid degradation exerts promising effects on limiting central demyelination and protects against the loss of oligodendrocytes, accompanied by suppressed neuroinflammation. This study provides the *proof-of-principle* evidence that harnessing S1P degradation is a promising strategy to hamper myelin damage in the context of MS.

Disclosures: J. Xiao: None. P. Teddu: None. N. George: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.01/I11

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Role of neuronal ISG15 in neurodegeneration

Authors: *G. MORALES¹, S. MUHAMMAD², B. CLARKSON²;
²Neurol., ¹Mayo Clin., Rochester, MN

Abstract: Background: ISG15 is induced in neurons by demyelination and elevated in MS patient cortical neurons. Our hypothesis is that ISG15 contributes to neuron loss in MS by impairing *protein and mitochondrial turnover*.

Methods: ISG15 activation was induced by IFN γ treatment in neurons. Protein turnover: murine cortical neurons were transduced with AAV1.TRE.mCherry-DD to drive Tet-ON expression of the mCherry tagged with a degradation domain (DD). Following induction DD-mCherry is rapidly degraded allowing measurement of proteasome activity. Mitophagy: murine cortical neurons were transduced with AAV1.Syn.GFP-mCherry-FIS1 (mito-QC) which targets mitochondria. Upon entry into the lysosome, GFP is rapidly quenched allowing quantification of

mitophagy (non-colocalizing mCherry signal). C57BL/6 and ISG15 KO mice were subjected to a cuprizone diet, immunofluorescence and confocal imaging to assess neuronal density changes in the cortex over time.

Results: In WT but not ISG15 deficient neurons; IFN γ treatment delayed DD-mCherry degradation. Using the mito-QC reporter, elevated mitochondrial content and mitophagy levels were observed in ISG15 KO cortical neurons compared to WT. Neuron density was preserved in ISG15 KO compared to WT.

Conclusion: IFN γ -induced ISG15 impairs protein turnover and mitophagy in neurons, and ISG15 deficiency protects neurons during demyelination. Future work will test how neuronal ISG15 activation impacts other degradation pathways such as autophagy during neurodegeneration.

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

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.02/I12

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIAID Grant R15 AI156879
NIGMS 5P20GM103427

Title: Lncrna Nostrill modulates neuronal antiviral response

Authors: *C. LEUTY¹, A. MARTA², E. LORENSON¹, A. SHIBATA¹;
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Abstract: Viral infection of central nervous system (CNS) neurons and glia triggers neuroinflammation and alters gene transcription. Neurons and microglia initiate antiviral responses; however, dysregulation of these mechanisms can result in neurodegenerative disease. Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD) is a chronic inflammatory and neurodegenerative disease of the CNS and is a mouse model for primary progressive multiple sclerosis (MS). Neurons are the primary site of infection in the TMEV-IDD model. Long non-coding RNAs (lncRNAs) can regulate neuroinflammatory gene transcription in neurons during viral infection. Using total RNA sequencing, we identified hundreds of differentially expressed lncRNAs in TMEV-infected neuronal cells compared to uninfected cells. RT-qPCR analysis confirmed that TMEV-infected neuronal cell lines significantly upregulate Nostrill ~2fold ($p < 0.01$, $n = 3$) and IRF7 ~87fold ($p < 0.01$, $n = 3$) compared to uninfected cells. Silencing Nostrill with RNAi constructs significantly reduced Nostrill expression by ~3fold ($p < 0.0001$, $n = 3$) and IRF7 by ~48fold ($p \leq 0.05$, $n = 3$), compared to a control silencing construct in infected neuronal cell lines. FISH probing for Nostrill showed differential

Nostrill localization in uninfected and TMEV-infected Neuro2A cells suggesting that Nostrill localization is important for regulating IRF7 expression. To assess whether Nostrill expression influences IRF7 protein synthesis and activation, Western blot and immunoprecipitation assays were performed using uninfected and TMEV-infected neuronal cell lines. These data show that TMEV infection increased phosphorylated-IRF7 by ~6fold ($p < 0.05$, $n = 4$) compared to uninfected cells. Ongoing studies show that Nostrill interacts with p65 of NF- κ B to regulate *Irf7* transcription. Future work will investigate other novel lncRNAs upregulated by TMEV viral infection to increase the understanding of gene regulation during neuronal antiviral immune responses.

Disclosures: C. Leuty: None. A. Marta: None. E. Lorensen: None. A. Shibata: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.03/J1

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R15 AI156879
NIH Grant 5P20GM103427

Title: Determining role of long non-coding RNA Nostrill in microglial marker expression in antiviral immune responses

Authors: *H. PFLUM¹, A. MARTA¹, A. SHIBATA²;
²Biol. Dept., ¹Creighton Univ., Omaha, NE

Abstract: Microglia play an essential role in central nervous system innate immune responses and dysregulation of microglial activity is associated with the development of neurodegenerative disease. Activated microglia can be neuroprotective or neurodegenerative and microglia protein expression is indicative of their state-specific activity. Long non-coding RNAs (lncRNAs) may regulate microglial gene transcription and state-specific protein expression. Here we investigate whether the lncRNA Nostrill regulates microglial antiviral gene transcription. Theiler's murine encephalomyelitis virus (TMEV) is a single-stranded RNA Cardiovirus that causes neurodegenerative demyelinating disease (IDD) in mice like progressive multiple sclerosis (MS) in humans. TMEM119 is a state-specific microglial protein that is upregulated in microglia at the periphery of demyelinating lesions in humans with MS. We show that the lncRNA iNOS Transcriptional Regulatory Intergenic lncRNA Locus (Nostrill) increases in TMEV infected mice. *Tmem119* transcription is significantly increased ~1.7fold in TMEV-IDD susceptible FVB/nJ mice compared to TMEV-IDD resistant C57Bl6 mice ($N = 10$, $p = 0.027$). Further in TMEV-IDD susceptible female mice, *Tmem119* transcription is significantly increased ~3fold compared to IDD-susceptible male mice ($N \geq 4$, $p = 0.00096$). Using BV2 microglial cell lines, the

function of Nostrill in regulating viral infection and microglial *Tmem119* transcription was evaluated. Silencing of Nostrill using a Nostrill-specific RNAi construct significantly increased viral load ~2.9fold compared to the infected silenced control construct (N=4, p=0.026). When infected with TMEV, *Tmem119* gene transcription is significantly increased ~2.5fold in BV2s (N=4, p=0.011). Silencing Nostrill in TMEV-infected BV2s blocks *Tmem119* transcription ~2fold (N=4, p=0.021). In TMEV-infected BV2s, *Iba1* transcription is increased ~2.6fold (N=3, p=0.0094) and is unaffected by Nostrill silencing. These data suggest that the transcription of the microglial state-specific protein TMEM119 during anti-viral immune responses to TMEV is regulated by Nostrill expression. Future studies will further evaluate the mechanism by which Nostrill regulates *Tmem119* transcription and influences microglial antiviral immune responses.

Disclosures: H. Pflum: None. A. Marta: None. A. Shibata: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.04/J2

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIAID Grant 1 R15 AI156879
NIGMS Grant 5P20GM103427

Title: Lncrna nostrill regulates the neuronal irf7-mediated antiviral response in a tmev-idd in vivo and in vitro model system

Authors: *A. MARTA¹, C. LEUTY¹, E. LORENSON¹, A. SHIBATA²;
²Biol. Dept., ¹Creighton Univ., Omaha, NE

Abstract: Viral infection in the central nervous system (CNS) is associated with increased risk of neurodegenerative disease. Dysregulation of neuronal and glial antiviral immune responses is associated with neurodegeneration. Understanding how gene transcription regulates antiviral immunity is necessary to identify novel therapeutic targets for neuroimmune-associated, neurodegenerative disease. Long noncoding RNAs (lncRNAs) are cell-specific regulators of gene transcription and may be differentially regulated in antiviral responses. We hypothesize that a novel lncRNA, Nostrill, and other lncRNAs, are differentially expressed by neurons upon viral infection and that lncRNA expression influences an IRF7-mediated antiviral response. To examine lncRNA expression and function in neuronal antiviral immune responses, in vivo and in vitro model systems were used. Theiler's Murine Encephalomyelitis Virus (TMEV) Induced Demyelinating Disease (IDD) was used to evaluate Nostrill expression during the acute phase of viral infection in TMEV-IDD resistant C57Bl6 mice and TMEV-IDD susceptible FVBnJ mice. TMEV infected FVBnJ mice upregulated Nostrill expression in the cortex compared to TMEV infected C57Bl6 mice (F1,29= 47.6, p<0.0001). TMEV infected FVBnJ mice also upregulated

IRF7 gene expression compared to TMEV infected C57Bl6 mice ($F_{1,30}=17.3$, $p<0.0003$). Nostrill and IRF7 expression were positively correlated with TMEV infection ($R=0.685$, $p<0.0001$). Fluorescent *in situ* hybridization (FISH) showed increased Nostrill expression in NeuN+ neurons of TMEV infected FVBnJ mice compared to TMEV infected C57Bl6 mice ($F_{1,16}=28.7$, $p<0.0001$). RNAi was used to silence Nostrill in Neuro2a cells and interrogate Nostrill-regulated gene transcription. Silencing of Nostrill increased TMEV viral burden in Neuro2a cells ($n=6$, $p=0.0019$). Transcriptomic analyses comparing gene expression in Nostrill silenced (siNostrill) Neuro2a cells following TMEV infection identified 100s of differentially expressed genes compared to TMEV infected Neuro2a cells transfected with a scrambled silencing construct (SiC). RT-qPCR demonstrated that *Irf7* was significantly decreased 48-fold ($n=4$, $p<0.014$) in TMEV infected SiNostrill Neuro2a cells compared to TMEV infected SiC Neuro2a cells. RNA immunoprecipitation showed that TMEV infection increased Nostrill interaction with NFkB p65 ($n=4$, $p<0.0001$). Chromatin immunoprecipitation will evaluate Nostrill-dependent NFkB p65 localization at the *Irf7* promoter. Nostrill is a candidate lncRNA for regulating the transcription of *Irf7* and other antiviral genes in neurons.

Disclosures: A. Marta: None. C. Leuty: None. E. Lorensen: None. A. Shibata: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.05/J3

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Duke Development Funds
National MS Society

Title: Spatial Profiling of Herpesvirus Transcripts in Multiple Sclerosis Spinal Cord Lesions Using Xenium In Situ Analysis

Authors: *E. HATCHELL¹, E. HOCKE², A. SMITH², D. HUBNER⁵, R. DUTTA⁶, M. LUFTIG³, S. GREGORY^{4,2};

¹Univ. Program in Genet. and Genomics, ²Duke Mol. Physiol. Inst., ³Dept. of Mol. Genet. and Microbiology, ⁴Dept. of Neurosurg., Duke Univ., Durham, NC; ⁵Vassar Col., Poughkeepsie, NY; ⁶Lerner Res. Inst., Cleveland, OH

Abstract: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system, thought to arise from the interplay between genetic susceptibility and environmental triggers, including viral infections. Epstein-Barr virus (EBV), a ubiquitous gammaherpesvirus that establishes latency in B cells, has been strongly associated with MS risk. Large scale longitudinal studies have shown that EBV seroconversion precedes disease onset and increases risk of developing disease 32-fold. Although EBV has been implicated in MS pathogenesis

through peripheral and cerebrospinal immune profiling, the direct localization of EBV transcripts within central nervous system tissue remains poorly defined. Human cytomegalovirus (CMV), a betaherpesvirus with neurotropic and immunomodulatory properties, has been suggested to play a divergent role. Reports have linked CMV seropositivity to reduced MS risk, but its presence and distribution in MS lesions is not well characterized. To spatially resolve herpesvirus transcript localization in MS tissue, we applied Xenium In situ Sequencing (10X Genomics) in fresh frozen cervical spinal cord sections from two donors with secondary progressive MS (SPMS) to localize the presence of EBV and CMV in the MS lesion environment (LME). We designed a custom panel including canonical central nervous system (CNS) gene markers, MS lesion markers, and probes targeting EBV and CMV transcripts. We localized viral RNA expression at host single-cell resolution and correlated these patterns with histological features. We establish that latent EBV transcripts were significantly upregulated in the dorsal root entry zone of sensory neurons into the spinal cord suggesting a noncanonical reservoir of latent EBV infection in the CNS and possible interactions between latent EBV and pathways at the CNS-Peripheral nervous system (PNS) interface. In contrast, CMV transcripts were confined to demyelinated areas of the spinal cord, implicating CMV presence in the inflammatory milieu of MS lesions. These findings will be replicated in addition to the n=2 discovery cohort, to show distinct spatial distributions of EBV and CMV in the context of the MS LME and that spatial transcriptomics can provide unique insights into viral involvement in neuroinflammation. These observations open exciting new possibilities for investigating viral contributions to MS pathogenesis through noncanonical localization patterns and interactions with host cells in the lesion microenvironment.

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Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.06/J4

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Double-stranded RNA antiviral signature in early multiple sclerosis

Authors: *V. GOUZOUASIS^{1,3}, I. SARRIGEORGIOU¹, M. TSIFINTARIS⁴, P. LYMBERI¹, L. PROBERT², A. GIANNAKAKIS³;

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Abstract: Viral infections have been implicated in the pathogenesis of multiple sclerosis (MS), yet robust methods to detect active viral replication remain limited. We developed and validated

a sensitive sandwich ELISA targeting double-stranded RNA (dsRNA)—a hallmark of viral replication—in plasma and cerebrospinal fluid (CSF) from treatment-naïve MS patients. Using monoclonal antibodies J2 and K2, dsRNA was measured in samples from 72 MS patients at first clinical onset and 22 healthy controls, employing Poly(I:C), a synthetic analogue of dsRNA, and hepatitis C virus RNA as assay positive controls. Plasma dsRNA levels were significantly elevated in MS patients compared to controls, particularly in those with atypical EBV reactivation (positive for anti-EBNA1 IgG and IgM antibodies). Additionally, we developed an indirect ELISA to measure IgG, IgA, and IgM antibodies targeting Poly(I:C). Plasma dsRNA levels correlated positively only with anti-dsRNA IgM Abs. In a validation cohort of 197 healthy individuals, IgM anti-dsRNA levels were significantly higher compared to MS patients, suggesting impaired acute-phase antiviral responses or altered antibody regulation in MS. To investigate immune activation, we profiled 13 antiviral cytokines. Plasma dsRNA and anti-dsRNA IgM levels were strongly correlated with IL-6, IP-10, IFN- λ 1, IFN- α 2, IFN- λ 2/3, and GM-CSF, a pattern not observed for anti-dsRNA IgG and IgA. These findings suggest that dsRNA detected at MS onset likely indicates ongoing or recent viral activity, inadequately neutralized by the immune system. Reduced anti-dsRNA IgM Abs and sustained cytokine elevations highlight a dysregulated antiviral response, potentially contributing to chronic neuroinflammation and disease progression. Our results underscore viral dsRNA as a promising mechanistic and diagnostic biomarker in early-stage MS.

Disclosures: V. Gouzouasis: None. I. Sarrigeorgiou: None. M. Tsifintaris: None. P. Lymberi: None. L. Probert: None. A. Giannakakis: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

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Program #/Poster #: PSTR166.07/J5

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Italian Ministry of Health RF-2021-12373319
MNESYS Project - PE000006
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Title: T and B cell-dependent synaptopathy in Multiple Sclerosis: protective effect of anti-CD20 treatment

Authors: *F. PALMERIO^{1,3}, S. BALLETTA⁵, A. TARTACCA¹, F. MARIANI^{1,3}, A. MUSELLA^{6,4}, V. ESCARRAT³, S. VELLUCCI³, F. DE VITO⁵, V. ROVELLA¹, A. BRUNO⁵, L. GILIO⁵, G. LAURITANO⁵, F. BUTTARI⁵, M. STAMPANONI BASSI⁵, D. CENTONZE², G. MANDOLESII^{6,4};

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Abstract: Multiple sclerosis (MS) is a chronic inflammatory and neurodegenerative disease of the central nervous system. While therapeutic advances have improved outcomes in Relapsing-Remitting MS (RRMS), Progressive MS (PMS) remains a major challenge due to its steady progression and poor response to most immunotherapies. Anti-CD20 monoclonal antibodies, such as Ocrelizumab, represent a key breakthrough, as they are the only immunotherapies shown to slow disability in primary PMS (PPMS). These therapies target B cells, which contribute to MS not only through antibody production but also via antigen presentation, T cell activation, and gray matter damage. Despite their efficacy, the mechanisms behind anti-CD20 benefits remain unclear. Emerging evidence suggests that inflammatory synaptopathy—defined by immune-mediated synaptic dysfunction and loss—drives neurodegeneration in MS. Using a chimeric ex vivo model, we showed that peripheral T cells from MS patients enhance glutamatergic transmission, replicating TNF-dependent excitotoxicity seen in murine MS models. In this study, we investigated whether Ocrelizumab modulates T cell-mediated synaptotoxicity and explored, for the first time, a potential synaptotoxic role of B cells. We developed a chimeric ex vivo model by incubating T cells—isolated from untreated PPMS patients (PPMS-T, N patients = 16) or Ocrelizumab-treated patients (Ocre-PPMS-T, N=19)—on C57BL/6 cortico-striatal slices. Patch-clamp recordings from medium spiny neurons revealed that PPMS-T cells enhanced sEPSCs, while Ocre-PPMS-T cells (≥ 2.5 years treatment) induced no synaptotoxicity, similar to T cell of healthy controls (N=7). Notably, TNF-dependent synaptotoxicity re-emerged after 5 years of treatment. Given the role of B cells in MS and their T cell-activating capacity, we extended the model to B cells. For the first time, we identified a synaptotoxic effect induced by PPMS B cells, although it was milder compared to that mediated by T cells from the same patients (N=7). Furthermore, ongoing experiments are evaluating whether B cells can restore T cell-driven synaptopathy in co-culture systems, independently of direct cell-to-cell contact, potentially through the diffusion of soluble factors. These findings highlight the dual contribution of B and T cells to synaptopathy in primary progressive MS. Ocrelizumab may exert early neuroprotective effects by modulating these lymphocyte subsets and interfering with their pathological cross-talk.

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Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

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Program #/Poster #: PSTR166.08/J6

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: University of South Alabama Intramural Funding

Title: Probing immune tolerance checkpoint integrity in Multiple Sclerosis

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Abstract: Background: Multiple Sclerosis (MS) is a predominant autoinflammatory demyelinating CNS disorder impacting about 2.9 million population worldwide. Although immune tolerance checkpoints are believed to limit autoreactivity in health, the mechanisms of failure in MS have historically been challenging to investigate as a causative autoantigen has remained elusive. Novel self and non-self-antigens are emerging candidates, yet immune checkpoint function against each remains understudied. The goal of this study is to interrogate B cell immune checkpoint function against putative antigens to identify fundamental structural components of CNS antigens associated with disease origins. Methods: To probe immune checkpoint function, monoclonal antibodies (mAbs) were generated from clonal CSF B cell populations isolated from 3 MS patients and infectious disease controls. Antigen specificity or common tissue-binding patterns for each was determined using human and mouse CNS tissue, cultured human astrocytes and neurons, glioblastoma model cells, and live cell-based assays. mAb CDR3 biophysical properties including amino acid length and charge, and antibody structural features were assayed to interrogate immune checkpoint function and unravel shared features of putative CNS antigens. Results: Three patterns of nervous system tissue-based binding included both neuronal and astrocytic, myelin-abundant, and nuclear; putative antigens included PLP-1, EBNA1/3, Glial CAM, MLC1, and MBP. Across both CD19⁺ B cells and CD138⁺ plasma cells, CDR3 lengths ranged from 5-11 amino acids, and nearly all were negatively charged (median, range) against largely uncharacterized antigens despite utilizing variable HV and HJ segments. Furthermore, the kappa(k): lambda(l) ratio was consistently high, 100% kappa in CD138⁺ cells and up to 12:1 in CD19⁺ cells. mAbs incited variable neurological tissue injury in complement-based cell and CNS explant assays, suggesting disease-relevance.

Conclusion: Peripheral immune checkpoint integrity is compromised in MS, releasing largely negatively charged B cell receptors. This consistent charge across variable antigenic clones may suggest a shared polar substrate such as glycolipids in disease pathophysiology. These findings inform the rationale design of future protocols to isolate neural and glial autoantigens.

Disclosures: N.N. Bhatt: None. J. Soltys: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.09/J7

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Lpa1 Receptor Binding Sites Are abundant In Multiple Sclerosis Patients Rim Lesions Associated With Tspo Activation And Disease Progression

Authors: ***D. BAGNOL**¹, **A. BROADHEAD**¹, **C. BACCEI**¹, **K. LORRAIN**¹, **G. C. EDU**¹, **M. M. POON**¹, **J. ROPPE**¹, **T. SCHRADER**¹, **L. VALDEZ**², **A. CHEN**¹, **D. S. LORRAIN**¹;
¹Contineum Therapeut., San Diego, CA; ²RayzeBio (current address), San Diego, CA

Abstract: Through the quantification of mRNA transcripts, Lysophosphatidic acid receptor type 1 (LPA1) was found to be enriched in glial cells and especially in oligodendrocytes. However, the exact cellular localization and distribution of LPA1 have not been well defined due to the lack of reliable tools for its protein detection. To address this, we designed PIPE-497, a highly selective LPA1 antagonist, and its tritiated analogue [³H]-PIPE-497 and characterized their binding properties. We confirmed that the specific binding of [³H]-PIPE-497 in rodent brain homogenates and in human brain tissue sections was concentration dependent, saturable and displaceable with cold PIPE-497 and other LPA1 antagonists. [³H]-PIPE-497 exhibited similar dissociation constants across all species examined, with a t_{1/2} of 11.2 minutes. With this tool, we were able to identify the localization of LPA1 in various settings from multiple species *ex vivo*, including the brain and spinal cord tissue sections from multiple sclerosis (MS) patients. In mouse and rat forebrain, [³H]-PIPE-497 binding was highest in the white matter tracts, and the observed binding intensity was altered in animals subjected to a variety of demyelinating conditions. In non-human primate and human brain, [³H]-PIPE-497 binding was also detectable in white matter tracts but was higher in some grey matter areas such as cortex, striatum, thalamus, hippocampus, pons and medulla. In human brain and spinal cord sections derived from MS patients, [³H]-PIPE-497 distribution was especially enriched in active and mixed active lesion rims, as well as in areas heavily infiltrated with activated microglia and foamy macrophages. Those lesion rims also had higher binding signal for [³H]-DPA-713, a translocator protein (TSPO) tracer associated with neuroinflammation and disease progression. Additionally, we also demonstrated that [³H]-PIPE-497 was a suitable tool to measure the LPA1 receptor occupancy of compounds of interest *in vivo* in a variety of compartments, including the brain. Based on these data, PIPE-497 was developed into a PET tracer, [¹⁸F]-PIPE-497, which is currently being evaluated clinically to assess the level of LPA1 and its distribution in the brain of healthy volunteers and patients with progressive MS.

Disclosures: **D. Bagnol:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **A. Broadhead:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **C. Baccei:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **K. Lorrain:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **G.C. Edu:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **M.M. Poon:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **J. Roppe:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **T. Schrader:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **L. Valdez:** A. Employment/Salary (full or part-time): RayzeBio. **A. Chen:** A. Employment/Salary (full or part-time): Contineum Therapeutics. **D.S. Lorrain:** A. Employment/Salary (full or part-time): Contineum Therapeutics.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.10/J8

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Elucidating CSF1R signaling to identify potential targets for neurological diseases

Authors: ***R. NIKITINA**, C. JAMES, B. WINNER, F. KRACH;
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Abstract: The colony stimulating factor 1 (CSF1) receptor (CSF1R) is a tyrosine kinase receptor essential for the development and physiological function of myeloid cells, including microglia. Consequently, CSF1R signaling has been implicated in several pathologies, such as amyotrophic lateral sclerosis, Alzheimer's disease, and CSF1R-related leukoencephalopathy (CRL), an adult-onset neurological disorder. However, immediate signaling pathways of CSF1R have not been fully resolved yet. Emerging evidence suggests that activated CSF1R may translocate to the nucleus, where it interacts with transcription factors. Understanding CSF1R signaling dynamics and transcriptional regulation may provide valuable insights into the mechanisms underlying CRL pathogenesis. My objective is to investigate CSF1R interactions during CSF1-mediated signal transduction using innovative APEX2-mediated proximity labeling in a human in vitro model. I hypothesized that CSF1R interactors depend on temporal CSF1 activation. To address this hypothesis, APEX2 labeling was first set up in Lenti-X293T cells. Potential CSF1R interactors were identified after purification with streptavidin-coated magnetic beads and mass spectrometry analysis. After long CSF1 incubation, the transcription factor FOS was detected close to CSF1R. To study the CSF1R interactome in a more physiological system, such as microglia-like cells, APEX2 was targeted to the C-terminal end of CSF1R in a reference iPSC cell line using CRISPR/Cas9. Accurately modified iPSC clones were identified by genomic PCR. In summary, APEX2-based proximity labeling was established as a proof of principle in Lenti-X293T cells. To transfer this method to microglia-like cells, APEX2 was introduced into iPSCs.

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Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.11/J9

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Gut microbiota modulate neuroinflammation via the gut-brain axis

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⁴Uniklinik Erlangen, Erlangen, Germany

Abstract: The gut-brain axis has emerged as a key bidirectional communication pathway between the intestinal microbiota and the central nervous system (CNS), playing an important role in health and disease. In multiple sclerosis (MS), a chronic autoimmune disease of the CNS, accumulating evidence suggests that microbial dysbiosis and gut-derived signals contribute to neuroinflammation. We hypothesize that bacterial effector molecules act as mediators along the gut-brain axis, influencing both peripheral and central immune responses. Using a reporter mouse model, we detected microbial components in the brain following inflammatory challenge, indicating potential trafficking from the gut to the CNS. To explore their functional impact, we stimulated human iPSC-derived microglia with bacterial effector molecules and identified distinct transcriptional responses via bulk RNA-sequencing. Similarly, primary murine glial cells exhibited altered cytokine profiles upon in vitro exposure to effector molecules from various bacterial species. In vivo, systemic administration of bacterial effector molecules disrupted blood-brain barrier (BBB) integrity, triggered immune cell infiltration, and activated CNS-resident glial cells, as shown by flow cytometry. Moreover, the detection of bacterial components in serum samples from MS and inflammatory bowel disease (IBD) patients supports the concept of impaired barrier integrity and systemic spread of microbial products. Together, these findings support a model in which bacterial effector molecules mediate microbiota-gut-brain communication and promote CNS inflammation. This work highlights the gut-brain axis as a key contributor to MS pathogenesis and presents new opportunities for targeting microbial-derived signals in neuroinflammatory diseases.

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Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

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Program #/Poster #: PSTR166.12/J10

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Waseda University Grant for Special Research Projects: BARD022647

Title: Myelin Debris Induces ATP Release and Calcium Oscillations in Astrocytes

Authors: *S. KINOSHITA¹, T. INOUE²;

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Abstract: Demyelinating diseases such as multiple sclerosis are characterized by the loss of myelin integrity, which disrupts rapid nerve conduction and ultimately leads to neurological deficits. Although immune cells, namely microglia in the brain, have long been recognized as key mediators of the injury response, emerging evidence indicates that astrocytes also play a pivotal role during the early phases of demyelination. We investigated the cellular mechanisms through which myelin debris induces astrocytic responses, with a particular focus on extracellular adenosine triphosphate (ATP) release and intracellular calcium (Ca) signaling. Primary astrocyte cultures were prepared from the hippocampi of embryonic day 17 (E17) ICR mice. The cultures were transfected with the extracellular ATP sensor GRAB_{ATP1.0} and loaded with the calcium indicator Fura-2. Bath application of a myelin fraction, prepared by density gradient centrifugation from adult mouse brains, triggered an immediate increase in extracellular ATP levels, followed by robust and oscillatory increases in intracellular Ca concentrations. These responses were completely abolished by the addition of apyrase, an ATP-degrading enzyme, suggesting that ATP acts as an autocrine and paracrine signal that induces Ca transients in astrocytes under demyelinating conditions. The ATP release-inducing activity of myelin fraction was retained following heat treatment but was significantly diminished by protease treatment, implicating proteinaceous factors are involved. Our findings support the possibility that myelin debris itself serves as an early intercellular signal to alert myelin disruption, which activates astrocytes. ATP released from astrocytes upon demyelination may in turn act as an early signal to modulate local cellular responses such as recruitment of microglia and remyelination by oligodendrocytes. These insights provide a novel perspective underlying demyelination and would facilitate developing new therapies for demyelinating disorders.

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Poster

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Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

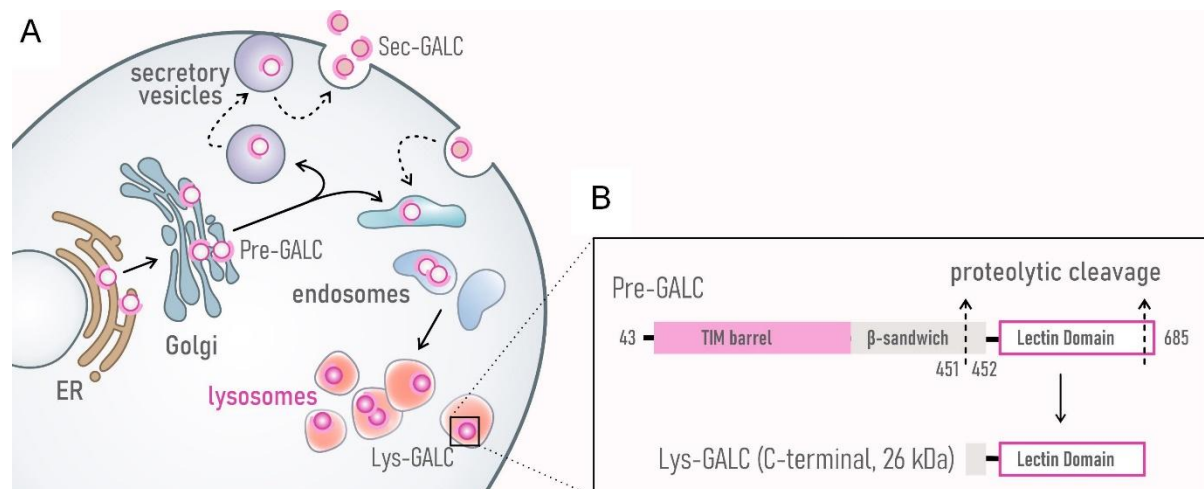
Support: Rosenau Family Research Foundation

Title: Residual galactosylceramidase activity correlates with psychosine levels in GALC missense variants cell model of Krabbe disease

Authors: *C. W. LEE^{1,2,3}, H. PENG^{1,2,3}, A. R. HERDT^{1,2,3},

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Abstract: Krabbe disease (KD) is an autosomal recessive disorder caused by loss-of-function mutations in the *GALC* gene, which encodes galactosylceramidase (GALC). A functional deficiency of GALC leads to the toxic accumulation of its substrate, psychosine, resulting in death of oligodendrocytes and subsequent demyelination. To date, approximately 40 clinically relevant pathogenic *GALC* missense mutation variants (MMVs) have been identified in KD patients. Although MMV is present in about 70% of reported KD cases, the pathogenic mechanisms and their correlations with clinical phenotype remain poorly understood. To address this, we performed a transient expression study on 13 KD-related MMVs in a *GALC* knockout human oligodendrocytic cell line, which showed a 21-fold increase in cellular psychosine levels. Upon analysis, residual *GALC* activity in the MMVs cells was dramatically reduced compared to wild-type *GALC* (WT), ranging from 0 to 9% of WT activity. Importantly, there was a significant correlation between the residual *GALC* activity and the age of clinical onset in reported cases with MMVs, whether in compound heterozygous (MM-null) or homozygous (MM-MM) genotypes. For example, severe MMVs associated with infantile-onset KD, such as p.G553R and p.T529M+p.I562T, had less than 1% activity, while milder MMVs associated with later-onset KD, such as p.G286D+p.I562T and p.I384T+p.I562T, had between 5-9% activity. To determine the effect of MMVs on substrate accumulation, we analyzed cellular psychosine levels from the lipid fraction of the MMV-transfected cells. As expected, we observed a *GALC* activity-dependent change in psychosine levels. There was a 5 to 21-fold increase in psychosine between mild and severe MMVs among the 13 pathogenic MMVs. Psychosine levels were significantly correlated with *GALC* activity but not with the age of clinical onset. In conclusion, we have successfully established a cell-based assay that has the potential to elucidate genotype-phenotype correlations and serve as a platform for drug discovery efforts targeting *GALC* MMVs.



Disclosures: C.W. Lee: None. H. Peng: None. A.R. Herdt: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

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Title: Defining and leveraging microglial and oligodendrocyte gene dynamics following demyelination to improve remyelination efficiency

Authors: *G. S. MELCHOR¹, M. BAYDYUK¹, R. K. SUTER², M. R. BULLARD¹, Z. MANAVI¹, J. HU³, J. K. HUANG¹;
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Abstract: Multiple sclerosis (MS) is a chronic, inflammatory disease that results in focal areas of demyelination throughout the central nervous system (CNS). Remarkably, the CNS has the intrinsic ability to remyelinate, or resupply myelin, to areas of demyelination. This process involves oligodendrocyte lineage cells (OLC), the myelin producing cells of the CNS, and a complex coordination with multiple CNS cell populations. Of particular interest are inflammation producing, activated glial cells such as microglia which have been shown to be intricately tied to the remyelination process. Based on previous research, microglial function is imperative for remyelination to begin in earnest, however, microglia dysregulation is also a suspected cause of remyelination failure in the later stages of MS. Here, we investigated microglia and oligodendrocyte lineage cell transcriptomic dynamics via high-resolution single nucleus RNA sequencing in the lysolecithin mouse model of remyelination, from 5 days post lesion (dpl) until 20dpl. We observed distinct microglia activation profiles in early vs late stages of remyelination, early signs of OLC progression, disease-associated profiles throughout the remyelination process, and an injury response in both cell populations that we define as both a gain of stress-related gene expression and a downregulation of homeostatic gene expression. This injury response extended into the latest measured timepoints in lesioned and nonlesioned tissue, the latter reminiscent of perilesional white matter in MS. We also delineated microglia and OLC communication pathways that provide insight into remyelination dynamics over time. We compared major findings to previously published datasets and further conducted a treatment study based on previous work in our lab indicating that amino acid-driven microglial metabolism is characteristic of early inflammatory activity in lesions. We found that targeting early microglial metabolism resulted in increased remyelination endpoint measurements and ameliorated the injury response profile seen in transcriptomic data analysis, providing a

potentially effective drug strategy to improve remyelination in MS, and further indicating the importance of microglial activation to remyelination.

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Poster

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Title: Deleterious consequences of PFAS exposure on myelin functions; a potential environmental risk for multiple sclerosis

Authors: *B. ZALC¹, V. VALCÁRCEL HERNÁNDEZ², L. BUTRUILLE³, E. MARTIN⁴, B. STANKOFF⁵, C. LUBETZKI⁶, P. BASSEREAU⁷, E. LERAY⁸, S. REMAUD⁹;

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Abstract: Over the past 40-50 years an increased incidence in multiple sclerosis (MS) is observed. Our working hypothesis is that exposure to perfluoroalkyl substances (PFAS) could accumulate in lipid-rich structures, such as myelin, thus disturbing myelin sheath stability and functionality. We investigated effects of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) on myelination and remyelination, using different experimental models. In *Xenopus laevis* Tg(*mbp:GFP-NTR*), a model of conditional demyelination, spontaneous remyelination is strongly inhibited by exposure in the swimming water to PFOS, but not PFOA. Impaired PFOS-induced remyelination translated by impaired performance on visual avoidance of a virtual collision test. Similarly, using mouse cerebellar slices transiently demyelinated by

lysolecithin, we showed that PFOS impaired remyelination, a deleterious effect rescued by adding thyroid hormone (TH). We explored the long-term impact of perinatal PFAS exposure on oligodendrogenesis, and myelination. PFOS - and to a lesser extent PFOA - accumulated into the myelin sheath of offsprings exposed to PFAS via the mother drinking water during late gestation and lactation. Perinatal PFOS exposure, but not PFOA, impaired neurogliogenesis within the adult subventricular zone and blocked OPC maturation. Transmission electron microscopy (EM) studies in the corpus callosum revealed that PFOS exposure results in persistent thinning and ultrastructural abnormalities of the myelin sheath, suggesting permanent alterations in myelin integrity and stability. Using an *in vitro* system based on the production of giant unilamellar vesicles (GUVs) made of myelin lipids, we showed that PFAS exposure affects the mechanical and biophysical properties. Having shown that early exposure to PFAS affected seriously remyelination in the adult, we questioned, using a spatial epidemiology approach, whether geographic environmental contamination of soil, water and air by PFAS correlates with a regional increase prevalence and incidence of MS. In summary, our data demonstrate that perinatal exposure to PFOS, and to a lesser extent to PFOA, lead to permanent alterations in myelin physiology, potentially increasing susceptibility and vulnerability to myelin disorders such as multiple sclerosis.

Disclosures: **B. Zalc:** None. **V. Valcárcel Hernández:** None. **L. Butruille:** None. **B. Stankoff:** None. **C. Lubetzki:** None. **P. Bassereau:** None. **E. Leray:** None. **S. Remaud:** None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.16/J14

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: An in vitro model for studying myelination and demyelinating diseases using iPSC-derived oligodendrocytes

Authors: ***K. TUTTIS RODRIGUES**, B. FRAHER, C. MYERS, C. TICAS RODAS, A. MANTEY, D. KURGANOVA, L. AGBOR, N. ECKERT, T. TANAKA;
Elixirgen Scientific Inc., Baltimore, MD

Abstract: Oligodendrocytes are glial cells of the central nervous system responsible for forming the myelin sheath around neuronal axons, thereby facilitating rapid nerve impulse conduction and protecting axons from degeneration. Demyelination and oligodendrocyte dysfunction are implicated in various neurodegenerative disorders, including multiple sclerosis, Alzheimer's disease, and Parkinson's disease. To better investigate the role of oligodendrocytes in these conditions, human induced pluripotent stem cell (hiPSC)-derived oligodendrocytes have been increasingly utilized. However, it is technically challenging to differentiate functionally myelinating oligodendrocytes. In this study, we aimed at developing functional hiPSC-derived

oligodendrocytes using the Quick-Tissue™ technology. Oligodendrocyte differentiation and maturation were assessed by RNA sequencing and quantitative real-time RT-PCR, targeting key oligodendrocyte markers. Our results showed that the iPSC-derived oligodendrocyte-like cells expressed mature markers for myelination including *CLDN11*, *GALC*, *CNP*, *MAG*, *PLP*, and *MBP*. To evaluate the cells' ability to wrap axon-like structures and form myelin, we employed a micropillar assay combined with immunofluorescence microscopy in a 96-well plate format. Three days after replating these oligodendrocyte-like cells on the micropillar plates, we confirmed that the cells successfully ensheathed the micropillars, with 83% of the population co-expressing O4 and MBP, indicating a high degree of functional differentiation. Thus, this platform including our hiPSC-derived oligodendrocyte-like cells offers a reliable in vitro model for studying oligodendrocyte biology, disease mechanisms, and drug screening. Furthermore, our Quick-Tissue™ technology enables the generation of oligodendrocyte-like cells originated from patients with inherited demyelinating diseases such as leukodystrophy, facilitating the evaluation of potential remyelinating therapies and improving our understanding of oligodendrocyte contributions to neurodegeneration.

Disclosures: **K. Tuttis Rodrigues:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **B. Fraher:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **C. Myers:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **C. Ticas Rodas:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **A. Mantey:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **D. Kurganova:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **L. Agbor:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **N. Eckert:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc. **T. Tanaka:** A. Employment/Salary (full or part-time): Elixirgen Scientific Inc..

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.17/J15

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Combining 3D Environment with Physioxia for Clinical-grade Human Bone Marrow MSC

Authors: ***A. BOG;**
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Abstract: To date, there is no effective way to stop the progression of multiple sclerosis (MS) or induce remyelination, but multiple clinical trials are underway using cultured bone marrow-derived human mesenchymal stem/stromal cells (MSC) to reduce inflammation associated with functional decline. Ambient-air culture ($\approx 18\%$ O₂) accelerates oxidative stress in MSC,

shortening proliferative lifespan and altering secretory output—an issue for MS where therapeutic benefit is thought to derive from the MSC secretome. Preliminary studies have shown that MSC have higher yields when grown at constant physiologic oxygen (5%O₂) in the Xvivo System. We have also shown that HIF-1α is modulated in MSC exposed to room air even briefly for media changes. Here we extend earlier findings by culturing MSC on 2D flat plastic and a novel 3D technology under physioxia or traditional room air incubator conditions. Recent studies have demonstrated that MSC viability and secretome are enhanced using a 3D bioprinted hydrogel, the Bio-Block™. The biomechanical signaling in the Bio-Block™ is more physiologically relevant as its elastic modulus recapitulates normal bone marrow environment (3.0 kPa). In traditional cell culture conditions (18% O₂ on flat plastic) MSC growth diminished over time whereas expansion continued at 5% O₂. In 2D and in the Bio-Blocks™, the cells maintained their morphology and their expansion out to Day 28 under physioxia. Imaging showed enhanced expansion with good viability in the Bio-Blocks throughout. Combining a physioxic macroenvironment and the biomechanical cues of the 3D microenvironment sustains MSC growth and normal morphology longer than traditional cell culture conditions for *in vitro* assays.

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

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.18/J16

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Charcot-marie-tooth disease type 1a (cmt1a) modeling using hipsc-derived schwann cell precursors and motor neurons

Authors: *L. NELSON¹, P. WALSH¹, V. TRUONG²;
²Stem Cell Engin., ¹Anatomic Inc., Minneapolis, MN

Abstract: Charcot-Marie-Tooth disease type 1A (CMT1A) is the most common inherited peripheral neuropathy, caused by a duplication of the PMP22 gene leading to dysmyelination and progressive motor dysfunction. While rodent models have provided foundational insights, species differences in myelination and Schwann cell development limit their translational relevance. To address this, we developed a human *in vitro* model of CMT1A using induced pluripotent stem cell (hiPSC)-derived Schwann cell precursors (SCPs) and motor neurons. In this study, we demonstrate the efficient generation of SCPs from both CMT1A patient and WT hiPSC lines through a rapid, 9-day directed differentiation protocol using defined media conditions. Syngeneic motor neurons were derived from the same hiPSC line within 7 days. Both

cell types were validated by immunocytochemistry, qPCR, and RNA sequencing, confirming SCPs expressed Schwann lineage markers, such as SOX10, S100b, and OCT6, and motor neurons expressed markers including ISL1, HB9, and CHAT. Co-cultures of SCPs and motor neurons were evaluated for alignment using phase contrast imaging and immunocytochemistry. To further characterize disease phenotypes, we performed qPCR using lineage-specific markers and identified consistent upregulation of PMP22 relative to SOX10 and S100B in CMT1A SCPs. These findings were validated at single-cell resolution using RNAscope. Ongoing studies include assessment of myelination capacity and screening of candidate small molecules and siRNAs targeting PMP22 expression. This human stem cell-based co-culture system offers a scalable and disease-relevant platform for modeling CMT1A pathogenesis, studying Schwann cell-axon interactions, and identifying therapeutic targets for demyelinating peripheral neuropathies.

Disclosures: **L. Nelson:** A. Employment/Salary (full or part-time): Anatomic Incorporated. **P. Walsh:** A. Employment/Salary (full or part-time): Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated. **V. Truong:** A. Employment/Salary (full or part-time): Anatomic Incorporated. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Anatomic Incorporated.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.19/K1

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: A case of the Miller Fisher variant of Guillain Barre Syndrome

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Abstract: Guillain Barre syndrome (GBS) is one of the most common causes of acute acquired weakness. It is an autoimmune, demyelinating disease characterized by progressive ascending polyneuropathy often provoked by a preceding illness. In this case, we discuss a young adult who presented with clinical features of the Miller Fisher variant (MFS) of GBS which usually presents as encephalopathy with ophthalmoplegia and ataxia. The differential diagnosis for this patient also included Bickerstaff encephalitis - a rare variant of GBS that shares clinical signs with MFS, but is also associated with anti-GQ1b antibodies that contribute to demyelination by attacking gangliosides. Even though most patients with MFS improve without treatment, it is important to recognize the signs of MFS because it can evolve to more progressive debility - such as worsening limb weakness or respiratory failure - without close monitoring. This case

represents a patient whose symptoms improved remarkably following administration of intravenous immunoglobulin (IVIG) and high-dose steroids.

Disclosures: S. Singh: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.20/K2

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Identifying DNA methylation signatures in cell-free DNA from cerebrospinal fluid to detect nervous system cell damage in multiple sclerosis and other neurological diseases.

Authors: C. STARVAGGI CUCUZZA^{1,2}, C. PRAKASH¹, C. NOLAN³, L. SARRE³, L. KULAR¹, *K. YARDLEY³, F. PUDDU³, M. NEEDHAMSEN¹, M. JAGODIC¹;

¹Clin. Neurosci., Karolinska Institutet, Stockholm, Sweden; ²Ctr. for Neurol., Academic Specialist Ctr. SLSO, Stockholm, Sweden; ³biomodal, Cambridge, United Kingdom

Abstract: Degenerative processes during Multiple Sclerosis (MS) progression are scarcely captured by currently available soluble biomarkers, hindering treatment development. Cell-free DNA (cfDNA) is composed of DNA fragments that are shed into extracellular biological fluids by dying cells and retain the DNA methylation signature of the cell of origin. Our work endeavours to utilize DNA methylation signatures in cfDNA from cerebrospinal fluid (CSF) to detect ongoing central nervous system (CNS) cell damage in MS and other neurological diseases. We profiled bulk methylation (mC) using enzymatic methylation sequencing (EMSeq) and/or true methylation (5mC) and hydroxymethylation (5hmC) using 6-base sequencing in cfDNA extracted from CSF of healthy controls and people with various neurological diseases, including MS, amyotrophic lateral sclerosis, narcolepsy type 1, movement disorders, and traumatic brain injury. While cfDNA extraction from CSF yielded an extremely low amount of DNA (<1 ng from 4 ml of CSF) for all but TBI samples, EMSeq and 6-base sequencing successfully generated sequencing libraries, with expected fragment lengths and good alignment scores, but with low genome coverage. To overcome the latter, we aggregated EMSeq reads and calculated methylation score for neuronal or glial damage. TBI samples showed significantly higher scores than HC, followed by a trend for increased scores in ALS, suggesting more extensive neuronal and glial cell death in these conditions. To increase sensitivity for neuronal damage, we quantified the neuron-enriched hmC modification with 6-base sequencing, and we confirmed higher neuronal DNA content in CSF from TBI CSF cfDNA. Clustering of samples based on methylation levels in regions that were enriched for hmC in TBI and neuronal control successfully separated HC from neurological conditions, including MS. In conclusion we demonstrate that analysis of DNA methylation modifications of cfDNA has the capacity of capturing a neuronal signature in cell-free CSF, although sensitivity remains a technical

challenge. Further studies are needed to implement cfDNA epigenetic analysis as real-time biomarker of neurodegeneration.

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Employment/Salary (full or part-time): biomodal Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); biomodal Limited. L. Sarre: A. Employment/Salary (full or part-time): biomodal Limited. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); biomodal Limited. L. Kular: None. K. Yardley: A. Employment/Salary (full or part-time): biomodal Limited. F. Puddu: A. Employment/Salary (full or part-time): biomodal Limited. M. Needhamsen: None. M. Jagodic: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.21/K3

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Ms-related changes in cerebral blood flow, metabolism, and processing speed

Authors: *J. MA¹, B. P. RYPMA²;

¹Univ. of Texas at Dallas, Dept. of Neurosci., Richardson, TX; ²Behavioral & Brain Sci., Univ. of Texas At Dallas, Dallas, TX

Abstract: Multiple sclerosis (MS) is an immune-mediated degenerative disease of the central nervous system that features cognitive dysfunction and processing speed decline. Neurovascular coupling in the brain involves acute localized blood flow increases in response to neural activity. As such, it is a vital part of healthy neural function and necessary for delivery of energy resources to active neurons. MS is known to disrupt the neural-glial-vascular system, resulting in changes to blood flow response and cerebral metabolism that may have implications for cognitive performance. In this study, we examined how MS-related changes in cerebral blood flow and metabolism would relate to cognitive performance. MS and HC participants who met inclusion requirements were scanned using a 3T MRI scanner with a dual-echo calibrated fMRI sequence, which provided near-simultaneous measures of blood-oxygenated level dependent (BOLD) signal and cerebral blood flow (CBF) during an in-scanner processing speed task. In the processing speed task, participants performed a block-designed parametrically varying Digit Symbol Substitution Test (DSST) in which they were required to match a probe digit-symbol pair to a given key. Response time (RT) was measured as the time from stimulus onset (i.e., appearance of the code table and probe-pair) to time that the participant responded. A hypercapnic gas challenge involving periodic inhalation of room air (4 min) and an iso-oxic 5% CO₂ solution (6 min) permitted calculation of cerebral metabolic rate of oxygen (CMRO₂). Data

were preprocessed, and average percent signal change from baseline was calculated in each voxel providing BOLD and CBF time series. A significant crossover interaction was found between CBF and group in predicting RT during the DSST ($p = .04$), in which MS patients exhibited higher CBF with faster RT, while HC exhibited higher CBF with slower RT. Additionally, a significant interaction was found between CMRO₂ and group in predicting RT during the DSST ($p < .01$), in which MS patients exhibited higher CMRO₂ with faster RT, while HC exhibited higher CMRO₂ with slower RT. These results suggest that MS pathophysiology disrupts cerebral blood flow response and metabolism, and these changes have implications for cognitive performance.

Disclosures: J. Ma: None. B.P. Rypma: None.

Poster

PSTR166: Multiple Sclerosis and Neurodegeneration: Viral, Immune, and Therapeutic Approaches

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR166.22/K4

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Modelling demyelination in a 3D CNS environment: Insights from organotypic cerebellar slices

Authors: *S. KRASSNIG, I. SCHILCHER, T. LÖFFLER, I. PEREZ-RUIZ, M. DAURER, S. FLUNKERT, M. PROKESCH;
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Abstract: Demyelinating diseases such as multiple sclerosis (MS) involve complex disruptions in myelin integrity and repair. To investigate the cellular mechanisms underlying demyelination and remyelination, we utilized organotypic cerebellar slice (OCS) cultures derived from early postnatal mice. Organotypic slice cultures preserve the native three-dimensional (3D) architecture and cellular diversity of the central nervous system, including neurons, oligodendrocytes, astrocytes, and microglia, in a spatially organized manner making them uniquely suited for studying complex cell-cell interactions. Additionally, organotypic tissue cultures exhibit responses in a setting that closely mimics in vivo conditions, while still allowing for precise experimental manipulation and high-resolution imaging. In the current study, OCSs were treated with lysophosphatidylcholine (LPC), cuprizone or pro-inflammatory stimuli to induce demyelination. Myelin pathology was assessed by automated western blotting or immunohistochemistry using confocal microscopy for myelin basic protein (MBP) and its degenerated form (dMBP), a marker for structurally compromised or fragmented myelin. In addition, NF-L secretion was monitored over time. Preliminary results show that acute demyelination can be reliably induced in OCSs. Further analyses of remyelination dynamics, dMBP distribution, and NF-L release are currently under investigation. The major novelty of this study lies in the direct comparison of distinct demyelinating insults within the same 3D ex vivo

system, and in the application of dMBP and NF-L as sensitive readouts for myelin and axonal pathology *in vitro*. This model provides a robust and accessible platform for studying the dynamics of myelin degeneration and repair *in vitro*, and for evaluating therapeutic strategies targeting remyelination.

Disclosures: **S. Krassnig:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **I. Schilcher:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **T. Löffler:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **I. Perez-Ruiz:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Daurer:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **S. Flunkert:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH. **M. Prokesch:** A. Employment/Salary (full or part-time): Scantox Neuro GmbH.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.01/K5

Topic: E.01. Somatosensation – Pain and Itch

Support: JSPS KAKENHI 21H03023
JSPS KAKENHI 23K21454
JSPS KAKENHI 25K02732

Title: Fyn gene expression in rat dorsal root ganglia after peripheral nerve block followed by pulsed radiofrequency

Authors: ***S. SUGINO**¹, K. KIDO², M. YAMAUCHI¹;

¹Anesthesiol. and Perioperative Med., Tohoku Univ., Sendai, Miyagi, Japan; ²Dent. Anesthesiol., Hokkaido Univ., Sapporo, Hokkaido, Japan

Abstract: Radiofrequency pulse therapy (PRF) is used in combination with various peripheral nerve blocks to manage chronic pain. Its action is to potentiate the analgesic effect and prolong the duration of action of local anesthetics; however, the underlying mechanism remains poorly understood. We hypothesized that PRF would be useful in postoperative analgesia. This study aimed to elucidate the mechanism of action of PRF in a rat model of postoperative pain. We used a total of 32 male SD rats (6-8 weeks of age, weighing 250-300 g). A surgical wound was made on the left plantar surface under isoflurane anesthesia. In addition, 0.4 mL of 0.375% ropivacaine was administered via a pole needle puncture from the ventral side of the middle of the left thigh. Immediately thereafter, high-frequency pulses (20 ms, 500 kHz) were applied at 2 Hz for 6 min near the sciatic nerve using a self-built device that did not allow the temperature to rise above 43°C (PRF combined group, n = 6). After emergence from anesthesia, a 75% decrease in spontaneous pain-related behavior was observed in the PRF combined group until postoperative day 2 compared with that in the control group, in which rats were not subjected to PRF after

surgery (n = 6) ($p < 0.01$, 2-way with ANOVA/Tukey test). This attenuation of PRF to spontaneous pain, 75-90% decrease, was also validated in the PRF alone group (n = 7), in which PRF alone was performed without sciatic nerve block after surgery, compared with the surgery alone control group (n = 6). Total RNA was extracted from L4-L6 dorsal root ganglia on the operated side in the PRF alone group (n = 4) and the control group (n = 3), and all gene expression levels were calculated using next-generation DNA sequencing with a bioinformatics approach. Gene expression was quantified for 32,883 genes, including non-coding RNAs. The Fyn gene was the most upregulated (24-fold) compared to that in the control group ($p < 0.0001$, Benjamini-Hochberg method). Since the FYN protein is a tyrosine kinase involved in Schwann cell differentiation and myelin regeneration in peripheral nerves, it may attenuate postoperative pain by restoring demyelination in the surgical wound.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.02/K6

Topic: E.01. Somatosensation – Pain and Itch

Title: Chronic constriction injury of the infraorbital nerve drives distinct transcriptional changes in trigeminal ganglion neurons

Authors: *L. COOK¹, M. HU¹, S. YUN³, B. HALL¹, K. YAMADA², A. B. KULKARNI¹;
¹Functional Genomics Section, ²Cell Biol. Section, NIH, Natl. Inst. of Dent. and Craniofacial Res., Bethesda, MD; ³Predictiv Care, Inc., Mountain View, CA

Abstract: Chronic orofacial neuropathic pain, including migraine and temporomandibular disorders, remains a major clinical challenge due to poorly understood underlying nociceptive mechanisms. The chronic constriction injury (CCI) model recapitulates features of human trigeminal neuropathic pain by inducing partial nerve ligation without complete axonal transection, enabling study of persistent pain state. To elucidate molecular drivers of chronic pain, we performed single-nucleus RNA sequencing on mouse trigeminal ganglia after infraorbital CCI and analyzed transcriptional changes at acute (Day 7) and chronic (Day 21) stages. Our analysis revealed that transcriptional remodeling was largely restricted to neurons. On Day 7, 752 genes were upregulated and 690 downregulated across all cell types, with 22.3% of upregulated genes in neuronal populations enriched in pain-related pathways from GO BP analysis, including neuroimmune activation, oxidative stress, ion channel modulation, and apoptosis. By Day 21, transcription was broadly suppressed in all cell types, with 1,223 genes downregulated and 178 upregulated. Notably, 19.9% of upregulated neuronal genes remained linked to pain-related pathways, indicating persistent maladaptive signaling and a failure to restore to normal gene expression. Comparative analysis with published transection datasets highlighted mechanistic differences between pain models. Atf3 upregulation was transient in

CCI but sustained in transection, supporting an injury-specific transcriptional response. Gene expression in CCI neurons included uniquely upregulated transcripts (Dgkb, Nrg3, Grm7) which were absent or minimally changed in transection datasets. Principal component and pathway analyses revealed that by Day 21, transcriptional signatures in select nociceptive subtypes diverged markedly from others, indicating subtype-specific transcriptional reprogramming. A mechanosensitive nociceptor subtype exhibited high dysregulation scores with upregulated genes linked to excitatory signaling and neuronal sensitization. Another c-fiber subtype showed enrichment of genes activating a tyrosine kinase pathway, implicating receptor-mediated neuroinflammatory and synaptic remodeling processes. Our findings suggest that failure to resolve injury-induced transcriptional programs in distinct sensory neuron subtypes likely drives ongoing peripheral sensitization, promoting chronic pain states. This work provides mechanistic insight into the transcriptional basis of CCI-induced pain chronification to help in identifying novel candidate genes as potential non-opioid therapeutic targets.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Program #/Poster #: PSTR167.03/K7

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH/NINDS grants NIH NS045594 and NS135157

Title: Targeted Sympathetic Denervation of the Dorsal Root Ganglion Induces Immediate Cell Death and Sensory-Motor Dysfunction, Rescued by Norepinephrine Supplementation

Authors: *D. DENARDIN LÜCKEMEYER¹, W. XIE², A. PRUDENTE², L. UNDERWOOD², J. A. STRONG², T. BERTA³, J.-M. ZHANG²;

¹Univ. of Cincinnati, Cincinnati, OH; ²Dept Anesthesiol., ³Anesthesiol., Univ. of Cincinnati, Col. of Med., Cincinnati, OH

Abstract: The sympathetic nervous system is essential for regulating inflammation, vascular tone, and sensory neuron excitability and is increasingly implicated in chronic pain. After peripheral nerve injury, sympathetic fibers sprout into sensory ganglia, contributing to sympathetically maintained pain. However, the role of sympathetic innervation in the survival and function of primary sensory neurons under normal conditions remains unclear. To investigate this, we performed targeted sympathetic denervation (TSD) by transecting lumbar postganglionic grey rami innervating L3 and L4 dorsal root ganglia (DRG). TSD induced sensory neuron death in both rats and mice immediately after the surgical sympathectomy. Behavioral testing demonstrated reduced mechanical and thermal sensitivity on the ipsilateral hindpaw measured by pinprick, alligator clip test and Hargreaves. Changes in mechanical

sensitivity were supported by the findings from in vivo calcium imaging, which revealed significantly fewer DRG neurons responding to mechanical stimulation of the hindpaws post-TSD on postoperative days 1, 3, 7, and 28. TSD also reduced sensory projections to the ipsilateral spinal dorsal horn and altered molecular profiles in the DRG, including upregulation of apoptotic proteins and downregulation of anti-apoptotic proteins. Intraplantar capsaicin injection evoked fewer paw flinches in TSD mice, likely due to loss of CGRP+ nociceptive neurons. Interestingly, TSD-induced cell death was prevented by continuous supplementation of NE via osmotic pumps beginning at the time of surgery and continued for at least 2 days. These findings demonstrate that sympathetic innervation supports adult sensory neuron survival via a NE-dependent mechanism and that its disruption induces cell loss and irreversible sensory dysfunction.

Disclosures: **D. Denardin Lückemeyer:** None. **W. Xie:** None. **A. Prudente:** None. **L. Underwood:** None. **J.A. Strong:** None. **T. Berta:** None. **J. Zhang:** None.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.04/K8

Topic: E.01. Somatosensation – Pain and Itch

Title: Gabaergic dysfunction and spinal neuroinflammation are involved in the development of neuropathic pain in a model of hemiparkinsonism.

Authors: ***S. A. MEJIA AMADOR**, F. J. PAZ, J. A. AVALOS, J. RAYA TAFOYA, R. DELGADO-LEZAMA, G. B. FLORAN;
Physiology, Biophysics and Neurosciences, Ctr. for Res. and Advanced Studies of the Natl. Polytechnic Inst. (CINVESTAV-IPN), Mexico, Mexico

Abstract: In addition to classic motor disorders, Parkinson's disease includes non-motor symptoms, including pain. This can be secondary to motor alterations or their treatment; however, up to 85% of patients also have neuropathic pain. This type of pain is frequently underdiagnosed and poorly treated due to limited knowledge about the pathophysiological mechanisms that generate it, significantly affecting the quality of life of the patient and their caregivers. In models of neuropathic pain, such as peripheral nerve ligation, it has been shown that extrasynaptic GABA A receptors can become pronociceptive by inducing depolarization rather than hyperpolarization in sensory neurons of the spinal dorsal horn (laminae I-III), a process mediated by microglial activation. In this study, we validated the presence of allodynia and hyperalgesia—clinical signs of neuropathic pain—in male Wistar rats with unilateral lesions of the dorsolateral striatum induced by 6-hydroxydopamine (6-OHDA). Both signs appear bilaterally and progressively from the first week post-injury, persisting for at least one month, suggesting the involvement of systemic mechanisms in addition to the dopaminergic deficit. To evaluate the participation of extrasynaptic GABA A receptors, furosemide (receptor inverse

agonist with α_6 subunit) was administered intrathecally, with a significant reversal of allodynia and hyperalgesia, suggesting a pro-nociceptive role of these receptors in this model. Additionally, by immunofluorescence, we observed a bilateral decrease in the expression of the KCC2 cotransporter in the dorsal and ventral horn of the spinal cord, evident from the first week and significant from the second-week post-injury. Active microgliosis was also identified, characterized by increased Iba1+ cells and morphological changes compatible with activation (from branched to hypertrophied). These findings support the hypothesis that mechanisms previously described in other models of neuropathic pain—such as neuroinflammation and GABA-mediated depolarization—are also involved in the development of neuropathic pain in the context of hemiparkinsonism.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

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Program #/Poster #: PSTR167.05/K9

Topic: E.01. Somatosensation – Pain and Itch

Support: MSMT, INTER-EXCELLENCE, INTER-ACTION, LUAUS25275

Title: Parallel multicomponent analysis identifies compartmentalized biomarkers in chemotherapy induced peripheral neuropathy.

Authors: A. BHATTACHARYYA, C. VASCONCELOS, D. SPICAROVA, *J. PALECEK; Inst. of Physiology, Acad. of Sci. of the Czech Republic, Praha, Czech Republic

Abstract: Chemotherapy induced peripheral neuropathy (CIPN) and neuropathic pain affects a significant proportion of patients. Available treatments are often ineffective with serious side effects. Extensive scientific research is underway to identify the molecular mechanisms and pathways involved in CIPN, with the goal of developing targeted therapies that could prevent it or alleviate the deleterious side effects. Here we used Bortezomib (BTZ) - a chemotherapy agent widely used in hematological malignancies as model for CIPN and conducted a biomarker search using parallel proteomic and metabolomic analysis of three different compartments: serum, cerebrospinal fluid (CSF) and serum derived-exosomes of both control and BTZ-treated groups. Adult male Wistar rats (200g) were treated with BTZ (0.2 mg/kg i.p., 5x 1-day apart, n=4) to induce CIPN and control group (CON, n=4) with saline. Behavioral test with electronic Von-frey filament confirmed development of mechanical allodynia within 14 days (CON 70.7 ± 0.2 SEM vs BTZ = 59.0 ± 0.1 SEM; paw withdrawal threshold, grams) that remained stable beyond 21 days (BTZ 58.4 ± 0.2 SEM). On day 21 serum and cerebrospinal fluid (CSF) from CON and BTZ animals were collected and stored at -80°C . Serum aliquots were processed via centrifugation and size-exclusion chromatography to isolate exosomes. Metabolomic analysis

used a combination of reversed-phase, hydrophilic interaction chromatography and electrospray ionization mass spectrometry to characterize both polar and lipid metabolites from the same sample. Proteomic analysis was performed in Orbitrap mass spectrometer coupled to nano UHPLC liquid chromatograph. Comparison of metabolomic profiles of the three compartments from the BTZ and CON animals showed significant ($\text{Log}_{10} p \leq 0.1$, $\text{Log}_2 \text{FC} \geq 1.5$) changes of the analyzed metabolites in these compartments, that were unique and non-overlapping. As an example after treatment with BTZ, 5-aminovaleric acid betaine was significantly increased in serum, whereas pyridoxal (pyridoxal phosphate) and Glutamic acid-Glutamine (Glu-Gln) increased in serum- exosomes and CSF respectively. These differentially expressed compounds play an important role in amino-acid metabolism, mitochondrial beta-oxidation pathway, increased oxidative stress and CNS damage. Detailed analysis of the samples will be provided. Our parallel multicomponent analysis provides an unique view of the metabolomic and proteomic changes in different compartments during CIPN. Obtained data may suggest new potential CIPN and neuropathic pain biomarkers and provide a better insight into the underlying mechanisms. Supported by MSMT project LUAUS25275

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Program #/Poster #: PSTR167.06/K10

Topic: E.01. Somatosensation – Pain and Itch

Support: NS045594
NS135157

Title: Cluster-firing dorsal root ganglion neurons are hyperexcitable with increased sensitivity to pericyte activation in mice with spared nerve injury

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Abstract: Clustered firings of sensory neurons, a newly observed phenomenon in the dorsal root ganglion (DRG), are associated with episodic neuropathic spontaneous pain in mice with peripheral nerve injury. We recently reported that clustered firings are evoked by vascular movements within the injured DRG and that blocking angiogenesis with an anti-VEGF monoclonal antibody effectively reduces neuropathic spontaneous pain and clustered firing. Given that pericytes around endothelial cells of blood vessels contribute to angiogenesis, we examined morphological and functional changes in the pericytes of the DRG in mice with spared

nerve injury (SNI). Immunostaining of the DRG on postoperative days 21-28 demonstrated an increased number of pericytes. This was confirmed using PDGFR β -Ai14 tdTomato reporter mice. Ex vivo calcium imaging showed that topical application of the pericyte activator U46619 (30 μ M) evoked multiple cluster firings. We further characterized the electrophysiological properties of the DRG neurons involved in cluster firing. Sharp-electrode intracellular recordings were performed on U46619-responding neurons. Results indicated that these neurons had higher excitability in both large- and small/medium-sized groups, as evidenced by more depolarized resting membrane potentials and decreased rheobase. Among the DRG neurons involved in clustered firing, over 50% had diameters between 30-40 μ m; approximately 30% were either very small (<20 μ m) or very large (>45 μ m). Our findings suggest that increased numbers of pericytes contribute to vascular response-evoked clustered firing after nerve injury, and that the cluster-firing neurons exhibit hyperexcitability.

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Poster

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Program #/Poster #: PSTR167.07/K11

Topic: E.01. Somatosensation – Pain and Itch

Title: Interaction of the opioidergic, dopaminergic, cholinergic, and antioxidant systems in the antihyperalgesic effect of *Rhus virens* in streptozotocin-induced diabetic rats

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Abstract: Diabetic peripheral neuropathy (DPN) is a frequent complication of diabetes mellitus that often leads to the development of chronic pain and hyperalgesia. Greater scientific efforts have been made to find new molecules with biological activity favorable to health. Thus, the objective of this work was to evaluate the antihyperalgesic effect of *Rhus virens* in DPN and to identify the possible mechanisms of action involved. A methanol extract from the aerial parts of *R. virens* (RvM) was obtained and 1,2,3,4,6-penta-O-galloyl-glucopyranose (PGG) was isolated from it. Streptozotocin-induced experimental diabetes was used to produce DPN. Oral administration of RvM (10-100 mg/kg) and PGG (10 mg/kg) were tested in the formalin test to measure secondary hyperalgesia. Additionally, naloxone (10 mg/kg), glibenclamide (10 mg/kg), L-NAME (10 mg/kg), haloperidol (1 mg/kg), and atropine (1 mg/kg) were used subcutaneously to determine the interaction of RvM with different pain pathways. Lastly, the sciatic nerve and spinal cord were obtained to determine protein carbonylation, lipid peroxidation, and superoxide-dismutase activity as markers of oxidative stress. The administration of RvM and PGG decreased the hyperalgesic behavior in diabetic rats, also, the opioidergic, dopaminergic, and cholinergic

systems of analgesia were determined to have a role in the RvM effect. Additionally, the oxidative stress markers were improved in the group administered with RvM. In conclusion, *R. virens* produces an antihyperalgesic effect through opioidergic, dopaminergic, cholinergic, and antioxidant mechanisms. Also, the PGG produced an antihyperalgesic effect in diabetic rodents. Hence, *R. virens* derivatives could be considered to treat complications of diabetes mellitus.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Program #/Poster #: PSTR167.08/K12

Topic: E.01. Somatosensation – Pain and Itch

Support: PAPIIT Grant No. IN227225

Title: Peripheral antinociception induced by local administration of oxytocin receptor biased agonists in female and male rats

Authors: *M. DÍAZ FUENTES¹, A. GONZÁLEZ-HERNÁNDEZ², A. ESPINOSA DE LOS MONTEROS ZÚÑIGA³, G. MARTINEZ-LORENZANA⁴, M. CONDES-LARA⁵;

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Abstract: Persistent pain can arise from peripheral nerve fibers or tissue damage and is associated with plastic changes in peripheral and central nociceptive circuits. These changes include peripheral and central sensitization, involving neuronal and glial—particularly microglial—modulation. These mechanisms exhibit sexual dimorphism, with females being more susceptible to pain conditions. Thus, finding molecules capable of diminishing sensitization despite this sexual dimorphism remains a topic that deserves attention. Oxytocin (OXT) has antinociceptive effects in various pain models by activating the oxytocin receptor (OTR). This receptor could be biased and activated by carbetocin or atosiban, recruiting intracellular pathways related to Gq or Gi proteins, respectively. However, whether peripheral administration of biased OTR agonists can prevent peripheral nociceptive sensitization and influence spinal microglial activity remains unclear. This study evaluated the antinociceptive effect of atosiban in Wistar rats sensitized with subcutaneous 1 % formalin injection. Peripheral pretreatment with atosiban reversed the persistent mechanical hypersensitivity induced by formalin. Interestingly, males were more sensitive to the atosiban-induced antinociception than females (1 vs. 10 µg/50 µl). In both cases, the antinociception elicited by atosiban was blocked by L-368,899 (OTR antagonist). Furthermore, pretreatment with SR 49059 (V1AR antagonist) seems to diminish the atosiban-induced antinociception in females, whereas, in males, it seems to enhance the atosiban effect. Epifluorescence imaging of lumbar spinal cord sections revealed

microglial morphological changes associated with atosiban treatment.

Our data show that peripheral administration of atosiban, a biased OTR-Gi agonist, blocked the development of mechanical hypersensitivity induced by formalin. There is also a potential sexually dimorphic crosstalk between the OTR and V1AR signaling. Moreover, morphological changes in spinal microglia correlate with treatment and suggest a potential role of glial modulation in the observed effects.

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Poster

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Program #/Poster #: PSTR167.09/K13

Topic: E.01. Somatosensation – Pain and Itch

Support: NS128543

Title: A novel lipidated 14-3-3 inhibitor peptide attenuates chronic pain behavior in mice

Authors: B. NGUYEN¹, R. G. POWELL², *A. BHATTACHARJEE¹;

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Abstract: 14-3-3 proteins are involved in the function and localization of various ion channels. They directly interact with channels, influencing gating properties and/or their trafficking. We designed a novel small, lipidated 14-3-3 inhibitor peptide based on difopein. Difopein is a highly specific and competitive inhibitor of 14-3-3 proteins but is not cell permeable. Small lipidated peptides however are cell penetrable and because they are membrane de-limited, they can specifically target membrane proteins and their interactors. Treating cultured dorsal root ganglion neurons with this novel lipidated 14-3-3 inhibitor peptide caused an increased potassium current density and a rightward shift in peak sodium current density compared to scrambled peptide control. Furthermore, the peptide inhibited signaling-dependent neuronal hyperexcitability. We then tested this peptide in multiple pain models. The lipidated 14-3-3 inhibitor peptide significantly decreased acute and chronic inflammatory pain and neuropathic pain behaviors in mice after local application. Like the other small lipidated peptides we have previously reported on, the lipidated 14-3-3 inhibitor peptide produced weeks of reduced pain behaviors identifying it as a putative local, long-lasting analgesic.

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Poster

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant NS045594
NINDS Grant NS135157

Title: Selective Knockout of the Glucocorticoid Receptors in Nav1.8 Neurons Attenuates Neuropathic Pain by Impairing Nerve Regeneration

Authors: *B. DA SILVA SOLEY, D. DENARDIN LÜCKEMEYER, W. XIE, J.-M. ZHANG;
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Abstract: Glucocorticoid receptors (GR) are widely expressed in both neuronal and non-neuronal cells in the dorsal root ganglion (DRG). While GRs in non-neuronal cells such as Schwann cells, are known to regulate nerve regeneration, their role in sensory neurons, especially in Nav1.8 neurons, remains unclear. Previous studies in nerve injury pain models demonstrated that persistent neuropathic pain is driven by nerve regeneration processes, and that disrupting regeneration can alleviate pain. In this study, we investigated the functional role of GRs in nociceptive DRG neurons by selectively knocking out GR in Nav1.8-expressing neurons in mice subjected to sciatic nerve crush injury. Behavioral assessments revealed that GR deletion increased mechanical withdrawal thresholds and prolonged paw withdrawal latencies in the von Frey and Hargreaves tests, respectively, indicating reduced mechanical sensitivity and altered thermal nociception. Additionally, at 4 days post-injury, GR knockout animals exhibited elevated mineralocorticoid receptor (MR) mRNA levels and upregulation of inflammation-related genes, suggesting an imbalance in MR/GR-mediated signaling pathways. Morphological analyses demonstrated decreased axonal regeneration and delayed reinnervation of the hindpaw skin in animals with GR knockout. These findings suggest that GR plays a crucial role in modulating the inflammatory environment to facilitate axonal regrowth and nerve repair following peripheral nerve injuries. Targeting GR in Nav1.8 neurons may offer a promising therapeutic strategy for neuropathic pain management.

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Poster

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Program #/Poster #: PSTR167.11/K15

Topic: E.01. Somatosensation – Pain and Itch

Title: Ptdp-1170, a peripherally restricted cannabinoid receptor agonist, attenuated oral cancer-induced nociception without catatonic effects

Authors: *N. H.-T. HUU-TU^{1,2}, Y. Mulpuri³, K. L. Whyland⁵, R. Patil⁶, Y. Kitaoka⁵, Z. Li⁷, A. M. Spokoyny⁸, A. C. Phung⁹, W. Paquette¹³, E. Cramer¹⁴, R. Lewis¹⁴, E. Freeman¹⁴, P. R. O'Neill¹⁵, C. M. Cahill¹⁰, G. Elezi¹¹, J. Whitelegge¹², V. John¹⁶, J. J. Campagna¹⁷, H. Seltzman¹⁸, I. Spigelman¹⁹, B. L. Schmidt⁴;

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Abstract: Although cannabinoids can alleviate cancer pain, their clinical utility is limited due to incomplete pain relief and central nervous system (CNS)-mediated side effects, including psychotropic and behavioral effects. In this study, we evaluated novel synthetic peripherally restricted cannabinoid receptor agonists (PRCBs), identified from a series of compounds selected for target specificity, peripheral selectivity, and in vivo efficacy, in a murine model of oral cancer pain. We synthesized PTDP-1170 and compared it with two reference PRCBs agonists, AZD1940 and PrNMI, which were obtained from a commercial vendor. To minimize CNS penetration, PTDP-1170 was designed with a high aqueous solubility (50 μ M) and efflux ratio (18.7), EC₅₀ = 4.8 nM at human CB1 receptors, as well as Ctox 50% = 28 μ M (Promega MultiTox-Fluor Multiplex Cytotoxicity Assay). Oral cancer nociception was induced in mice (8 weeks old, C57BL/6J male mice, Cat.# 000664, Jackson Laboratories, Bar Harbor. N=5 mice/group) by injecting conditioned media collected from a human oral squamous carcinoma cell line (HSC-3, Cat.# 0623, JCRB, Japan) into the middle part of the tongue. Oral cancer nociception and the analgesic efficacy of the three PRCBs, were assessed using a series of von Frey fibers to measure facial nociception scores at 1-, 3-, 4-, 5-, 6-, 12-, and 24 hours after cancer supernatant injection into the mouse tongue. PRCB treatments were given 2 hours after the cancer supernatant injection. CNS side effects of PRCBs were evaluated by an open-field assay measuring catatonia, including ambulation time, moving speed, and track length at 2 hours post-treatment. All drugs were dissolved in 1:64 DMSO in 25% sweet, condensed milk and administered via intragastric gavage. We found that AZD1940 and PrNMI partially reduced cancer supernatant-induced nociception in the tongue (58.97% and 43.28% pain reduction at 2 hours post-treatment, respectively). PrNMI, but not AZD1940, induced catatonia, which is a central effect. Our newly synthesized PTDP-1170 nearly abolished cancer supernatant-induced nociception in the tongue [97.18% pain reduction at 2 hours after treatment, 1.29 ± 0.15 versus 1.25 ± 0.09] without eliciting central catatonic effects. PTDP-1170, a peripherally restricted cannabinoid receptor agonist, provides superior cancer pain relief than the existing PRCBs while

avoiding central effects, making it a promising therapeutic candidate for treating oral cancer pain.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Title: Resveratrol alleviates paclitaxel-induced peripheral neuropathy by modulating oxidative stress

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Abstract: Chemotherapy-induced peripheral neuropathy (CIPN) is a major dose-limiting side effect of cancer treatment, characterized by sensory disturbances, chronic pain, and motor dysfunction. Paclitaxel, a widely used chemotherapeutic agent, induces severe CIPN by causing oxidative stress, mitochondrial dysfunction, and peripheral nerve demyelination. Conventional analgesics like gabapentin and pregabalin are frequently prescribed for CIPN, but its clinical efficacy is inconsistent. Resveratrol, a natural polyphenol, exerts neuroprotective effects through its antioxidant and anti-inflammatory properties and helps maintain mitochondrial homeostasis and redox balance. This study evaluated the potential of resveratrol to attenuate pain and peripheral nerve damage in a mouse model of paclitaxel-injected CIPN and the underlying mechanisms.

CIPN was induced in mice by intraperitoneal injection of paclitaxel. Resveratrol was administered daily via intraperitoneal injection from post-injection day (PID) 7 to 13. Behavioral assessment was conducted using von Frey filaments to evaluate mechanical hypersensitivity. On PID13, dorsal root ganglia (DRG), sural nerves, and plantar skin were collected for molecular and histological analysis. Western blot was performed to measure the expression of oxidative

stress-related proteins (AMPK, PGC-1 α , SOD2) in the DRG and myelin-associated proteins (MBP, PMP22, MPZ) in the sural nerve. Dihydroethidium (DHE) staining was used to detect the levels of reactive oxygen species (ROS) in the DRG. Transmission electron microscopy (TEM) was conducted to observe ultrastructural alterations in the sural nerve. Intraepidermal nerve fiber (IENF) density was also assessed in hindpaw skin.

Resveratrol treatment significantly attenuated mechanical hypersensitivity. It also reduced oxidative stress in the DRG, activated the AMPK-PGC-1 α pathway and upregulated SOD2 expression. Resveratrol restored myelin protein levels and structural integrity in the sural nerve. TEM revealed reduced demyelination and axonal degeneration, while IENF analysis showed improved preservation of epidermal nerve fibers.

These findings demonstrate that resveratrol alleviates CIPN by reducing oxidative stress and peripheral nerve damages induced by paclitaxel. Our results suggest that resveratrol may serve as a potential therapeutic strategy for managing CIPN.

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Poster

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH NIAMS R01AR079713

Title: Exogenous Artemin Causes Chronic Pain Hypersensitivity and Originates from Subchondral Bone in OA Models

Authors: *A. VIGNESHWAR^{1,5,6,7}, A. GUPTA^{2,5,6}, D. LASCELLES^{3,5,8,9,10}, S. K. MISHRA^{4,6,8,7},

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Abstract: Clinical Osteoarthritis (OA) characterized by increased pain and reduced mobility, affects a large proportion of the population and severely impairs quality of life. Recently, we identified that artemin (ARTN), a glial-derived neurotrophic growth factor, was increased in dogs, cats, and humans with naturally occurring OA-pain. In dogs, specifically, we demonstrated a significant correlation between increased artemin and pain, a finding further supported by the upregulation of its receptor, GFR α 3, in sensory neurons. Moreover, sequestering ARTN reduced

pain hypersensitivity and limb-use in rodent OA models. Here, we extend these findings by evaluating the systemic effects of artemin on pain hypersensitivity and identifying its source in joints.

To understand the role of artemin (ARTN) in osteoarthritis (OA) pain, we administered ARTN (600 ng) intraperitoneally (i.p.) in naïve mice. We then measured their sensitivity to mechanical, heat, and cold stimuli for 42 days. ARTN-injected mice showed significantly increased thermal sensitivity at 4 hours, with a 43% reduction in heat response latency and a 34% decrease for cold. This heightened sensitivity was sustained at 24 hours (49% heat and 36% cold) and up to 42 days (41% heat and 38% cold). Mechanical hypersensitivity also developed, showing a 51% decrease in response at 24 hours injection, and was sustained up to 42 days (65% decrease). Next, to examine if ARTN-induced pain hypersensitivity is mediated via its receptor, we locally administered ARTN or saline in the hind-paw in wild-type and GFRa3 mutant mice. ARTN produced dose-dependent thermal (48-68% heat; 35-39% cold) and mechanical (39%) hypersensitivity in wild-type mice but was absent in mutant mice. To pinpoint the source of ARTN, we analyzed *Artn* gene expression in various OA models. These included chemical (monoiodoacetate, MIA), surgical (destabilization of the medial meniscus, DMM) murine stifle OA models, and naturally occurring pet dog hip OA (subchondral bone and synovial tissues). We found significantly increased *Artn* in proximal tibial subchondral bone in both MIA and DMM mice (~5 fold). Additionally, *Artn* was significantly increased in distal femoral subchondral bone (~2.3 fold) and synovium (~3 fold) of MIA mice. Similarly, *Artn* was significantly increased ~17 fold in proximal femoral subchondral bone of canine hip OA.

Our work suggests that systemic ARTN is sufficient to drive long-term pain hypersensitivity and implicates subchondral bone as a major source of ARTN in OA-pain. Future studies will assess joint-level protein expression of ARTN and the mechanisms underlying ARTN-induced chronic sensitization.

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Poster

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Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R61NS133264

Title: Behavioral characterization of a rat model of chronic discogenic low back pain

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Abstract: Low back pain associated with disc degeneration is a leading cause of chronic pain and has a substantial economic impact in the United States. Treatments for discogenic low back pain exhibit poor long-term efficacy highlighting an important unmet medical need. Efforts to improve pain management are hampered by limited knowledge of the mechanisms underlying low back pain. Improving our understanding of the mechanisms driving this chronic pain is hampered by a lack of well-characterized and validated preclinical models. Thus, we are examining the time-course of pain-like behaviors in male and female rats in a discogenic low back pain model with the goal of replicating this model across two independent laboratories. To model discogenic low back pain, male and female rats were injured by lumbar puncture and scraping of the L5-L6 intervertebral disc. In the sham animals, discs are exposed without any puncture or scrape. We evaluated multiple behavioral measures including well characterized measures of pressure algometry and grip strength to examine deep pressure hypersensitivity and axial stretch induced pain. Consistent with prior studies, rats with disc injury demonstrated decreased mechanical thresholds to pressure on the dorsal surface of the L5/L6 lumbar junction as well as diminished grip strength compared to shams by 12 weeks post-injury. These observations indicate that this model of low back pain is reproducible across 2 independent laboratories.

Disclosures: A. Del Greco: None. G.C. Allison: None. E. Reddick: None. S.M. Caparaso: None. P. Caradonna: None. R. Wachs: None. T.E. King: None.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.15/L3

Topic: E.01. Somatosensation – Pain and Itch

Support: NIGMS R16GM153601
NIGMS 5P30GM145497

Title: Sex differences in emergence of nerve injury and ongoing joint pain in a mouse model of knee joint arthritis pain

Authors: M. MUETH¹, A. DEL GRECO², P. CARADONNA², B. J. HARRISON², *T. E. KING²;

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Abstract: Joint pain is heterogeneous, categorized as intermittent pain with joint use that dissipates with joint rest or constant joint pain that fails to abate with rest. Females report more severe joint pain compared to males. A murine model of arthritis knee joint pain was used to examine the hypotheses that constant joint pain is associated with increased nerve injury and that females develop constant pain and nerve injury at earlier stages of arthritis compared to males. Monosodium iodoacetate (MIA) was injected into the intra-articular space of the knee joint of

male and female mice. Behavioral analysis was performed at 2 weeks post-injection followed by collection of dorsal root ganglia (DRG) for analyses of ATF3, a marker of nerve injury. Behavioral analysis included static weight asymmetry on an incapacitance meter, constant pain assessed by analgesia induced conditioned place preference, and behavioral and postural changes in freely moving mice through analysis of video using machine learning using the BlackBox platform. Dorsal root ganglia (DRG) were collected following behavioral testing and expression of ATF3 mRNA assessed using rt-qPCR and immunohistochemical analysis for co-localization with markers for CGRP and NF-200 assessing peptidergic and myelinated sensory fibers. A subset of animals received an injection of WGA-CF640 retrograde tracer into the tibialis anterior adjacent to the joint. Females and males showed weight asymmetry on the incapacitance meter. Females showed analgesia-induced CPP at a 5-fold lower dose compared to males. Principal component analysis shows different behavioral patterns between males and females, and between saline controls and MIA treated mice. Sex differences were evident in postures of male and female mice irrespective of saline or MIA treatment. Increased expression of activating transcription factor-3 (ATF3) mRNA was observed in DRGs of females and males that developed constant joint pain. Analysis of ATF3 in DRG from animals with WGA-CF640 tracer injected into the tibialis anterior muscle adjacent to the knee joint 7 days prior to collection demonstrated little overlap between ATF3 and retrograde label. Together, these data indicate that females show enhanced susceptibility to develop constant joint pain. ATF3 expression was observed in females treated with lower concentrations of MIA corresponding to development of analgesia-induced CPP indicating that nerve injury is a contributing factor to observed sex differences in the development of constant joint pain. In conclusion, females show enhanced susceptibility to constant joint pain and nerve injury.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.16/L4

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH/NIDCR R03DE030996.

Title: Fibronectin expression is associated with patient reported oral cancer pain

Authors: S. PATEL¹, S. NEEMCHARAN¹, L. ARBEX², N. HUU-TU², N. GHADIRIAN³, A. CALDERON-RIVERA⁴, K. GOMEZ^{5,4}, M. KHANNA³, R. KHANNA⁴, *A. BHATTACHARYA²;

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Abstract: Introduction. Oral cancer patients report severe pain while talking and chewing. Cancer resection cures pain, suggesting pain is initiated and maintained in the cancer microenvironment. Oral cancer pain is attributed to sensitization of primary afferent neurons by mediators released by the cancer microenvironment. We identified 40 overexpressed genes in patients with metastatic cancers who also reported high pain. The identified genes are enriched for functions in extracellular matrix organization, lymphangiogenesis and angiogenesis. Fibronectin (FN1), an extracellular matrix glycoprotein, was the most significantly up-regulated “pain and metastasis” gene. There are over 20 alternatively spliced human FN1 isoforms. The EDA isoform of fibronectin (Fn EDA) is expressed in pathological conditions including cancer, but not in normal adult tissues. Our goal is to evaluate whether Fn EDA is an oral cancer pain mediator. **Methods.** FN1 and Fn-EDA expression were evaluated by immunohistochemistry in tissue samples from patients, and in preclinical models. The nociceptive potential of Fn EDA, and impact of Fn EDA antagonism were analyzed in preclinical models. **Results.** Spatially distinct expression patterns were observed. FN1 was predominantly expressed in the stromal cells, whereas Fn-EDA was expressed in cancer cells and adjacent immune cells. FN1 and Fn-EDA expression correlated with high pain scores (stromal FN1 vs. pain, $r = 0.639$; cancer-cell Fn-EDA vs. pain, $r = 0.554$ respectively, $n = 10$ cases). FN1 and Fn-EDA expression was also spatially distinct in preclinical models of oral cancer pain. Injections of Fn-EDA recombinant protein evoked mechanical allodynia which was blocked with a Fn EDA function blocking antibody. Fn-EDA increased female mouse trigeminal ganglion (TG) neuronal excitability, which was prevented by Fn EDA antagonism. **Conclusions.** Our findings suggest FN1 and Fn-EDA overexpressed in painful and metastatic cancers are positive regulators of nociceptive signaling in oral cancer. Identification of Fn EDA as a novel oral cancer pain mediator will lay the foundation for clinical studies to assess targeting Fn EDA for attenuation of cancer pain.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Program #/Poster #: PSTR167.17/L5

Topic: E.01. Somatosensation – Pain and Itch

Support: R01AG047928 (JP)
the American Lebanese Syrian Associated Charities (ALSAC)

Title: High-resolution single-cell proteomic profiling of human dorsal root ganglion neurons in cancer-associated pain using lcn

Authors: *Y. JIAO¹, C.-Y. HO², J. WANG³, M. CHU⁴, J. PENG¹;

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Abstract: Abstract:

Cancer-associated pain affects approximately 30% of patients and is linked to the activity and sensitization of specific nociceptor subtypes in the dorsal root ganglion (DRG). However, effective treatments are still limited due to an incomplete understanding of the underlying mechanisms, particularly at the single-neuron level. Human DRG tissue has unique nociceptor subtypes absent in rodent models, providing a clinically relevant platform for pain research. We hypothesized that single-cell proteomic profiling of human DRG neurons could reveal key molecular mechanisms driving cancer-associated pain. Laser capture microdissection (LCM) enables the precise isolation of DRG neurons, and when combined with data-independent acquisition mass spectrometry (DIA-MS), allows for comprehensive molecular characterization. In this preliminary study, we developed an LCM-based workflow to capture single DRG neurons from fresh-frozen human tissue, followed by DIA-MS for proteomic analysis. DRG tissues from five cancer pain patients and three control individuals were sectioned and stained with the NeuN antibody. NeuN-positive neuronal somata (~50 µm in diameter) were isolated using LCM, with 12-15 neurons collected per case, totaling 109 neurons for analysis. Proteins were extracted, trypsin-digested, and analyzed by DIA-MS. On average, ~5,100 proteins were quantified per neuron, with 8,517 unique proteins found across all samples at a 1% FDR threshold. Among these, 100 of the proteins matched a curated list of 165 DRG neuron markers, confirming successful neuron isolation and enabling subtype classification. Differential expression analysis showed 221 proteins significantly altered in cancer pain neurons ($p < 0.05$; >2 SD). Preliminary bioinformatic analysis revealed dysregulation in immune and inflammatory pathways, ion channels, G protein-coupled receptors, nerve injury markers, and cell cycle regulators. In summary, this pilot study is the first high-resolution, single-neuron proteomic profiling of human DRG in cancer-associated pain. Our findings provide a molecular foundation for understanding nociceptor sensitization and show potential therapeutic targets.

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Poster**PSTR167: Peripheral Mechanisms of Persistent Pain**

Location: SDCC Halls B-H

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Program #/Poster #: PSTR167.18/L6

Topic: E.01. Somatosensation – Pain and Itch

Support: Department of Defense W81XWH-19-2-0037

Title: Peripheral signatures of chronic pain resolution in human sciatic nerve post-amputation

Authors: *F. C. DIAS¹, B. DARWISH¹, A. MOLLOY¹, S. JAYACHANDRAN¹, B. GOOLSBY¹, A. MCGINNIS², J. SU¹, M. FONSECA¹, A. ROBERTS¹, C. DONNELLY¹, T. VANDEVEN²;

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Abstract: Pain is a common consequence of injury, typically subsiding as healing occurs. However, in some cases, pain persists and transitions into chronic pain, a debilitating condition that significantly diminishes quality of life. Despite its prevalence, the mechanisms underlying the development of chronic pain remain poorly understood. In this study, we sought to identify molecular and cellular predictors of long-term pain outcomes in a cohort of service members who experienced traumatic battlefield amputations. Sciatic nerve samples were collected from each participant as they underwent definitive lower limb amputation revision surgery. Participants were classified as “resolvers” or “non-resolvers” based on pain outcomes, with non-resolvers defined as those reporting a numeric rating scale score of 3 or higher at any time point beyond three months post-surgery. Quantitative proteomic analysis was performed using LC-MS/MS, complemented by immunoprofiling of cytokines, chemokines, and vascular injury markers via the Meso Scale Discovery platform. Subsequent immunohistochemical assays were used to determine the localization of proteins which were differentially expressed between pain resolvers and non-resolvers. Unexpectedly, sciatic nerves from pain resolvers exhibited more robust inflammatory signatures relative to nerves from non-resolvers. Of the 55 analytes evaluated, several markers were enriched in nerve tissues of resolvers, including pro-inflammatory chemokines and vascular injury factors (CCL2, CCL11, CCL13, ICAM1, CCL22, TSLP) as well as IL-1RA. Expression of these markers was detected in many cell types, including endoneurial and epineurial fibroblasts, pro-inflammatory (M1-like) perivascular macrophages, and nearby vasculature within the sciatic nerve sheath. Ongoing work is leveraging pharmacologic and genetic knockout approaches to identify how at identifying how early activation of these innate immune signaling networks aids in long-term resolution of chronic neuropathic pain. Collectively, our work adds support to an evolving conceptual framework in which acute inflammation can augment long-term pain resolution.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

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Program #/Poster #: PSTR167.20/L7

Topic: E.01. Somatosensation – Pain and Itch

Support: NRF-2023R1A2C3002798
RS-2023-00302281
NRF-2021R1C1C2005440

Title: Glial-neuronal interaction drives sensitization of large sensory neurons in neuropathic pain: insight from multimodal analysis

Authors: J. CHO¹, Y. JOO¹, J.-Y. PARK¹, H. PARK¹, *H.-I. KIM²;

¹Gwangju Inst. of Sci. and Technol., Gwangju, Korea, Republic of; ²GIST, Gwangju, Korea, Republic of

Abstract: Peripheral nerve injury triggers complex cellular and molecular response in the dorsal root ganglia (DRG) and spinal cord, contributing to chronic neuropathic pain. Although somatosensory neurons (SSNs) and satellite glial cells (SGCs) are known to modulate neuronal excitability, the mechanisms of glial-neuronal interaction underlying the generation of neuropathic signals remain poorly understood. In this study, we investigated the pathological changes and intercellular interactions between SSNs and SGCs in DRG, and in rostrally connected to corresponding spinal cord following spinal nerve ligation (SNL). Immunohistochemical study revealed the significant upregulation of Iba1 and GFAP in DRG and ipsilateral dorsal horn. GFAP fluorescence was more pronounced around large sensory neuron, indicating the preferential gliotic reaction in this subset. Longitudinal fluorodeoxy-glucose microPET (FDG-micoPET) imaging showed the progressive increase in regional metabolism in the dorsal horn and in fasciculus gracilis, suggesting that A β fibers may contribute to the transmission of pathological signals involved in the development of allodynia. Transcriptomic analysis revealed that large SSNs showed upregulation of immediate-early genes (Fos, Atf3), inflammatory mediators (Cxcl1), and injury markers (Tac1). SGCs showed proliferation-related activation (Mki67, Gfap). NicheNet analysis identified several glial-derived factors (LAMA2, VEGFA, MIF, IL34, S100B) as potent modulators of neuronal gene expression. Large-diameter somatosensory neurons (SSNs) showed a greater upregulation of pain-associated differentially expressed genes (DEGs) compared to small SSNs, indicating selective sensitization of large SSNs by glial-derived signals, which may underlie mechanical allodynia. Collectively, our results highlight a glial-neuronal signaling network centered on large SSNs, with pathological signals converging at dorsal horn and dorsal column. These findings offer mechanistic insight and identify candidate pathway for therapeutic targeting in glial-neuronal interactions associated with mechanical allodynia.

Disclosures: J. Cho: None. Y. Joo: None. J. Park: None. H. Park: None. H. Kim: None.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

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Program #/Poster #: PSTR167.21/L8

Topic: E.01. Somatosensation – Pain and Itch

Support: NRF-2023R1A2C3002798
RS-2023-00302281
RS-2023-00302281

Title: Astrocytic GABA Synthesis and Neuronal KCC2 Downregulation Drive Tonic Excitation in Neuropathic Pain: A Single-Cell Transcriptomic Validation

Authors: J. CHO¹, Y. JOO¹, ***J.-Y. PARK**¹, M.-H. NAM², H. PARK¹, H.-I. KIM¹;
¹Gwangju Inst. of Sci. and Technol., Gwangju, Korea, Republic of; ²Brain Sci. Inst., KIST, Seoul, Korea, Republic of

Abstract: Neuropathic pain arises from complex glial-neuronal interactions following peripheral nerve injury. Our previous study demonstrated that tonic GABA release from reactive astrocytes via monoamine oxidase B (MAO-B) leads to pathological excitation of dorsal horn neurons through the downregulation of KCC2 (SLC12A5), contributing to mechanical allodynia and increased metabolic activity in the spinal cord. However, the cell-type-specific transcriptional alterations underlying this mechanism have remained poorly understood. To address this gap, we performed single-cell RNA sequencing of L5 spinal cord tissues from control and neuropathic pain model rats (spinal nerve ligation, SNL), focusing on neurons, astrocytes, and microglia. Differential gene expression and Gene Ontology (GO) enrichment analyses were conducted, with further visualization of GABAergic and gliotic markers. Astrocytes in the pain group showed significant astrocytic GABA synthesis pathway activation, with GAD1 showing substantial upregulation alongside robust GFAP expression and gliogenesis pathway enrichment. Neurons showed significant downregulation of Slc12a5 (KCC2), along with increased excitability and transcriptional stress. Microglia displayed classical pro-inflammatory activation, with enrichment of immune-related pathways. GO analysis of astrocytic DEGs revealed overrepresentation of neurotransmitter metabolic processes, while neuronal DEGs were enriched in response to stimulus and membrane depolarization. These findings reinforce and expand our prior mechanistic model by providing single-cell transcriptomic evidence for maladaptive astrocyte-to-neuron signaling. The combination of MAOB-driven GABA synthesis and KCC2 downregulation orchestrates a pathophysiological state of tonic excitation in dorsal horn neurons. This astrocyte-neuron interaction represents a key driver of neuropathic pain and a promising target for therapeutic intervention.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Topic: E.01. Somatosensation – Pain and Itch

Support: Uemura Fund UEMURA-2024-2
KAKENHI Grant-in-Aid for Scientific Research 25K12959

Title: Neutrophil accumulation and neutrophil elastase upregulation in the trigeminal ganglion following trigeminal nerve root compression contribute to the pathogenesis of orofacial allodynia

Authors: *Y. ZHOU, S. HITOMI, K. IWATA, M. SHINODA;
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Abstract: Trigeminal neuralgia is a neuropathic pain characterized by sudden and severe facial pain, primarily caused by compression of the trigeminal nerve root by surrounding blood vessels. However, the exact pain mechanisms remain unclear. Recent studies have reported that neutrophil infiltration into the dorsal root ganglia (DRG) contributes to chronic pain by sensitizing DRG neurons. Neutrophil elastase (ELA2) signaling through protease-activated receptor 2 (PAR2) in DRG neurons has been reported to induce pain hypersensitivity. This study aimed to elucidate the role of neutrophils in the trigeminal ganglion (TG) in the pathogenesis of orofacial allodynia following trigeminal nerve root compression (TNC). TNC was applied in 7-week-old male Sprague-Dawley rats (230~250 g, n=5~8 per group) by inserting a glass rod through the skull to continuously compress the left trigeminal nerve root (TNC group). In the sham group, a glass rod was inserted without compressing the trigeminal nerve root. Mechanical head-withdrawal threshold (MHWT) and grooming frequency to acetone stimuli were assessed in the left whisker pad skin. After TNC, MHWT was significantly decreased, and grooming frequency was increased. Activating transcription factor-3 (ATF-3) immunoreactivity in the TG neuron on post-treatment days 3 and 7 indicated TG neuronal injury induced by TNC. An increase in ELA2-immunoreactive (IR) cells in the trigeminal root on day 7 demonstrated neutrophils accumulation following TNC. Immunohistochemistry and western blotting were applied to investigate the expression of ELA2 in TG on day 7. ELA2-IR cells were observed in both groups, with a higher amount in the TNC group compared to the sham group. In addition, Fluoro-Gold (FG) was injected into the left whisker pad skin to label the TG neurons innervating the left whisker pad skin. Immunohistochemical analysis was conducted to examine the expression of PAR2, a receptor activated by ELA2, in TG neurons. FG-labeled PAR2-IR neurons were observed in the TG. Moreover, continuous administration of an ELA2 antagonist or a PAR2 antagonist into the TG until day 7 attenuated the decrease in MHWT and the increase in grooming frequency. These findings suggest that TNC induces TG neuronal injury and neutrophils accumulation in TG. The increased ELA2 released from the neutrophils likely activates PAR2 expressed in TG neurons, contributing to the development of orofacial allodynia.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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NRF of Korea (RS-2023-00304323).

Title: Igfbpl1 in drg nociceptors drives neuropathic pain and neuroimmune crosstalk via igf1r-perk signaling

Authors: *E. ACQUAH^{1,2}, A. SAKIB², Y. R. KIM³, S. OH⁴, E. CHUNG⁵;

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Abstract: Neuropathic pain arises from aberrant neuronal and immune responses following peripheral nerve injury. Recent studies highlight the role of growth factor signaling in chronic pain, yet the contribution of IGFBPL1—an IGF-binding protein-like molecule involved in modulating IGF bioavailability and signaling—remains unexplored. Here, we identify IGFBPL1 as a critical regulator of nociceptor sensitization and neuroimmune interactions within the dorsal root ganglia (DRG) following nerve injury. Using chronic constriction injury (CCI) and spared nerve injury (SNI) mouse models, we demonstrated that IGFBPL1 is predominantly expressed in A-fiber and C-fiber nociceptors in mouse DRG, where it activates phospho-ERK signaling pathway via the IGF1 receptor (IGF1R). Functional inhibition of IGFBPL1, using IGFBPL1 siRNA and neutralizing antibody, significantly and persistently alleviated neuropathic pain sensitivity (reduced mechanical and thermal hypersensitivity by 50% and 45% respectively for up to 6 weeks) and improved motor function in IGFBPL1 knockdown mice. Ex vivo electrophysiological recordings demonstrated decreased spontaneous and evoked firing in DRG neurons following IGFBPL1 blockade. Additionally, DRG tissues showed reduced macrophage (F4/80) infiltration and downregulation of inflammatory cytokines—IL-1 β , IL-6 and TNF- α , indicating IGFBPL1's role in neuronal sensitization and neuroimmune activation. Together, our findings establish IGFBPL1 as a novel regulator of neuropathic pain and a potential therapeutic target for translational strategies aimed at alleviating chronic neuropathic pain.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Program #/Poster #: PSTR167.24/L11

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant NS136108

Title: Sting-il-6 signaling in sensory neurons mediates cisplatin-induced neuropathic pain

Authors: *Y. SAHLLOUL¹, S. LEE², B. LIMA ADJAFRE³, A. PRUDENTE⁴, T. M. CUNHA⁵, T. BERTA²;

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Ribeirao Preto, Brazil

Abstract: Viral infections commonly cause temporary pain and discomfort. These infections can sometimes lead to persistent painful neuropathies, highlighting an important link between viral recognition mechanisms and neuropathic pain. Our previous research established that stimulator of interferon genes (STING) signaling activation in sensory neurons is crucial for viral recognition and pain processing. Notably, the chemotherapy agent cisplatin, known to cause painful neuropathy, triggers the release of mitochondrial DNA (mtDNA) and activates STING signaling in acute kidney injury. We therefore hypothesized that cisplatin-induced painful neuropathy occurs through STING signaling activation in sensory neurons. Our findings demonstrate that wild-type (WT) mice treated with cisplatin developed mechanical hypersensitivity, characteristic of neuropathic pain. This response was accompanied by increased cytosolic mtDNA levels and elevated expression of STING and pro-inflammatory cytokine interleukin 6 (IL-6) transcripts in dorsal root ganglia (DRGs), while type I interferon (IFNB1) remained unchanged. Consistent with these findings, conditional knockout mice lacking STING expression in nociceptive DRG neurons (Nav1.8-Cre;STING^{fl/fl}) showed reduced mechanical hypersensitivity after cisplatin exposure and failed to upregulate IL-6 in DRGs. Similarly, systemic administration of the STING antagonist C-176 attenuated mechanical hypersensitivity and normalized DRG IL-6 expression. Furthermore, IL-6-deficient mice exhibited the same phenotype as those with STING deletion or blockade, while loss of the interferon receptor (IFNAR) had no effect. These results confirm that STING operates through an IL-6-dependent downstream pathway after cisplatin exposure, which is independent of IFN signaling. Collectively, our findings reveal a novel mtDNA-STING-IL-6 signaling axis within sensory neurons that connects viral mechanisms to painful neuropathies, potentially offering new therapeutic targets.

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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

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Program #/Poster #: PSTR167.25/L12

Topic: E.01. Somatosensation – Pain and Itch

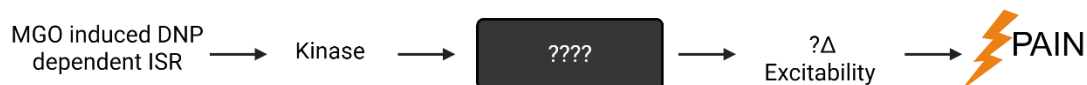
Support: R01DK134893

Title: Eukaryotic initiation factor 2A mediated integrated stress response drives nociceptor sensitization in diabetic neuropathic pain

Authors: *S. NAKISLI¹, A. NACKVI², B. WOODALL², M. CHATTOPADHYAY³, T. J. PRICE⁴, M. YOUSUF²;

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Abstract: Diabetic neuropathic pain (DNP) is a prevalent and poorly treated complication of diabetes. Methylglyoxal (MGO), a reactive glycolytic byproduct elevated in diabetic patients, has been implicated in DNP pathogenesis by activating the integrated stress response (ISR). The ISR regulates protein synthesis through phosphorylation of eukaryotic initiation factor 2 α (p-eIF2 α) and thereby promotes neuronal hyperexcitability and pain hypersensitivity. Eukaryotic initiation factor 2A (eIF2A) is hypothesized to influence non-canonical modes of translation during the ISR, yet its role in DNP remains poorly understood. We investigated the role eIF2A in mediating ISR-dependent nociceptor sensitization. Mechanical hypersensitivity was assessed using von Frey assays in both male and female mice. MGO induced robust mechanical hypersensitivity in wild-type animals, but this effect was absent in eIF2A knockout mice, implicating eIF2A as a mediator of ISR-driven pain. In human dorsal root ganglia (DRG) explants and primary cultured human nociceptors, MGO exposure increased expression of ISR markers, including p-eIF2 α , eIF2A and ATF4 protein. Electrophysiological recordings and calcium imaging revealed that MGO increased neuronal excitability in human and mouse nociceptors. All experimental design included biological replicates of n = 3-6/group, and sex as a biological variable. Appropriate controls were used in all conditions. These findings establish eIF2A as a functional effector in MGO-induced nociceptive behavior and demonstrate that ISR activation in peripheral sensory neurons contributes to MGO derived-DNP pathophysiology. Our results support targeting the ISR, and specifically eIF2A-dependent translation, as a novel therapeutic strategy for the treatment of diabetic neuropathic pain.



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Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.26/L13

Topic: E.01. Somatosensation – Pain and Itch

Support: Innovation and Technology Commission ITS/099/23FP
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Title: Serum Metabolomics Study of Mouse model of Diabetic Peripheral Neuropathy: A
Therapeutic Approach

Authors: *X. CHEN, Z. HE, N. AU, X. ZHU, C. H. MA;
Dept. of Neurosci., City Univ. of Hong Kong, Kowloon, Hong Kong

Abstract: Diabetic peripheral neuropathy (DPN) affects roughly 50% of diabetes patients and is one of the most prevalent complications of types 1 and 2 diabetes mellitus (T1D and T2D). It is primarily characterized by distal symmetric polyneuropathy, manifesting as sensory deficits, neuropathic pain, and motor impairment. Without effective treatment, these symptoms often progress to diabetic foot ulcers and lower-limb amputations, significantly impacting patient morbidity. While accumulating evidence links gut dysbiosis to metabolic and neurodegenerative disorders, its involvement in DPN remains poorly understood. In this study, we explored the role of gut microbiota in DPN pathogenesis and assessed fecal microbiota transplantation (FMT) as a potential therapeutic strategy. Using a streptozotocin (STZ)-induced T1D mouse model, we found that FMT significantly alleviated mechanical and cold allodynia. Multi-omics analysis- with the integration of 16S rRNA sequencing and untargeted serum metabolomics- revealed that FMT altered the profiling of both gut microbiota and serum metabolites. Notably, one identified metabolite demonstrated *in vitro* and *in vivo* efficacy in enhancing dorsal root ganglion neurite outgrowth and mitigating neuropathic pain in T1D mice. Our findings establish gut dysbiosis as a critical mediator of DPN, and highlight the neuroprotective role of metabolites. These results underscore the therapeutic potential of modulating the gut microbiota-metabolite axis to impede DPN progression. This study advances our understanding of gut-brain interactions in diabetes and opens new avenues for treating diabetes-associated complications, including DPN.

Disclosures: X. Chen: None. Z. He: None. N. Au: None. X. Zhu: None. C.H. Ma: None.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.27/L14

Topic: E.01. Somatosensation – Pain and Itch

Support: National Institute for Research of Metabolic and Cardiovascular Diseases (EXCELES, LX22NPO5104) - Funded by the European Union – Next Generation EU.

Title: Analysis of eicosanoids upregulated during development of diabetic neuropathic pain

Authors: *C. VASCONCELOS, A. BHATTACHARYYA, J. PALECEK;
Inst. of Physiology, Acad. of Sci. of the Czech Republic, Praha, Czech Republic

Abstract: Painful diabetic peripheral neuropathy (DPN) is a common complication of diabetes, contributing significantly to patient morbidity and healthcare burden. Conventional analgesics and glucose-lowering therapies offer only limited relief. As a result, research is focused on identifying molecular pathways linking diabetes associated metabolic disturbances, such as impaired energy metabolism, dyslipidemia, and systemic inflammation, to neuropathic pain development. A pre-clinical study using rat model of diabetes was used for parallel analysis of eicosanoids in three compartments: cerebrospinal fluid (CSF), serum and serum exosome fraction. Three groups (each n=16, 50% male-female, Wistar, 200 gm) were tested: rats on normal diet (CON), on high fat diet (HFD) and HFD with single dose of streptozotocin (HFD-STZ) (60 mg/Kg). Fasting glucose level, body weight and glucose tolerance test showed that HFD-STZ group developed diabetes like condition within 5 weeks of STZ injection. At the 8th week, CSF and serum aliquots were collected, serum exosome fraction isolated and kept in -80°C until analysis. A solid-phase extraction (SPE) of the non-polar fraction of the sample obtained by bi-phasic extraction was used to identify low-abundant eicosanoids. For eicosanoids detection, a quadrupole/linear ion trap mass spectrometer (SCIEX QTRAP 5500) operated in multiple reaction monitoring (MRM) coupled with a liquid chromatograph (Dionex/Thermo Ultimate 3000 RSLC) was used. Behavioral tests showed that mechanical allodynia developed preferentially in female HFD-STZ rats and was not present in CON and HFD rats. Our results showed highly differentiated distribution of eicosanoids between the three compartments studied and also based on the experimental group. Most robust changes of eicosanoids expression levels were in serum and were minimal in CSF. As an example, comparison of CON to HFD showed that 2-18:1-glycerol is significantly upregulated in serum of HFD whereas no eicosanoid was significantly upregulated in the CSF. Comparison of CON to HFD-STZ showed that 2-22:6 glycerol and 17-HDHA is upregulated in HFD-STZ serum whereas 1-18:1 and 2-18:1 glycerol are upregulated in the CSF. HFD and HFD-STZ group comparison showed upregulated 17-HDHA and 22:6 glycerol in the serum of HFD-STZ. Overall, our results indicate that upregulation of eicosanoids in specific fluid compartments are altered independently to each other during the development of painful diabetic neuropathy in animal models and may play an important role in the pathological processes. Supported CARDIA, LX22NPO5104 Next Generation EU.

Disclosures: C. Vasconcelos: None. A. Bhattacharyya: None. J. Palecek: None.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.28/L15

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R01NS131571

Title: Mitochondrial uncoupling drugs induce AMP kinase-dependent metabolic flexibility in a human dorsal root ganglion-derived neuronal cell line

Authors: J. J. AMES¹, E. ADDLESON², *D. C. MOLLIVER²;

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Abstract: Increasing evidence supports the involvement of sensory neuron metabolic remodeling in the transition from acute to chronic pain. Dorsal root ganglion (DRG) neurons show elevated glycolytic activity and reduced mitochondrial respiration in chronic pain models (the neuronal Warburg effect). We previously found that the mitochondrial uncoupling drug BAM15 acutely inhibits excitability in putative mouse nociceptors through activation of KATP channels and is anti-hyperalgesic in inflammatory and neuropathic pain models in vivo. Here, we examined signaling pathways activated by BAM15 in the human DRG-derived HD10.6 cell line. BAM15 increased mitochondrial respiration, as measured by Seahorse assay, by dose-dependently reversing inhibitory phosphorylation of pyruvate dehydrogenase (PDHA1), while suppressing mitochondrial hyperpolarization, which typically leads to enhanced production of reactive oxygen species. In addition, BAM15 significantly increased phosphorylation (activation) of AMP-activated protein kinase (AMPK) at T172, measured by western blot. These effects were blocked by co-treatment with the AMPK inhibitor dorsomorphin (40 μ M). AMPK is a central regulator of pathways promoting cellular energy production and has been reported to mitigate nociceptor hyperexcitability. The cancer drug pacritinib was identified in a published kinase screen as an inhibitor of LKB1; 40 μ M pacritinib suppressed BAM15-induced AMPK phosphorylation, indicating that the activation of AMPK by BAM15 is dependent on LKB1. Despite its mitochondrial uncoupling activity, BAM15 did not significantly reduce cellular ATP levels measured by luciferase assay. However, co-administration of dorsomorphin or pacritinib with BAM15 led to rapid ATP depletion, indicating an obligate role for AMPK in maintaining ATP levels in response to bioenergetic stress. Furthermore, dorsomorphin abolished BAM15-induced increases in respiration, implicating AMPK as a key mediator of BAM15-induced mitochondrial respiratory support. Ongoing experiments are examining the links between antinociceptive actions of uncoupling drugs such as BAM15, the uncoupling-induced regulation of metabolic flexibility by AMPK, and mechanisms of metabolic remodeling that occur in the transition from acute to chronic pain.

Disclosures: J.J. Ames: None. E. Addleson: None. D.C. Molliver: None.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.29/M1

Topic: E.01. Somatosensation – Pain and Itch

Support: F32NS138223
R37NS108278
R01NS070711

Title: Episodic pain in Fabry disease is mediated by a heat shock protein-TRPA1 axis.

Authors: *J. D. ENDERS^{1,2}, E. PRODOEHL², A. SRIRAM², C. L. STUCKY^{3,2};

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Abstract: Fabry disease is the most common lysosomal storage disorder, arising from loss of function mutations in *GLA* and subsequent accumulation of its substrate, globotriaosylceramide. Two-thirds of patients with Fabry disease suffer debilitating pain attacks triggered by exercise, fever, and exposure to environmental heat. These patients face an even greater risk of heat-related episodic pain in the face of global climate change. Almost nothing is known about the biological mechanisms underlying heat-induced pain crises in Fabry disease, and there is no preclinical model available to study Fabry pain crises. Here, we established the first model of heat-induced pain attacks in Fabry disease by exposing transgenic Fabry rats to environmental heat. Heat exposure precipitated robust mechanical hypersensitivity, closely matching temporal features reported by patients with Fabry disease. At the cellular level, heat exposure sensitized Fabry dorsal root ganglia (DRG) neurons to agonists for transient receptor potential cation channel A1 (TRPA1), but not TRPV1. The heat shock response, which normally confers heat-resilience, was impaired in Fabry disease, and we demonstrated that heat shock proteins (HSP70 and HSP90) regulate TRPA1. Strikingly, pharmacologically inhibiting HSP90 completely prevented cellular and behavioral sensitization by environmental heat in Fabry disease. Together, this work establishes the first model of episodic pain in Fabry disease, implicates the heat shock response in heat-evoked pain episodes, and identifies a novel heat shock protein-TRPA1 regulatory axis.

Disclosures: J.D. Enders: None. E. Prodoehl: None. A. Sriram: None. C.L. Stucky: None.

Poster

PSTR167: Peripheral Mechanisms of Persistent Pain

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR167.30/M2

Topic: E.01. Somatosensation – Pain and Itch

Title: The role of Netrin-4 in the DRG neurons under chronic pain after peripheral nerve injury

Authors: *N. YAMAWAKI, T. ITOKAZU, T. NAKANISHI, T. YAMASHITA;
Graduate School of Medicine, Osaka University, Osaka, Japan

Abstract: Peripheral nerve injury (PNI) due to surgery or trauma causes neuropathic pain. Despite its high prevalence, current treatments are not sufficient, and the underlying mechanisms remain unclear. We previously showed that Netrin-4-deficient rats exhibited reduced pain after PNI. It has been reported that Netrin-4 binds to Laminin- γ 1, a basal lamina component, and induces its disruption. These findings suggest that Netrin-4 may contribute to pain via basal lamina breakdown. In this study, we revealed that Netrin-4 is expressed in the dorsal root ganglion (DRG), which plays a key role in pain transmission. After PNI, the expression of Laminin- γ 1 in the DRG was reduced. Notably, administration of the Netrin-4 antibody alleviated this expression change. We also found that direct injection of a Netrin-4 antibody into the DRG produced an analgesic effect. These results suggest that targeting Netrin-4-Laminin- γ 1 interaction may represent a novel therapeutic strategy for neuropathic pain.

Disclosures: N. Yamawaki: None. T. Itokazu: None. T. Nakanishi: None. T. Yamashita: None.

Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.01/M3

Topic: E.02. Somatosensation – Touch

Support: NIH Grant U19 NS107466
NIH Grant U19 NS137920
BSF Grant 2024631
NIH Grant U24 EB028942

Title: The biomechanical link of touch to object position and encoding in the vibrissa system

Authors: *D. GOLOMB¹, R. LIU², P. YAO⁵, A. FASSIHI³, R. FARKASH⁶, K. SEVERSON⁷, D. H. O'CONNOR⁸, D. KLEINFELD⁴;

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³Physics, Univ. of California San Diego, San Diego, CA; ⁴Physics, Neurobio., Univ. of California San Diego, La Jolla, CA; ⁵Neurosci., UC San Diego, La Jolla, CA; ⁶Departments of Physiol. and Cell Biol., Ben Gurion Univ. of the Negev, Beer-Sheva, Israel; ⁷Brain and Cognitive Sci., MIT, Cambridge, MA; ⁸Zanvyl Krieger Mind/Brain Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Rodents sense their surroundings by palpating their vibrissae against objects, which leads to touch-induced forces on the vibrissa shaft that are converted to neuronal signals. How

are these forces, or the torques they induce, used to determine the location of touch within the plane of whisking? Torques, measured in terms of bending, are determined by the interaction between a vibrissa, the motor plant that encompasses the follicle that supports the vibrissa, the muscles that move the follicle, and an object. We quantify the mechanical cues and the neuronal responses in the trigeminal ganglion (TG) that enable animals to locate objects. First, we observe vibrissa touch and bending during behavioral experiments. We found that freely moving animals tend to tap an object at a "sweet spot", i.e., near the protracted part of the sweep and two-thirds of the distance from the base to the tip of a vibrissa. To analyze touch over the full range of motion, we used experiments on head-fixed rodents, computational modeling, and theoretical analysis. We find that animals continue to protract and bend their vibrissa after the initial contact, such that the duration of contact varies linearly with phase-in-the-whisk-cycle upon contact. The torque generated by touch is a monotonic function of both the point of contact on the shaft and the duration of contact. The computed slope of the bending torque as a function of the phase of initial contact fits experimental observations. Using an analytical theory, developed in the limit of slow and small-amplitude whisking, we derive a formula for the bending torque as a function of the radial and azimuthal object location. The formula accurately predicts contact location from encoded signals. It also explains why the bending torque increases first supra-linearly and then sub-linearly as the phase of initial contact decreases from π (contact at maximum protraction). Biophysically, vibrissae act like flexible and tightly- but not rigidly-clamped beams for most contacts. Functionally, mechanical signals from a single vibrissa, as well as the corresponding firing patterns of rapidly- and some slowly-adapting TG neurons, are sufficient to locate a point of contact in a plane.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.02/M4

Topic: E.02. Somatosensation – Touch

Support: EU Horizon 2020 Marie Skłodowska-Curie grant agreement No 860949

Title: From Vibrissae to Cortex: A Computational Model of Whisker-Based Sensory Signal Integration in the Ascending Somatosensory Pathway

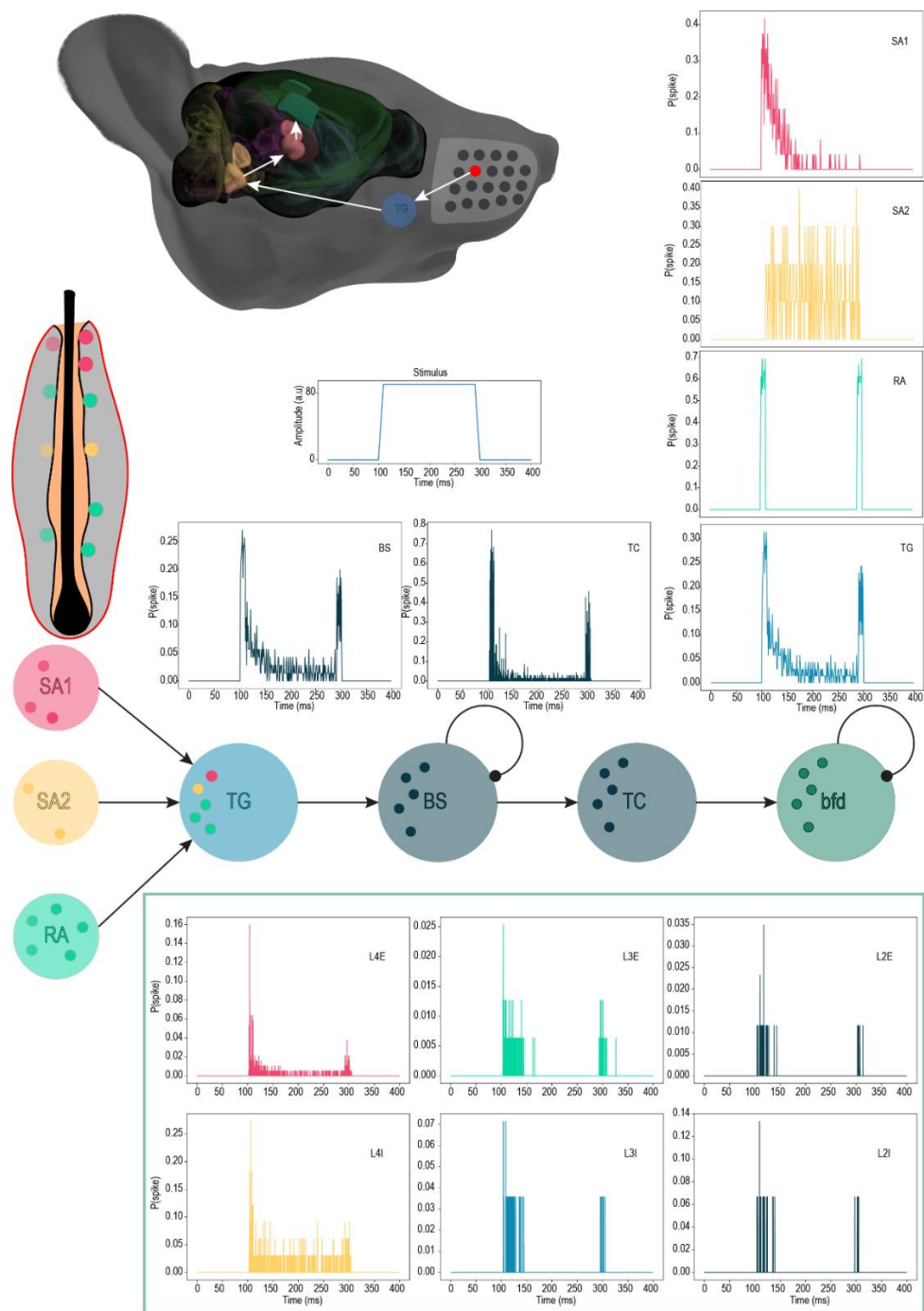
Authors: *N. RAULT¹, T. CELIKEL²;

¹Donders Inst. for Brain, Cognition and Behaviour, Radboud university, Nijmegen, Netherlands;

²Sch. of Psychology, Georgia Inst. of Technol., Atlanta, GA

Abstract: Extracting and integrating sensory information is crucial for interacting with our environment. While cortical processing of touch is heavily studied, the contributions of

subcortical structures in the ascending somatosensory pathway are often underestimated. We developed a computational model of the rodent whisker pathway, simulating signal transmission from a virtual whisker (WhiskIt) driving distinct mechanoreceptor populations (SA1, SA2, RA), through the trigeminal ganglion, brainstem, thalamus, and into interconnected excitatory and inhibitory populations within cortical layers (L4-L2). By applying a wide range of whisker stimuli (varying deflection direction, force, speed, location, and vibration frequency) and employing decoders alongside information-theoretic measures, we quantitatively assessed stimulus representation and information flow at each stage. Our results reveal significant subcortical processing. Information transfer, measured at both single-neuron and population levels, peaks sharply in the thalamus, coinciding with signal decorrelation, before declining notably in subsequent cortical layers. Similarly, decoding accuracy diminishes progressively through the cortical hierarchy compared to the thalamus. This strongly suggests the ascending pathway, particularly the thalamus, performs substantial integration and optimization, actively transforming signals rather than acting as simple relays. Consequently, the cortex may not aim solely for the highest fidelity stimulus representation but rather for features extracted through this subcortical refinement.



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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.03/M5

Topic: E.02. Somatosensation – Touch

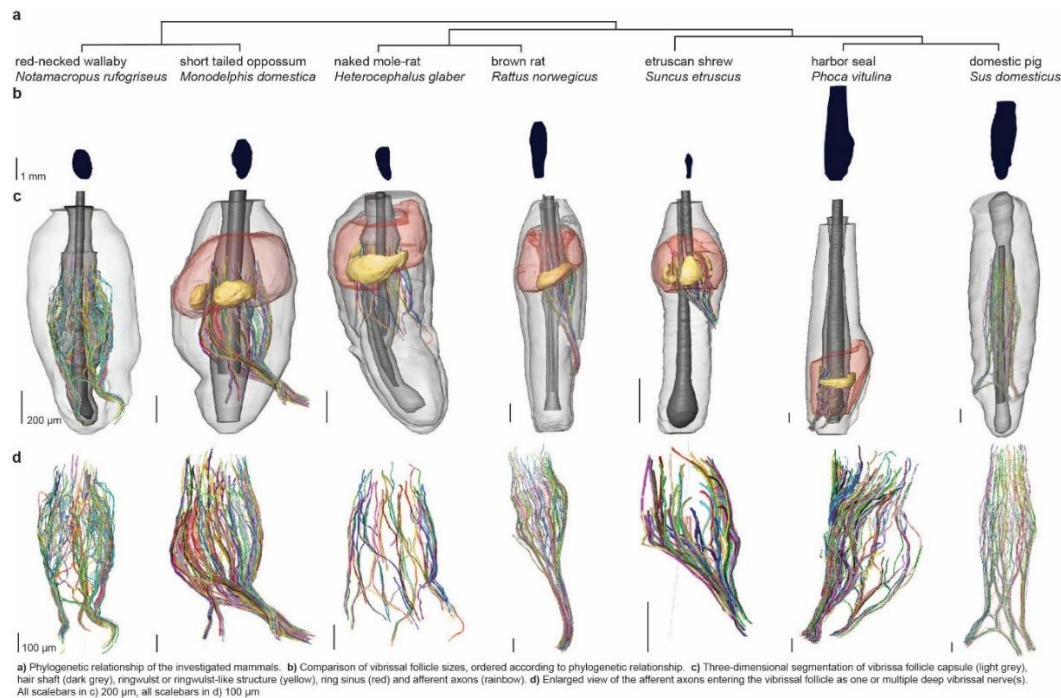
Support: DFG EXC-2049 – 390688087
DESY beamtime proposal I-20220980 and I-20240117
SFB1456/A3 Mathematics of Experiment

Title: Comparative analysis of vibrissa follicle architecture and innervation across mammals

Authors: *K. STRAUB¹, L.-G. HARDER¹, B. GERHARDT^{1,2}, J. ALFKEN³, T. SALDITT³, M. BRECHT^{1,4};

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Abstract: The vibrissa follicle is an intricate mechanosensory organ, which derives tactile information by an interaction of afferent innervation with accessory structures. Establishing structure-function relationships has been challenging because the follicle is complex, blood-filled, and encapsulated. We confronted these challenges through X-ray tomograms obtained at the DESY synchrotron radiation source and determined vibrissa follicle architecture across a diverse array of mammals. Thus, we obtained three-dimensional reconstructions of vibrissae follicles associated with different lifestyles and different phylogenetic backgrounds. We compare these features across rat, mouse, naked mole-rat, Etruscan shrew, cat, harbor seal, domestic pig, elephant, short-tailed opossum, and red-necked wallaby and made the following observations: 1. All vibrissa follicles under study share a common architecture including a blood-filled collagenous capsule, dense innervation by one or multiple deep vibrissal nerves and trabeculae anchoring the vibrissa inside the capsule. 2. Innervation profiles point toward common relationships of afferent types and accessory structures across mammals. 3. In the two marsupial species (wallaby, opossum) we observed highly branched afferents and no ringwulst; in the opossum, two bean-shaped collagenous corpuscles and associated afferents are present at a ringwulst-like position. 4. In eutherian mammals afferents showed less branching. Most eutherian species had a ringwulst. 5. In elephants the ringwulst might have been lost and in pigs, afferent innervation and accessory tissue point to a secondary, use-dependent reduction of the ringwulst. 6. A small number of similar afferent types dominated across mammals: lanceolate-, Merkel- and - where a ringwulst was (once) present - club-like afferents were observed. The occurrence of Ruffini afferents appeared to differ across mammals. We conclude that comparative work helps to establish follicle structure-function relationships.



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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.04/M6

Topic: E.02. Somatosensation – Touch

Support: DFG EXC-2049 – 390688087
DESY I-20220980
DESY I-20240117
ESRF Is-3401
SFB1456/A3 Mathematics of Experiment
BrainPlay ERC Synergy Grant

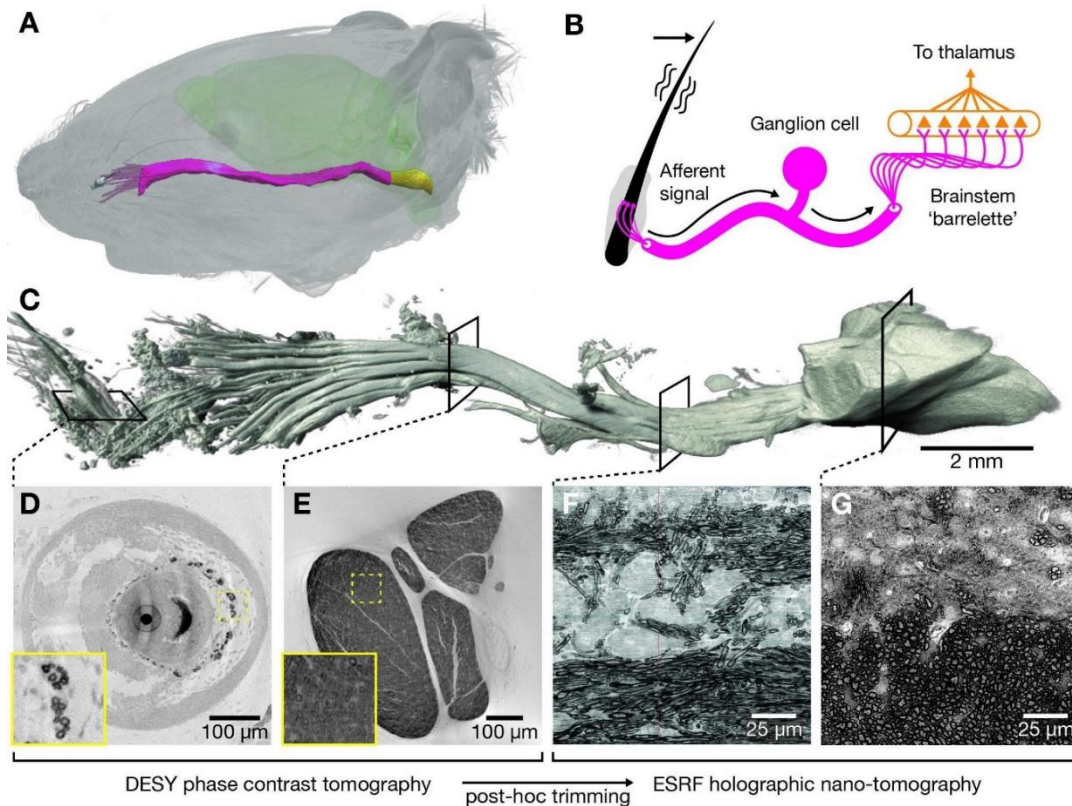
Title: Afferents reconstruction reveals linear angular topography of trigeminal ganglion and brainstem barrelettes

Authors: *B. GERHARDT^{1,2}, M. MUGNAINI¹, M. ECKERMANN^{3,4}, P. LADENBURGER¹, J. ALFKEN⁵, P. MEYER⁵, P. CLOETENS⁴, T. SALDITT⁵, M. BRECHT^{1,6};

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Synchrotron Radiation Facility, Grenoble, France; ⁵Inst. for X-ray Physics, Georg August Univ. Göttingen, Göttingen, Germany; ⁶NeuroCure Cluster of Excellence, Berlin, Germany

Abstract: The size of the mammalian brain poses a challenge to connectomic research on the input-output structure of circuits. Mostly limited to sub-cubic millimetre samples, the mammalian networks under study often do not include the relevant inputs making it hard to assign functional meaning to these connections. To overcome this difficulty, we used synchrotron X-ray imaging at the GINIX (P10-beamline, DESY, Hamburg) and at the ID16A beamline (ESRF, Grenoble) to scan a 1.5 cm mouse vibrissa-to-brainstem sample. Through this, we resolved the entire trigeminal pathway of the C2 vibrissa follicle at 650 nm at GINIX and corresponding targeted subset regions in the ganglion and brainstem at 100 nm at ID16A. In the vibrissa somatosensory system, we have a solid understanding of the macroscopic vibrissa-to-barrelette/barreloid/barrel pathway, but we do not know how the more than 100 afferents innervating a single vibrissa are organized microscopically and relative to each other. Here we address this question by semi-dense afferents end-to-end mapping. The vast majority of vibrissal afferents is tuned to the angle of vibrissa displacement, making the radial arrangement of axon terminals around the shaft of particular relevance for encoding. We describe the trajectories of identified C2 afferents through the trigeminal nerve and branching patterns in the ganglion and brainstem principal trigeminal nucleus (PrV), from which we infer mapping of information. In the ganglion we discover a hitherto unknown microtopographic organization which lays out the angular positions of axon terminals in a linear and rostro-caudally extending sequence. In the PrV barrelette, afferents branch in a rostro-caudal sequence that again corresponds to the angular position of their terminals in the follicle. Together, our results indicate a micro-somatotopic organization of the trigeminal vibrissa system which performs a radial-to-linear transformation of angular topography from the follicle to the brain. We conclude that large-scale synchrotron imaging allows for comprehensive mapping of circuit inputs.



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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.05/M7

Topic: E.02. Somatosensation – Touch

Support: DARPA ElectRx grant BAA 15 06

Title: Hysteresis in cutaneous mechanosensory in mouse hairy skin

Authors: *Y. BABA¹, E. A. LUMPKIN²;

¹Univ. of California Berkeley, Berkeley, CA; ²Mol. & Cell Biol., UC Berkeley, Berkeley, CA

Abstract: Studying the ex vivo skin nerve preparation revealed that more than half of the slowly adapting neurons (SAs) did not meet the criterion of SA1, which is characterized by high-frequency discharge, a low threshold, and an irregular spike discharge pattern. Some of them must belong to A-delta mechanosensory neurons (AM), which are known to be nociceptors.

Hereafter, all SA neurons, including AMs that do not meet the SA1 criteria, will be referred to as “SAX.” This project analyzed the physiological properties of SAX and proposed some criteria for SAX classification. The optimal stimulation of SAX was achieved by indenting the skin. SAXs were classified into two subgroups based on their dynamic phase response. One had a spike discharge during this phase, which was dynamic SAX (dySAX), while the other did not, resulting in non-dynamic SAX (ndySAX). Their spike frequency during the static phase ranged from 5 to 40 Hz in the dySAX and from 1 to 20 Hz in the ndySAX. All dySAXs and some ndySAXs that exceeded 5 Hz during the static phase showed intensity-dependent responses. A particular phenomenon of the non-constancy of the response is that their spike discharge is influenced by previous circumstances (which have some hysteresis). For example, after the high-frequency discharge during 5-second indentation, the next under-threshold stimulation sometimes triggered spikes. The effects varied but could last up to 120 seconds. Another phenomenon is a burst discharge (more than 3 times higher frequency than the other static frequency) during constant force indentation. The burst location during constant force indentation was varied, and the burst duration ranged from 0.5 to 2 seconds. Sometimes, two bursts were observed. The higher the intensity, the higher the probability of burst occurrence was. Also, the probability would be affected by the previous spike discharge caused by stimulation. According to the multi-unit recording observation, the burst location and burst duration of each SAX were independent. These data suggested that 1) SAX has at least three sub-groups: dySAX, intensity-dependent ndySAX, and non-intensity-dependent ndySAX. 2) The difficulty of classifying SAX lies in time-valued characters, in other words, some hysteresis. This property would be caused by individual physiological characteristics, such as ion channel properties, the surrounding circumstances of keratinocytes and neurons, and so on. Further study of the mechanism of hysteresis helps classify the sensory system of hairy skin and may also be relevant to pain research.

Disclosures: Y. Baba: None. E.A. Lumpkin: None.

Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.06/M8

Topic: E.02. Somatosensation – Touch

Support: ERC Grant Sensational Tethers 789128
Deutsche Forschungsgemeinschaft SFB958

Title: Tenm4 is an essential component of tethers required for touch sensation

Authors: *L. DALMASSO, A. HUANG, M. KHALLAF, E. NELLO, L. SUÁREZ ARTILES, S. KUNZ, A. SCHÜTZ, P. MERTINS, G. R. LEWIN;
Max Delbrück Ctr. for Mol. Med., Berlin, Germany

Abstract: Our ability to perceive touch depends on specialized mechanosensory neurons in the skin that detect nanometer-scale mechanical displacements and convert them into electrical signals. Key molecular components of this mechanotransduction process have recently been identified, including the mechanosensitive ion channels Piezo2 and Elkin1¹. However, the precise mechanisms by which mechanical forces are transmitted to and gate these channels remain poorly understood. We hypothesize that activation of these channels in response to tactile stimuli requires mechanical coupling to the extracellular matrix (ECM) via specialized protein tethers. In sensory neurons cultured on laminin, these tethers appear as electron-dense extracellular filaments, bridging the gap between neurites and the matrix². In our search for the molecular identity of these structures, we have narrowed the list of candidates to a small group of ECM-associated proteins, with the transmembrane protein Tenm4 emerging as the most compelling candidate. We have previously demonstrated that Tenm4 is critically required for normal touch sensation *in vivo*, possibly by participating in the formation of these extracellular tethers through interactions with other ECM proteins in the skin³. In the present study, we show that Tenm4 localizes specifically to the tether structures in cultured sensory neurons, as revealed by immunogold labeling combined with transmission electron microscopy (TEM). Additionally, using affinity purification and proximity biotinylation, followed by mass spectrometry, we identified multiple ECM proteins as potential Tenm4 interactors in the skin. These findings support a model in which Tenm4 plays a central role in tether assembly and function by linking mechanosensitive ion channels to the ECM, thereby enabling efficient force transmission during tactile stimulation. 1. Chakrabarti, S. *et al.* Touch sensation requires the mechanically gated ion channel ELKIN1. *Science* **383**, 992-998 (2024). 2. Hu, J., Chiang, L.-Y., Koch, M. & Lewin, G. R. Evidence for a protein tether involved in somatic touch. *EMBO J.* **29**, 855-867 (2010). 3. Khallaf, M. A. *et al.* TENM4 is an essential transduction component for touch and pain. Preprint at <https://doi.org/10.1101/2024.10.10.617546> (2024).

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.07/M9

Topic: E.02. Somatosensation – Touch

Support: NIH R00NS119739

Title: Contributions of central and peripheral somatosensory system components to texture discrimination

Authors: *E. KENT¹, P. LIU¹, Y. LEE¹, R. LAMPRECHT², E. ALVAREZ-PAMIR¹, W. GOOLSBY¹, A. J. EMANUEL¹;

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Abstract: The precise roles of somatosensory system components in texture perception remain incompletely understood and are debated. Previous investigations into roughness perception largely focused on innate preferences, which do not capture the full capacity of the nervous system to discriminate between rough and smooth surfaces, or have used genetically intractable animals. We developed a learned texture discrimination paradigm in which a water-restricted, whisker-trimmed mouse traverses a corridor with 3D-printed interchangeable textured floors prior to making a decision to turn left or right. Mice were trained to associate rough (1.5-mm cone height) or smooth (0.0-mm cone height) floors with specific turn directions to receive a water reward. Once animals reached expert-level performance ($\geq 75\%$ accuracy), we systematically tested their ability to discriminate between smooth and intermediately rough textures (intermediate cone heights) to determine their psychometric thresholds. To investigate the neural basis of texture discrimination, we evaluated performance in mice lacking Merkel cells (Merkel cKO: K5-Cre;Atoh1 flox/flox), mice lacking Meissner corpuscles (Meissner cKO: AvilCre;TrkBflox/flox), and mice with chemogenetic silencing (via expression of hM4D(Gi)) of forepaw and hindpaw regions of primary somatosensory cortex (S1). Both Merkel cKOs and Meissner cKOs achieved expert-level performance in similar numbers of sessions as their littermate controls (12.8 ± 2.3 vs 9.8 ± 1.4 sessions and 8.3 ± 1.0 vs. 10.6 ± 1.1 sessions for Merkel and Meissner cKOs, respectively; mean $\pm$ SEM). Merkel cKOs and Meissner cKOs also had comparable psychometric thresholds to their littermate controls (0.58 ± 0.10 vs. 0.60 ± 0.05 mm, and 0.59 ± 0.05 vs. 0.58 ± 0.10 mm, respectively). Expert mice expressing hM4D(Gi) performed worse at discriminating 1.5- and 0.0-mm cone height floors during sessions after clozapine-N-oxide (CNO) injections, which is expected to decrease S1 activity, compared to sessions after control saline injections (correctness of $91 \pm 1\%$ and $70 \pm 4\%$ for CNO and saline, respectively). Notably, performance after CNO was significantly above chance (50%). Moreover, mice with silenced S1 showed no significant differences in their psychometric thresholds compared with their control sessions (0.38 ± 0.03 vs. 0.64 ± 0.2 mm). In sum, we found that S1 activity appears to be important for normal texture discrimination, but that neither Merkel cells nor Meissner corpuscles, individually, are required.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.08/M10

Topic: E.02. Somatosensation – Touch

Support: Leverhulme Trust Research Project Grant RPG-2022-031

Title: Assessing the role of glabrous skin morphology in touch perception via in-vivo volumetric skin layer reconstruction and tracking

Authors: *J. HALL¹, G. GONZALEZ SALAS DUHNE¹, O. WALLIS¹, C. HOWARTH¹, B. P. DELHAYE², H. P. SAAL¹;

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Abstract: Human glabrous skin is characterized by its ridged structure. Whether and how this morphology affects the activation of low-threshold mechanoreceptors is debated. Two major skin layers lie between the surface, where forces act, and the dermo-epidermal junction, where shallow mechanoreceptors (Merkel cells and Meissner corpuscles) are located: first the stratum corneum (SC), formed of dead skin cells, and second the viable epidermis (VE). The ridged structure of the fingerprint is reflected throughout both layers with additional so-called intermediate ridges found on the basal surface of the VE. Both the Merkel cells and Meissner corpuscles are positioned such that they are aligned with this ridged structure, implying the importance of this microstructure in receptor activation.

Here, we developed a novel pipeline to image and segment volumetric sections of SC and VE skin layers in glabrous skin using optical coherence tomography (OCT). Additionally, by automatically tracking the location of sweat ducts, sub-surface deformation of the skin layers at the scale of individual ridges can be calculated. Furthermore, psychophysical testing using a two-point oriented discrimination task and Von-Frey filament force threshold testing is used to establish perceptual thresholds on different regions in the hand and foot which differ in their morphology.

Preliminary data from the sensitivity analyses shows that not only do skin thickness and mechanoreceptor density contribute to sensitivity, but also the size of the ridges may be an important factor. These measures explain to some extent the large perceptual differences observed between the hand and the foot. In addition, strain measurements within the skin suggest that the direction of ridges may influence local touch perception and that ridges might concentrate deformation towards the edges of tactile stimuli. These measurements contribute to understanding of how the morphology of the skin shapes tactile sensing.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.09/M11

Topic: E.02. Somatosensation – Touch

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193217 (Z.K.S)

D.D.G. is an investigator of the Howard Hughes Medical Institute.

Title: Structural and biomechanical basis of pacinian vibration tuning

Authors: *Z. K. SARAFIS^{1,2}, J. TURECEK^{1,2}, A. HANDLER^{1,2}, S. CAMERON^{1,2}, D. D. GINTY^{1,2};

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Abstract: Pacinian neurons are low-threshold mechanoreceptors that detect high-frequency mechanical vibrations. Their sensitivity and tuning to vibration arise from the Pacinian corpuscle, a specialized end organ found in deep tissues across species, which consists of a central axon surrounded by concentric lamellar layers. Furthermore, Pacinian neurons have a range of vibration tuning and sensitivities. It has remained unclear how the corpuscle structure enables exquisite tuning to vibration, and whether vibration tuning is dependent on corpuscle shape, size, and location. Using mouse genetic tools, in vivo electrophysiology, and whole tissue clearing, we measured the relationship between the structure and location of individual Pacinian corpuscles and their functional tuning. We found anatomically organized heterogeneity in corpuscle and axonal structure. We observed that both corpuscle location and structure account for variance in Pacinian vibration tuning properties. Finally, we found that tissue biomechanics also determine the sensitivity and tuning of Pacinian neurons. These findings suggest that multiple variables, including end organ structure, location, intrinsic properties, and tissue mechanics shape sensory neuron tuning, and can provide sources of variance that enables population coding of mechanical vibration stimuli.

Disclosures: Z.K. Sarafis: None. J. Turecek: None. A. Handler: None. S. Cameron: None. D.D. Ginty: None.

Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.10/M12

Topic: E.02. Somatosensation – Touch

Title: Physical determinants of perceived vibration intensity: Insights from haptic feedback at the human wrist

Authors: *S. BONNET¹, R. H. WATKINS¹, R. ERICSSON¹, H. DAUMAS², R. ACKERLEY¹;
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Abstract: Understanding how controlled mechanical vibrations applied to the skin translate into subjective touch sensations is key to advancing our understanding of somatosensory processing and perception. While prior research has established psychophysical thresholds and

discrimination levels for vibrotactile stimuli, little is known about how the mechanical dynamics of skin transmission shape subjective intensity ratings, critical for providing effective graded haptic feedback. Here, we investigated how vibration, measured via accelerometers at the actuator and at the skin surface, predicts perceived intensity, while modifying the frequency, amplitude, and waveform shape. Healthy human volunteers signed informed consent forms and the study was approved by an ethical committee. Twenty participants wore a custom-designed vibrotactile wristband (V.RTU, France) on their dominant hand, positioned on the flexor tendons around 2 cm from the wrist crease. To control for physical factors that could affect skin mechanics, we measured and standardized skin temperature and hydration level and assessed tactile sensitivity at the wrist using calibrated monofilaments. Two accelerometers recorded mechanical signals: one embedded within the wristband and another placed 1 cm away on the skin, enabling precise tracking of vibration propagation through the tissue. Participants received 225 randomized 2 s vibrotactile stimuli varying in frequency, amplitude, and waveform shape, and provided continuous free ratings of perceived intensity after each trial. Perceived intensity increased with amplitude, and increasing frequency followed a non-linear pattern, peaking near 150 Hz, which corresponds to the vibrator's mechanical resonance, before decreasing at higher frequencies. Waveform shape also influenced perception, with square waves rated as most intense, sinusoidal intermediate, and sawtooth least intense. Measured acceleration emerged as the most robust predictor of perceived intensity, capturing the combined effects of frequency, amplitude, and shape. Coherence, phase, and the root-mean-square (RMS) ratio revealed systematic variations across stimuli that were modulated by individual factors such as age, skin hydration, temperature, and tactile sensitivity. Sinusoidal waveforms produced the highest RMS ratio, while sawtooths exhibited the greatest coherence. These findings offer insights into the mechanisms of peripheral mechanotransduction, informing the design of precise haptic feedback systems, sensory prosthetics, and neurorehabilitation technologies.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.11/M13

Topic: E.02. Somatosensation – Touch

Support: CNRS MITI

Title: Influence of applied force on the perception and peripheral encoding of stroking touch

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Abstract: C-tactile (CT) afferents or C-low threshold mechanoreceptors (C-LTMRs) are unmyelinated, slowly-conducting fibers that fire optimally to slow, gentle, stroking touch. In humans, studies have shown that they fire optimally to stroking at 1-10 cm/s, with decreased activity to slower or faster strokes, producing an inverted-U shaped relationship, which correlates with ratings of pleasantness (Löken et al., 2009, Nat Neuro). This relationship has generated an abundance of studies investigating pleasantness ratings, linking them to CT activity. Many studies have used a single stroking force of 0.4 N, although the work of Löken et al. (2009) investigated 0.2 N stroking and found no differences in CT firing, nor perception. A more recent study (Ali et al., 2021, PloS One) showed that stroking delivered at 0.4 N was rated more pleasant than when delivered at lower (0.05 N) or stronger (1.5 N) force. We aimed to investigate the relationship between the force and velocity of stroking touch. All experiments were on healthy human volunteers that signed informed consent forms and the studies were approved by ethical committees. In a psychophysical study, we applied strokes over the ventral forearm using a soft brush on 21 participants using a robot. We tested 5 stroking velocities (0.3, 1, 3, 10, 30 cm/s) and 6 forces (0.2, 0.4, 0.8, 1.2, 1.6, 2 N). After each stroke, participants rated the pleasantness, from very unpleasant to very pleasant, and intensity, from very weak to very strong. We found significant main effects of force and velocity for pleasantness and intensity perception, as well as an interaction between force and velocity for pleasantness. There was an inverted-U shaped relationship between velocity and pleasantness at each force, although for slower velocities (0.3 and 1 cm/s), there was no effect of force, but from 3 cm/s, 2N was perceived less pleasant. The forces of 0.4 and 0.8 gave the overall highest pleasantness curves. Intensity perception increased linearly with the velocity and force. We also obtained microneurography recordings from two CTs in the antebrachial nerve over the same stroking velocities, at 0.05, 0.4, and 1.5 N. The mean instantaneous firing frequency showed an inverted-U shaped curve over the velocities that increased with force. As per the pleasantness perceptual data, preliminary analyses find that there were larger differences in the force curves for faster stroking. Overall, these data relate the activity in CT afferents to the pleasantness of touch, and provide new insights into how this is modified by both velocity and force.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.12/M14

Topic: E.02. Somatosensation – Touch

Support: NIH Grant R01AT012048

Title: Contributions of C-fibers versus A-fibers to the Pleasantness of C-tactile Affective Touch

Authors: *B. ALBINNI^{1,2}, L. CRANKSHAW², E. JONES², V. ALASHA², M. ZIMMERMAN², J. ROSS², N. SCHUSTER², E. SAID², L. CASE²;

¹UCSD, La Jolla, CA; ²Anesthesiol., Dept. of Anesthesiology, Univ. of California, San Diego, La Jolla, CA

Abstract: The unmyelinated C-tactile (CT) afferent pathway is optimally activated by slow, gentle stroking and is closely associated with pleasant affective touch perception. Emerging evidence indicates that its perception involves complex interactions with A β fibers at both the spinal and cortical levels. However, the necessity and sufficiency of A β and C-fibers for the pleasantness of slow gentle stroking is unclear. We tested this in a within-subject protocol involving preferential blockade of A and C-fibers on separate days. Nineteen healthy human adults participated in the study (age $M=26.5$, $SD=5.9$; 11 female, 6 male, 2 nonbinary). A-fiber blockade was induced by compression of the superficial radial nerve; C-fiber blockade was induced via injection of lidocaine or bupivacaine. Sensory function was assessed at baseline, as well as in frequent cycles after the onset of the nerve block, and included cold threshold (A δ ; tested with thermode), touch detection (A β ; cotton swab and vibration detection), and warm threshold (C-fibers; tested with thermode). At baseline and after confirmation of significant loss of either A β or C-fiber function, an affective touch and pain modulation task was administered to the blocked arm and then to the control arm involving calibrated moderate heat pain, gentle CT-targeted brushing, and then a second heat pain stimulus. Due to individual variability in block effectiveness, data were analyzed according to changes in A β , A δ , and C-fiber related functions rather than block type. A generalized linear mixed model with changes in touch, cold, and warmth detection as fixed effects showed that touch detection significantly predicted changes in pleasantness ratings ($F(1,14.7)=6.4$, $p=0.02$; $\beta=2.5$), while cold did not ($p=0.53$). Mean pleasantness ratings (where 0 = neutral and 100 = extremely pleasant) on the test arm after nerve block were higher for participants with no A β touch loss ($M=28.8$, $SD=36.1$ ($N=13$)), compared to participants with at least 50% loss ($M=7.4$, $SD=18.3$ ($N=10$)). Ratings on the control arm for these sub-groups of participants differed much less ($M=35.8$, $SD=35.4$ vs $M=28.8$, $SD=19.7$). Warmth threshold showed a trend in predicting changes in touch pleasantness ($F(1,18.7)=3.7$, $p=0.07$; $\beta=-2.15$), with a similar pattern of mean ratings after nerve block. These results suggest that A β input plays a key role in the pleasantness of “CT” slow gentle stroking, and that C-fibers (e.g. CT fibers) likely do as well. These data support the role of integration of multiple sensory afferent types in human pleasant touch perception. Further analyses will explore how these fiber types impact touch-induced pain modulation.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.13/M15

Topic: E.01. Somatosensation – Pain and Itch

Support: BBSRC PhD Studentship (IER)

Title: Channel-specificity in human thermosensation: Do warm and cold sensations arise from "labelled lines"?

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Abstract: Why do sensations differ in quality? “Labelled line” theories suggest each peripheral receptor class results in a distinct experience. Warmth and cold sensations have been linked to distinct skin receptor classes, activated by restricted temperature ranges. However, no psychophysical study has shown that cold and warm responses derive from separate psychophysical channels. Further, many central ‘polymodal’ neurons respond to either warm or cold, suggesting sensory quality could result from mixed selectivity processing rather than sparse peripheral coding. We delivered small temperature increases, decreases, or catch trials, to the hand dorsum of 28 healthy participants, in random order. Participants first detected whether any thermal stimulus was present, and then identified whether it was an increase or a decrease. Measuring both detection and identification responses allowed us to compare various psychophysical models. First, models with separate sensory warm and cold channels fitted the data better than single-channel models, suggesting two sensory qualities were indeed present. Second, signal detection models, based on continuous channel activation, fitted better than “High Threshold” models including a sensory threshold function. Third, in the best-fitting models, the channels did not overlap. We conclude that warmth and cold are indeed labelled lines, and we discuss the implications for channel-specific theories of sensation.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.14/M16

Topic: E.02. Somatosensation – Touch

Title: A healthy gut microbiome needs the gentle touch

Authors: *F. P. MCGLONE, C. MURGATROYD;
Manchester Metropolitan Univ., Manchester, United Kingdom

Abstract: Introduction: Chronic stress causes many adverse changes in the gut and the brain such as increased release of glucocorticoids and widespread inflammation. Imbalance in the gut microbiome leads to gut microbiota contributing to intestinal permeability allowing bacteria to cross the intestinal mucosa, accessing both immune cells and neuronal cells of the enteric nervous system. Stress decreases gut bacteria diversity - Affiliative tactile interactions buffer social mammals against neurobiological and behavioural effects of stress. Here we ask ‘does C-LTMR directed touch impact on diversity of the gut microbiome?’

Methods: Female Lister hooded rats stroked for 1-minute at the C-LTMR targeted velocity or non C-LTMR velocity, 18 times over 7 days. Anxiety scores measured; extraction for microbial DNA from fecal pellets; nanopore sequencing performed using 10 ng of extracted DNA from each sample.

Results: Slow stroking was associated with a significant reduction in anxiety-related behavior; a significant increase in diversity and richness in the microbiome; significant increases and decreases in several specific genera of bacteria, many of which are known to have important roles in regulating inflammation and gut health.

Discussion: Anxiety and stress are linked to altered microbiome composition, with reduced diversity and richness, measures associated with poorer physical and mental health, obesity and inflammatory diseases. Results presented here are the first to suggest the existence of a Skin-Gut-Brain Axis where C-LTMR directed stimulation (gentle touch) could modify the gut microbiome, impacting positively on improving gut and brain health.

Disclosures: F.P. McGlone: None. C. Murgatroyd: None.

Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

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Program #/Poster #: PSTR168.15/N1

Topic: E.02. Somatosensation – Touch

Support: NCCIH R00AT009466
VA I01 CX002591

Title: Depression levels increase both experimental pain and affective touch perception in individuals with Fibromyalgia and healthy controls

Authors: *L. CRANKSHAW¹, B. ALBINNI¹, E. JONES¹, J. ROSS¹, M. ZIMMERMAN¹, V. ALASHA¹, S. HU², N. SCHUSTER¹, L. CASE^{1,3};
¹Anesthesiol., ²Sch. of Med., UCSD, La Jolla, CA; ³VA San Diego Healthcare Syst., San Diego, CA

Abstract: Individuals with chronic pain exhibit heightened sensitivity to noxious as well as non-noxious stimuli, and often report reduced touch pleasantness. Fibromyalgia (FM) is a nociplastic pain condition with elevated rates of trauma history and psychological comorbidities including

depression. Whether affective sensory alterations in FM are caused by chronic pain or affective symptoms is unclear. In 40 human adults with FM and 40 healthy controls (mean age = 39.8 ± 12.9 , 75 female), we collected (un)pleasantness and intensity ratings of evoked heat pain (45°C) and affective touch (defined as pleasantness of C-tactile targeted gentle brushing versus tapping). Respiration rate (RR) was collected before and during test stimuli. Questionnaires measuring depression, anxiety, trauma history, and chronic pain levels were collected at baseline. Sex differences were not assessed given the majority female sample. Using linear regression, we tested whether individual differences in depression, trauma history, chronic pain level, or RR predicted the (un)pleasantness of pain or affective touch. FM patients exhibited elevated heat pain ratings ($p = 0.02$) and reduced touch pleasantness (brushing pleasantness $p = 0.01$; affective touch preference $p = 0.14$) as well as elevated depression, anxiety, trauma, and pain levels (all $p < 0.01$) compared to controls. Only depression emerged as a significant predictor of pain experience ($p = 0.01$), and depression was also a significant predictor of affective touch preference ($p < 0.01$). An exploratory analysis demonstrated a similar influence of anxiety. We also found a positive association between heat pain ratings and concurrent ($p = 0.01$), but not baseline, RR. Results were consistent across FM and healthy controls. Our results are novel in demonstrating a concurrent effect of depression scores in increasing pain *and* increasing affective touch preference, which we interpret as heightened discrimination of the valence of hedonic sensory signals. In addition, our data suggest that evoked pain modulates RR but that baseline RR is not a significant influence on pain.

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Poster

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Program #/Poster #: PSTR168.16/N2

Topic: E.02. Somatosensation – Touch

Support: Good Nature Institute
NIH R01MH114994

Title: Anatomical characterization of oxytocin receptors in innervation of the anogenital area of neonatal mice.

Authors: *A. GONZALEZ¹, E. A. HAMMOCK²;
²Psychology, ¹Florida State Univ., Tallahassee, FL

Abstract: The postnatal period is a crucial time for sensory-dependent development of many biological and psychological processes. In mice, postnatal oxytocin (OXT) synthesis is influenced by early sensory experience and congenital loss of oxytocin receptors (OXTR). Alterations in OXT synthesis co-occur in many socio-emotional disorders. Interestingly,

peripheral nervous system-specific deletion of OXTRs from early development alters adult social behaviors indicating an important behavioral contribution of peripheral OXTR. Many peripheral OXTR binding sites have been identified in the neonatal mouse and prairie vole. One peripheral site of OXTR expression is the anogenital area (AGA) in male and female neonates. In many non-human mammals, maternal licking of postnatal pup's AGA contributes to proper development of social, sexual, and micturition circuits. In the present study, we begin to identify the function and cell-specific expression of OXTRs in the neonatal AGA using several approaches. For functional analyses, OXTR-EGFP postnatal day (P) 8 mice were randomly assigned to either a handled-only control group, or one of three stimulation groups: 1) saline control, 2) oxytocin treated, 3) atosiban treated. A soft bristled paint brush was dipped into one of the three stimulation solutions and applied to the neonatal AGA for 30 seconds at a stroke rate of 3 Hz to mimic maternal licking. Video recordings of the conditions were scored for motor movement. For anatomical analyses, OXTR-EGFP, OXTR-Cre x Ai148d (GCamp6f), and Avil-Cre x Ai148d (GCamp6f) mice were deeply anesthetized and perfused with 4% paraformaldehyde on P0. After cryoprotection in sucrose, tissues were sectioned in the sagittal plane at 20µm. Immunohistochemistry was performed on slides incubated with antibodies against calcitonin gene related peptide (CGRP, to label Aδ and C-fibers) and EGFP (to enhance the endogenous OXTR reporter). Images at 10x and 40x magnification were captured using confocal microscopy. On P8, activation of these receptors by topical application of oxytocin decreased motor movement in males and females, while dampening these receptors through the application of atosiban increased motor movement. Preliminary anatomical analyses indicate specific OXTR reporter expression in the glans of the neonate on some nerve fibers and other cells at P0.

Disclosures: A. Gonzalez: None. E.A. Hammock: None.

Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

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Program #/Poster #: PSTR168.17/N3

Topic: E.02. Somatosensation – Touch

Support: F31 NS135947
R01 NS136228
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L.I.F.E. Foundation Research Award
Callahan Foundation
McKnight Foundation

Title: The effect of chronic stress on inhibitory modulation of tactile feedback

Authors: *J. MOSKO^{1,2}, J. CONNER², C. TUFO², E. AZIM²;

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Abstract: The constant flow of sensory information into the nervous system is fundamental for interaction with the world. The brain's ability to flexibly adjust sensitivity to various sensory stimuli is context-dependent and can be shifted on acute or chronic time scales. This dynamic regulation can be advantageous or maladaptive; prey animals may benefit from becoming temporarily hypersensitive to sensory cues elicited by a predator, but chronic shifts in sensory processing may become detrimental and debilitating. Importantly, a chronic shift in internal state can impact sensory regulation - for example, stress induced by social isolation has significant effects on several measures of affective behavior. We find that chronic stress can lead to an aberrant increase in tactile sensitivity. However, the neural circuit mechanisms underlying this shift in responsivity to touch remain unclear. The cuneate nucleus of the brainstem is responsible for transmitting sensory information originating from the forelimbs and anterior trunk region to the thalamus and primary somatosensory cortex, among other brain regions. Our recent work showed that local inhibitory networks envelop the cuneate, and perturbing the activity of these inhibitory neurons can bidirectionally modulate the gain of tactile signaling. We are exploring how top-down pathways that target these inhibitory networks might be involved in adjusting the strength of sensory signaling on short time scales and how the function of these circuits is affected by chronic stressful experiences.

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Poster

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Program #/Poster #: PSTR168.18/N4

Topic: E.02. Somatosensation – Touch

Support: NIH Grant NS45248
CONACYT Grant 219707

Title: Sensory control of the CPG circuitry in the in vitro mouse spinal cord

Authors: *A. SALCEDO-CARRILLO¹, E. SALCEDO³, J. N. QUEVEDO²;

²Physiol., ¹CINVESTAV del IPN, Mexico City, Mexico; ³CINVESTAV, Mexico City, Mexico

Abstract: Sensory feedback -from proprioceptive and cutaneous afferents- modulates both burst timing and amplitude, adjusting locomotor programs to different terrains and gating modes. The stereotypic responses evoked by stimulation of selective pathways, such as the resetting of locomotor cycle, the stumbling correction response or the enhancement of either flexion or extension, may provide insights into how sensory information modulates the Central Pattern Generator (CPG) network. We investigated how proprioceptive and cutaneous afferent

stimulation modulates the CPG circuitry in the in vitro mouse spinal cord, given the relevance to characterize afferent inputs in different types of CPG interneurons in transgenic mice. In neonatal BALBc mice (P1-3), bulbospinal neuraxis was dissected; in some cases, hindlimbs were not removed, and peripheral nerves left intact to be electrically stimulated. Fictive locomotor episodes were produced by applying NMDA (5-7 μ M), 5-HT (4 μ M), DA (50 μ M) and veratridine (10 nM) to aCSF bath. In order to activate low threshold afferents, peripheral cutaneous and muscle nerves were stimulated every six step cycles with trains of 60 pulses (2-4 xT) at 200 Hz triggered by VR-L2 (flexor) or VR-L5 (extensor) active phases. Low threshold afferents stimulation in the ipsilateral DR-L2, triggered off the ipsilateral VR-L5 activity, produced a shortening of ongoing bursting and an early onset of the subsequent L2 activity, i.e. a resetting to flexion. Stimulation of ipsilateral DR-L5 -triggered off the ipsilateral VR-L2 activity- evoked resetting to extension, i.e. a shortening of the ongoing bursting and an early onset of the subsequent L5 activity. On the other hand, ipsilateral cutaneous stimulation of the Superficial Peroneal nerve showed variable effects in either flexor or extensor phases, some of which resemble a stumbling correction response. As it has been described in several mammalian models (like adult cats and rats), the CPG circuitry is modulated by propriospinal sensory information through selective pathways, even at early stages of development.

Disclosures: A. Salcedo-Carrillo: None. E. Salcedo: None. J.N. Quevedo: None.

Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.19/N5

Topic: E.02. Somatosensation – Touch

Support: NIH Grant NS45248
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Title: Locomotor-driven primary afferent depolarization (CPG-PAD) in the in vitro rat spinal cord.

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Abstract: Primary afferent depolarization (PAD) modulates sensory input into the spinal cord. During locomotion, sensory afferent membrane potential oscillates in phase with the step cycle (CPG-PAD). However, the origin of this phenomenon, as well as its underlying mechanisms and physiological role, is still unknown. Moreover, recent insights suggest that PAD facilitates action potential propagation through afferent fibres axonal branching points, challenging the classical view that PAD drives presynaptic inhibition (PSI). This study aims to elucidate the nature of CPG-PAD and its functional role in modulating the synaptic efficacy of afferent fibres during locomotion. In the isolated neonatal rat spinal cord preparation, we studied the role PAD plays in

modulating sensory information of group Ia afferents. Tonic and phasic dorsal root potentials (DRPs) were evoked by electrical stimulation of dorsal roots (DRs), and the monosynaptic reflex (MSR) was recorded in the ventral root. The amplitude of phasic PAD increased gradually with DR electrical stimulation strength. The phasic component of PAD became occluded as tonic PAD reached a plateau. Conditioning stimulation of low-threshold afferent fibres applied to an adjacent DR produced predominantly a temporal facilitation and an amplitude increase of the monosynaptic reflex (MSR). In addition, when PAD depressed the MSR amplitude, GABA_B receptor antagonist CGP55845 abolished MSR depression, suggesting that this receptor type drives PSI. Finally, in a two-compartment chamber, we recorded the oscillatory CPG-PAD during locomotor episodes evoked by the application of NMDA, 5-HT and DA, even when the DR was not in direct contact with drugs; the oscillation's crest occurred predominantly during the flexion phase, and it brought along an increase of dorsal root reflex (DRR) frequency. In conclusion, it is possible to record CPG-PAD in the in vitro rat spinal cord. This phenomenon may facilitate the propagation of action potentials during flexion. CPG-PAD could promote sensory information arrival to the spinal cord during the swing phase, which is the most unstable period of the step cycle to be disturbed by obstacles.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR168.20/N6

Topic: E.02. Somatosensation – Touch

Support: U19 NS137920

Title: Trigeminal ganglia cell projections to motor V

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Abstract: The neurons in the trigeminal ganglia provide sensory input from receptors in the head to the brainstem. The predominant and best studied targets of the trigeminal ganglia lie in the trigeminal nuclear complex. However, little is known about the extent of trigeminal input to “non-trigeminal” targets, although the existence of such direct afferent projections is supported by early HRP (Jacquin et al 1982) and WGA- HRP tracing (Marfurt and Rajchert ,1991) studies. Here, we report virus-based labeling of a population of trigeminal ganglion neurons with pre-motor inputs to cranial motor nucleus V, a non-trigeminal target.

Our labeling paradigm is based on staged injections of virus to identify monosynaptic inputs from premotor neurons. This methodology has provided a comprehensive map of CNS neurons

that are premotor to motor V, to facial nucleus, and to the hypoglossal nucleus (Takato et al 2021). We extend our examination to trigeminal ganglia in mice where the premotor inputs to motor V are labeled. The masseter muscle is unilaterally injected with an AAV-retro-Cre. Subsequently, cre-dependent helper and G-deleted rabies virus are injected into motor V. This restricts monosynaptic labeling to premotor neurons which project to the masseter motor neuron pool. We section whole-heads with the cryo-jane method to build high-fidelity 3d models of trigeminal ganglia along with GFP- labelled premotor neurons. This data is imported into our BrainSharer platform, which supports web-based data-sharing (brainsharer.org). In our preliminary studies, we observe labeling of 100s of neurons bilaterally, with predominant labeling in the trigeminal ganglion ipsilateral to the masseter injection. The wide distribution of trigeminal ganglion premotor neurons signifies a representation of ophthalmic, maxillary, and mandibular peripheral territories. Consistent with the distribution of labelled somata, axonal labeling is observed in ophthalmic, maxillary and mandibular nerve branches. Intra-oral label of nerve terminals in hard palate rugae was also observed. As a control for false identification based on confounding autofluorescence, GFP fluorescence is immuno-localized. This work suggests that in addition to the well-characterized, sensory innervation of motor V by spindle afferents via the mesencephalic V nucleus, other sensory modalities may also directly innervate motor V motor neurons via the trigeminal ganglia. Ongoing work aims to identify the peripheral topography and sensory modality of trigeminal ganglia neurons that are premotor to motor V.

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Poster

PSTR168: Somatosensory Peripheral Mechanisms and Spinal Circuits

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Topic: E.02. Somatosensation – Touch

Support: Training Program in Neural, Computational, and Neuromechanical Approaches to Motor Control T32NS12176
The University of Chicago Initiative for Maximizing Student Development (IMSD) 5T32GM152395-02
US Office of Naval Research grant N00014-22-1-2187

Title: Proprioception Underlying Static Substrate-Based Postures in Dwarf Hawkfish

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Abstract: Standing, perching, and other approaches for maintaining a stable body position are routine functions of vertebrate limbs. While limb-based proprioception is known to be critical for such behaviors in humans and other terrestrial vertebrates, much less is known about its role in

fish that use pectoral or pelvic fins (respectively, arm and leg homologs) to perch. Here, we examine the physiology and function of mechanosensory innervation in the specialized free pectoral fin rays of dwarf hawkfish (*Cirrhitichthys falco*), a reef fish that uses these rays to maintain stable postures on coral and other surfaces. Through electrophysiological recordings of the pectoral fin sensory nerves that innervate these free rays, we discovered activity that persists while fin rays are held in static, bent positions that mimic their posture while the hawkfish perches on substrates. This activity scales with the amplitude of the bend, indicating that information about fin ray position is available to the fish, not just in movement but in static positioning. During fin ray movement, we saw additional fast adapting responses. The presence of both burst firing in response to movement and sustained firing through the duration of the static bend revealed proprioceptive capabilities that seem specific to fish adapted to maintaining posture on substrates. Spike sorting identified afferents with diverse response profiles to movement and static position, suggesting that specialized afferents are responsive to different mechanical perturbations of the free rays. To examine the importance of mechanosensory input from the limbs in substrate-based postures, the dwarf hawkfish's ability to maintain its position in flow was assessed before and after bilateral transection of the free rays' sensory nerves. Post-transection, hawkfish displayed reduced positional stability, changes in body orientation relative to flow direction and altered fin ray posture indicating a decline in performance. These findings expand our understanding of proprioceptive systems in humans and other mammals by indicating that complex limb-based mechanosensory feedback supporting postural control likely arose in aquatic ancestors, prior to the water-land transitions. Through examining a simpler fish model for forelimb posture, we can isolate fundamental mechanosensory processes underlying proprioception offering insights into the neural basis of proprioception more broadly in vertebrates.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR169.01/N8

Topic: E.02. Somatosensation – Touch

Support: ETRI KOREA 25ZB1330
NRF KOREA RS-2020-00302489

Title: Thalamic VPL Encoding of Vibrotactile Stimuli Across Frequencies in Mice: A Multi-Channel Electrophysiological Study

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Abstract: The somatosensory system processes tactile information via specialized peripheral mechanoreceptors that respond to distinct vibratory frequencies. While high-frequency vibrotactile coding—particularly its transformation from precise temporal to rate-based coding in the thalamus—has been extensively studied, the central processing of lower frequency vibrations remains less well understood. The ventral posterior lateral (VPL) nucleus of the thalamus is a critical relay that integrates diverse peripheral inputs. Understanding how these distinct frequency ranges are encoded and organized within the VPL is crucial for deciphering tactile perception.

This study investigates how VPL neurons in B6 mice encode vibratory stimuli (10-300 Hz) applied to the hindpaw. Our primary goal is to characterize how VPL neuronal firing patterns and rates change across this broad frequency spectrum, focusing on potential differential processing for frequency ranges linked to specific peripheral mechanoreceptor types. We also aim to explore any topographical organization of vibratory processing along the VPL's rostrocaudal axis.

We performed acute extracellular recordings in the VPL nucleus of urethane-anesthetized B6 mice using a 2×8 multichannel electrode array. This array allowed simultaneous recording from both rostral and caudal VPL regions, enabling us to examine potential variations in response profiles along this axis. Vibratory stimuli (10-300 Hz) were delivered to the contralateral hindpaw via a custom piezoelectric stimulator. Neural data, including spike times, were acquired for subsequent analysis.

We anticipate that VPL neurons will show diverse, frequency-dependent response profiles, reflecting the integration of various peripheral inputs. We will explore how vibratory frequency information is encoded in the VPL, considering the potential shift from temporal coding to rate-based encoding, especially at higher frequencies. We also hypothesize that these frequency-specific response properties might exhibit a topographical organization along the VPL's rostrocaudal axis. These findings should offer fundamental insights into the central nervous system's mechanisms for encoding vibrotactile stimuli, thereby enhancing our understanding of tactile perception.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Program #/Poster #: PSTR169.02/N9

Topic: E.02. Somatosensation – Touch

Support: ETRI Korea 25ZB1330
NRF Korea RS-2020-00302489

Title: An experimental study on SA and RA tactile mechanoreceptor selective neural spike firing in mice according to frequency and intensity of sinusoidal microdisplacement stimulation for virtual tactile signal generation

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Abstract: To implement virtual tactile technology that feels like touching an object in virtual reality (VR), augmented reality (AR), and mixed reality (MR), wearable device technology equipped with a mechanism unit that provides pressure or vibration to gloves or clothes is being developed. However, since these devices are heavy and uncomfortable to wear, it is necessary to develop a technology that can feel pressure, vibration, and texture by using microdisplacement stimulation or electrical stimulation for easy-to-wear accessories such as finger rings when driving a car or wearing a smartphone or smart glasses. To this end, an experimental study was conducted to precisely decode the neural spike firing signals of peripheral and cranial nerves and to check whether similar neural spike signals were fired using microdisplacement stimulation while applying vibration and pressure stimulation to tactile mechanoreceptors. In order to decode the mechanoreceptor response to tactile stimulation, an electrophysiological experiment was conducted on the peripheral nerves of mice under vibration and pressure stimulation conditions. In the experiment, an 8-10-week-old C57bl/6 mouse was used, and 10-100Hz vibration was applied using a stimulation rod equipped with a piezoelectric stimulation device for microdisplacement stimulation, and then 10-100mN force was applied to the pressure stimulation rod to obtain a neural spike response. We measured and analyzed the neural spike firing patterns with frequency and intensity of the sinusoidal microdisplacement stimulation in SA (Slowly Adaptive) and RA (Rapidly Adaptive) tactile mechanoreceptor single nerve isolated from the hind paw saphenous nerves of mice. Based on an exponential attenuation firing rate decoding model of SA neural firing that appears when pressure stimulation is applied, we appropriately adjusted the frequency and intensity of the sinusoidal microdisplacement stimulation to confirm the possibility of SA and RA neural firing similar to pressure stimulation, and we used these principles to develop a microdisplacement stimulation encoding model that responds to pressure stimulation. In addition, we studied the transmission process of vibration and pressure stimulation according to the peripheral and cranial neural tactile pathways by measuring the cranial spike signals in mice according to the frequency of the micro-displacement stimulation.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Topic: E.02. Somatosensation – Touch

Support: MRC Discovery Medicine North (DiMeN) Doctoral Training Partnership (MR/N013840/1)
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Title: Plantar cutaneous afferent responses to naturalistic loads and simulated responses during gait

Authors: ***L. D. CLELAND**¹, E. E. HOWE², A. V. VANDERHAEGHE¹, L. P. MCSWEENEY³, N. STRZALKOWSKI⁴, H. P. SAAL³, L. R. BENT⁵;
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Abstract: The skin of the plantar sole conveys tactile feedback relating to the surfaces we interact with that is essential to balance maintenance during gait. Prior research has characterised the response patterns of cutaneous receptors (slowly adapting (SA) and fast adapting (FA) type I and II) using low-force vibratory stimuli. Such stimuli enable accurate identification of firing thresholds and canonical response properties, but do not represent the stimuli regularly experienced during natural behaviours such as gait, limiting applicability to tactile feedback that occurs during movement. To expand these data, we recorded firing rates from 20 low threshold afferents innervating mechanoreceptors in the plantar skin of the human foot sole. Using microneurography we examined the relationship between load and cutaneous responses; we presented novel high-load ramp-and-hold stimuli orthogonally to the foot sole, reaching forces that are representative of those experienced during gait. Firing rates of SA afferents show a moderate, positive correlation with pressure (SA1 $r=.30$, SA2 $r=.54$), whereas FA1 afferents only show a weak positive relationship with pressure ($r=.10$). The firing rates of slowly (SA1, SA2 $r=.25$) and FA1 ($r=.22$) afferents possess similarly weak correlations with the rate of change of pressure. Even at high background loads, SA afferent responses are maintained to both dynamic and static stimulation. Conversely, FA1 afferent responses show no preference for low or high rates of loading, under high background loads. Taken together, the relationship between SA afferent firing and pressure suggests that SA afferents may provide essential information relating to the rate of loading of pressure on the foot sole during high impact activities, providing reliable information relating to background load. These data also allowed us to fit a computational model of cutaneous afferents in the foot sole, to enable simulations of population responses to dynamic spatiotemporal pressure patterns. Simulations of cutaneous responses during gait predicted that the centre of activity of the afferents precedes the pressure experienced by the foot sole by 100ms during the step cycle on average. Computational modelling of population responses can therefore provide new-found insights into the contributions of cutaneous feedback in shaping movement. Understanding the patterns of tactile responses across different behaviours can provide guidance regarding intraneural stimulation that could be implemented within neuroprosthetic devices to restore sensory feedback.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Program #/Poster #: PSTR169.04/N11

Topic: E.02. Somatosensation – Touch

Support: 5R01HD054453

Title: Breakdown in the cortical hierarchy of predictive processing in barrel cortex of Fragile X syndrome mice

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Abstract: Proposed deficits in predictive coding may underpin autism spectrum disorder (ASD) symptoms, such as sensory hypersensitivity to unexpected events. Predictive coding postulates that circuits in the cerebral cortex construct internal models of the world to anticipate incoming sensory inputs. Discrepancies between predicted and actual sensory information generate prediction error (PE) signals, which subsequently refine these internal models. We investigated if predictive processing circuits differ in the *Fmr1* knockout (KO) mouse model of ASD. We recorded from neurons across different layers in the barrel field of primary somatosensory cortex (S1) of both wild-type (WT) and *Fmr1* KO mice using in vivo two-photon Ca²⁺ imaging. A prediction paradigm was implemented by stimulating whiskers under three distinct contexts: (1) a highly predictable protocol of repetitive whisker deflections of low amplitude, randomly (10% probability) interrupted by a deviant stimulus of higher amplitude; (2) a reversed protocol where the low amplitude stimulus became the deviant within a background of repetitive higher amplitude stimuli; and (3) a non-predictable control protocol in which five different amplitudes were presented randomly with equal probability. In WT mice, neuronal responses to deviant stimuli, whether of higher or lower amplitude than expected, were enhanced in layer 4. Conversely, in layer 2-3, responses to deviant stimuli varied significantly: higher amplitude deviant stimuli elicited significantly larger responses than in the control context, whereas lower amplitude deviant stimuli evoked attenuated responses. This context-dependent modulation was also observed, albeit to a lesser extent, in putative layer 1 recordings. These findings in WT mice are consistent with a recently proposed model of predictive processing (Keller and Mrsic-Flogel, 2018), supporting specific computations performed by PE neurons to calculate the discrepancy between actual and predicted sensory input. In contrast to WT mice, *Fmr1* KO mice displayed an overall reduction in neuronal responses to whisker stimulation across all conditions; however, layer 4 responses to deviant stimuli were disproportionately enhanced, suggesting that unexpected bottom-up sensory input is exacerbated in *Fmr1* KO mice. Importantly, layer 2-3 neurons did not exhibit the context-dependent modulation observed in WT animals, although it was present in putative layer 1 neurons. While *Fmr1* KO mice appear capable of computing sensory prediction errors, this comparison seems to occur higher in the cortical hierarchy, potentially involving top-down inputs from higher-order areas.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Program #/Poster #: PSTR169.05/N12

Topic: E.02. Somatosensation – Touch

Title: Vision-based tactile sensor for real-time estimation and conversion to human-perceptible signals

Authors: *S. BAE¹, P. SUNGBAE¹, D. BAE², K. KIM², K. BAK², H. KIM², H. JUNG³, Y.-J. KIM⁴, S. CHUN²;

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Abstract: Tactile sensing and perception play a central role in robotics and human machine interfaces. In particular, contact pressure must be accurately estimated, as it provides essential information about the physical interaction between the robot and its environment. Accurate estimation of contact pressure requires a tactile sensor capable of capturing detailed deformation patterns. The TacTip sensor, known for its soft elastomer structure and embedded markers that enable high-resolution tactile imaging, allows for pressure distribution estimation through heatmaps. Building on these strengths, it was employed to estimate quantitative contact pressure in this study. We developed a pressure estimation system that integrates a TacTip-based vision tactile sensor with a convolutional neural network (CNN) trained on paired image and force data. Training utilized synchronized datasets of contact images and corresponding ground-truth force values obtained via a calibrated force sensor. The CNN learned to associate visual marker displacement patterns with applied pressure, enabling real-time quantitative contact pressure prediction under diverse contact conditions. Furthermore, the inferred pressure was effectively translated into tactile signals consistent with human tactile perception thresholds, allowing direct generation of perceptible haptic sensations. Our approach extends the original TacTip by enabling real-time pressure inference and perceptually aligned signal transformation with vision-based tactile sensor. These results suggest that vision-based tactile sensing may support future developments in cognitive robots capable of tactile interaction with humans.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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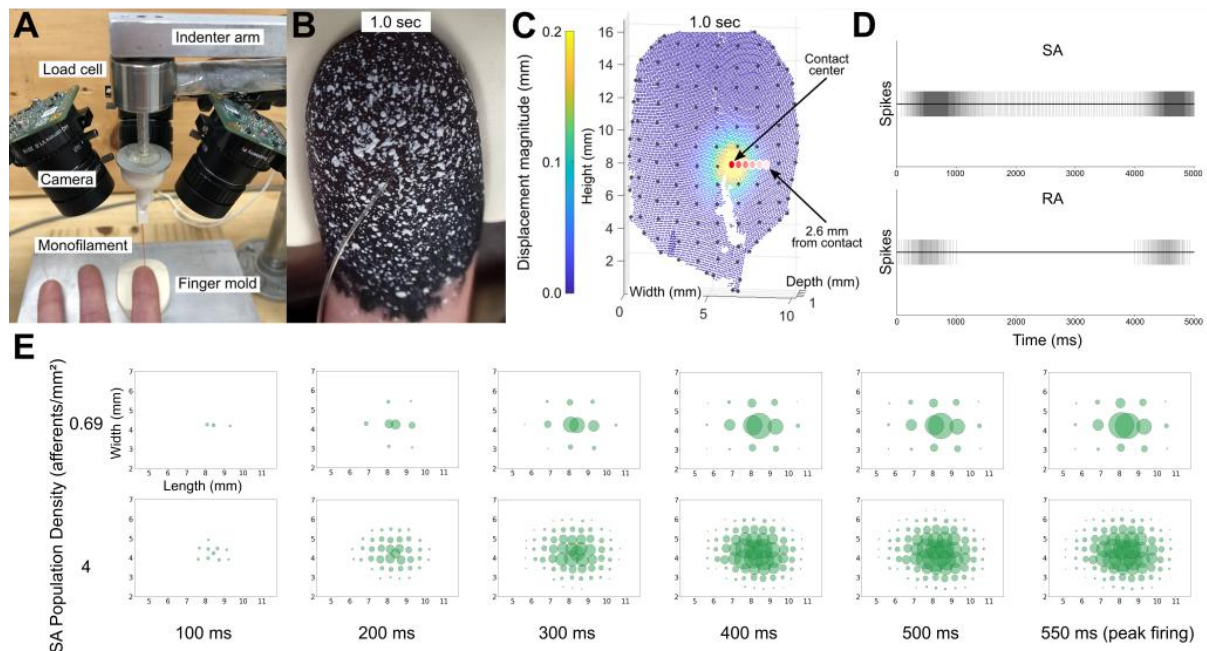
Topic: E.02. Somatosensation – Touch

Support: NIH Grant U24AT011970
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Title: A stimulus-independent biophysical model of slowly and rapidly adapting mechanosensitive afferents at single unit and population levels

Authors: A. PAPPU, *A. KAO, M. REZAEI, G. J. GERLING;
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Abstract: A diverse population of mechanosensitive afferents in the skin encodes the mechanical events that shape our sense of touch. While prior work has examined how skin surface deformation relates to perception, less is known about how spatiotemporal stress and strain patterns drive afferent-level responses. Because human microneurography is limited to single-unit recordings, computational models are essential for estimating population activity. Prior models are often stimulus-dependent—requiring precise stimulus location relative to a receptive field—and partially data-driven, limiting generalizability to novel inputs. We design and evaluate a biophysical model that predicts slowly and rapidly adapting afferent responses to low-force monofilament indentation on the human fingertip. Skin surface deformation was measured at perceptual thresholds (0.4-3.6 g) using high-resolution (25 pixels/mm) 3D digital image correlation. These measurements were used to derive spatiotemporal stress fields, which were input to a generator function that converts stress into mechanotransduction current. The function incorporates afferent-specific time constants and linear transformation coefficients to reproduce adaptation dynamics, and passes current to a leaky integrate-and-fire model to generate spikes. By tuning model parameters, we systematically modulate both peak and steady-state firing properties. Notably, receptive field size emerged as a tunable feature, varying by approximately 50% across tested parameter ranges, and spanning 5-20 mm², in agreement with prior literature. Sensitivity analysis confirmed that varying the slowly inactivating time constant (100-500 ms) altered peak firing frequency from 35-335 Hz for a fixed stimulus (3.6 g) while varying afferent population density (0.11-4 afferents/mm²), including the realistic value of 0.69, produced distinctions in cumulative afferent firing over time. Together, these findings offer a flexible, physiologically grounded framework for predicting tactile population responses to naturalistic stimuli.



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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Program #/Poster #: PSTR169.07/N14

Topic: E.02. Somatosensation – Touch

Support: NIH Grant DP2

Title: Characterizing strain differences in maternal-infant interactions in laboratory mice

Authors: *C. R. SOBRIAN¹, S. MARTIN³, D. BAMBAH-MUKKU²;

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Abstract: In altricial mammals, interactions with primary caregivers in the earliest days of life are crucial for the development of social behaviors in adulthood. While considerable progress has been made in the elucidation of adult neural dysfunction underlying the effects of early life neglect in mice, we know relatively little about how the infant mouse brain processes maternal sensory cues. Moreover, there are considerable differences in maternal behavior between different strains of laboratory mice, but the effects of this differential behavior on infant development has not been studied at high molecular and cellular resolution. We used high resolution videography to examine maternal behaviors toward PND 1-3 male and female infant

pups in 129Sv/Ev, C57Bl6J and Swiss Webster mice. Our analyses reveal broad variation in maternal behaviors including previously uncharacterized differences in the interactions of dams with male and female pups. We will also discuss experiments aimed at identifying the sensory mechanisms used by dams to distinguish male and female pups. Our experiments provide an ethologically relevant platform to understand the neural underpinnings of maternal-infant interactions at high cellular and molecular resolution.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Topic: E.02. Somatosensation – Touch

Support: Barkley Foundation

Title: Robust fNIRS Quantification of Tactile-Evoked Cortical Hemodynamics with Comprehensive Auxiliary and Short-Separation Regressors

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Abstract: Functional near-infrared spectroscopy (fNIRS) is a promising noninvasive tool for quantification of cerebral hemodynamic response (HR) in somatosensory experiments. Our prior work explored application of fNIRS in sensorimotor tasks and demonstrated HR encoding of tactile stimulus velocity (Hozan et al., 2018, 2019, 2020), while also highlighting challenges from physiological and measurement noise. This study presents an enhanced fNIRS design and analysis pipeline to more robustly capture cortical encoding of stimulus velocity by addressing these confounding variables. **OBJECTIVE:** To robustly quantify differential stimulus-evoked HR to different tactile traverse velocities on the dominant hand, and to incorporate noise regression via short-separation (SS) channels and auxiliary physiological recordings (AUX). **METHODS:** Twenty-two neurotypical adults (11F) received patterned pneumotactile stimuli at 4 velocities (20, 25, 31 & 39 cm/s). fNIRS data (16 sources, 18 detectors, 8 SS detectors) were acquired bilaterally over primary somatosensory (S1) and motor (M1) cortices (Brodmann Areas 1-7). A subset of auxiliary signals was concurrently recorded including accelerometer-based head movement, respiration, cardiac pulse, and EMG for eyeblinks and forearm contractions. Data analysis utilized a General Linear Model (GLM) via the NIRS Toolbox (Santosa et al., 2018), complemented with custom code (github: mhozan/TacVel-fNIRS) for AUX processing and integration. **RESULTS:** The level of physiological noise correction profoundly impacted findings. Without SS or AUX regressors, no significant task-related activations were observed. Including only SS regressors revealed task-related activations in expected cortical areas;

however, some activity was observed in cortical regions inconsistent with neuroanatomy. The full model, incorporating both SS and AUX signal regressors within a linear mixed-effects framework (accounting for random effects of age, sex, experiment session, head circumference, and hair characteristics), yielded the most robust and physiologically plausible results. This model consistently identified 4-7 statistically significant channels for HbO and HbR near contralateral S1 and showed velocity-specific characteristics. GLM variants were used to study the impact of participant's hair color, type and length. **CONCLUSION:** Comprehensive physiological noise regression, leveraging both SS and AUX measurements, is critical for accurately mapping task-evoked fNIRS readings to the underlying neural activity, especially in characterizing cortical hemodynamic responses induced by complex tactile stimulation.

Disclosures: **M. Hozan:** None. **J. Greenwood:** None. **S.M. Barlow:** None.

Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR169.09/N16

Topic: E.02. Somatosensation – Touch

Support: R21NS138989
R01NS092367
R01NS123681

Title: Circuit mechanisms for deviance detection in sensory cortex using 2-photon voltage imaging

Authors: ***L. C. GOMEZ**¹, M. FARYAL², M. KIM⁴, S. LEE⁶, G. ZHANG⁷, M. Z. LIN⁸, N. JI⁵, D. FELDMAN³;

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Abstract: The brain makes dynamic predictions based on sensory context and encodes unexpected stimuli more strongly than expected or recurring stimuli. This can be observed using an oddball paradigm in which a low-probability deviant stimulus is embedded within a sequence of repeated standard stimuli. In humans, such deviant stimuli evoke a delayed (~200 ms latency) EEG response, the mismatch negativity (MMN), that likely represents a top-down signal. In rodent sensory cortex, deviant stimuli trigger stronger responses than the same stimuli presented in a context where no single stimulus is expected, reflecting a prediction error signal. This 'true' deviant response may be analogous to the MMN, but what information it encodes, and its circuit basis, are debated. We studied deviant responses to unexpected whisker tactile signals in mouse somatosensory cortex (S1) using high-speed two-photon (2p) imaging of genetically encoded

voltage indicators (GEVIs). This method offers high temporal resolution and the ability to track both spiking and subthreshold dynamics in genetically defined cell types, enabling the characterization of the spatiotemporal organization of deviant responses.

We imaged neural responses in S1 using the GEVI ASAP6.2 to calibrated single-whisker deflections in an oddball paradigm as mice performed an auditory detection task. In L2/3 pyramidal (PYR) cells, deviant stimuli elicited late (150-250 ms latency) subthreshold and spiking activity compared to the same stimuli presented in a context with no specific whisker expectation. This deviant response was topographically organized, being strongest for deviant whiskers 1 row/arc from the imaged column and decreasing with distance. This indicates that deviant responses contain information about the deviant identity, and do not simply represent surprise. The long latency is consistent with the MMN and potential top-down or neuromodulatory circuit origin.

We tested for involvement of VIP or NDNF interneurons, which are driven by sensory, top-down, and modulatory inputs and thus may relay deviance signals to PYR cells. L2/3 VIP cells exhibited deviant-evoked subthreshold depolarization with a latency and spatial organization matching PYR cells. However, deviant-evoked VIP spiking was variable and modest on average, suggesting that only a subset of VIP cells may participate in driving PYR deviant responses. In early preliminary data, NDNF cells in L1 showed deviant-evoked spiking at 80-150 ms latency for whiskers one row/arc from the imaged column. Overall, this voltage imaging approach is providing novel insights into the circuit mechanisms underlying deviance detection in sensory cortex.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Topic: E.02. Somatosensation – Touch

Support: NIH Grant NS097344
The Hock E. Tan and Lisa Yang Center for Autism Research at Harvard University
Howard Hughes Medical Institute

Title: Flexible temperature light touch interactions across subcortical somatosensory circuits

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Abstract: Functionally distinct thermal and mechanosensory afferents converge in the spinal cord dorsal horn- the first central site where signals of environmental temperature and gentle touch can interact, yet how dorsal horn circuits combine them to shape perception remains poorly understood. We used large-scale *in vivo* electrophysiological recordings in anesthetized mice and a range of well-controlled tactile and thermal stimuli applied to the skin to characterize sensory coding in laminae I-V dorsal horn interneurons and across distinct projection neuron populations: postsynaptic dorsal column (PSDC) and anterolateral tract (ALT) projection neurons, optotagged using viral strategies for PSDCs and Phox2a^{FlpO}; R26-FSF-ReaChR mice for ALT subtypes. Across the dorsal horn interneuron population, innocuous and noxious cooling and heating were represented in a distributed manner that extends far beyond the thermoreceptor-recipient laminae I and II. Analysis of 653 single units revealed thermal thresholds tiling the spectrum of thermal stimuli from 0 °C to 50 °C. We found that temperature intensity-response relationships in the cold and heat ranges were different: a steep increase in the number of responsive neurons was observed when temperature increased from warm to noxious heat, whereas a more gradual increase was found in the cold range. Hierarchical clustering of temperature and touch-evoked responses is ongoing; preliminary results reveal that 76.3% of dorsal horn interneurons are polymodal, encoding temperature and innocuous mechanical force with distinct adaptation kinetics and reflecting extensive convergence of mechanoreceptor and thermoreceptor input. Despite this extensive convergence at the population level, optotagged projection neurons revealed segregated encoding. PSDC projection neurons encoded gentle touch and noxious heat, while ALT projection neurons showed diverse sensory tuning: (1) superficial ALT subtypes were narrowly tuned to temperature, (2) deep dorsal horn ALT neurons to mechanical indentations, and (3) a third group was found to be polymodal, broadly encoding both thermal and mechanical signals. These findings position the dorsal horn as a dynamic integrator that non-linearly transforms temperature and touch inputs into parallel, functionally distinct ascending outputs. Ongoing work will combine cell-type-specific silencing, large scale electrophysiology in awake mice, and closed-loop behavioral assays to identify spinal nodes whose modulation could restore altered touch and temperature perception in sensory disorders.

Disclosures: A. Chirila: None. D.D. Ginty: None.

Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR169.11/O2

Topic: E.02. Somatosensation – Touch

Title: Generating virtual tactile signals to stimulate human tactile nerves

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Abstract: Providing realistic tactile experiences to users in virtual environments is very important in applications such as virtual reality, digital twins, and robots. Until now, research on generating virtual tactile signals has been used methods such as collecting vibration data of contacted objects/surfaces using acceleration sensors and reproducing them through vibration actuators. However, analog sensor data cannot deliver realistic tactile sensations that are heterogeneous with digital neural firing patterns directly perceived by humans. In this study, we conducted research on collecting pressure and vibration information of contact surfaces using flexible and sensitive tactile sensors and converting the output analog sensor data into digital neural firing patterns that obtained by recorded response patterns of mouse nerves ex vivo to pressure and vibration stimuli to the hindpaw. Tactile sensors mimicking slow adaptive (SA) and fast adaptive (FA) tactile receptors were fabricated, and real-time data were collected while rubbing different surfaces. After signal processing, the sensor output data was converted into the digital neural firing patterns. Finally, the electrical/vibrational stimulation corresponding to the final measured pressure and vibration was applied to the user, and the system was verified through a tactile perception test.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Program #/Poster #: PSTR169.12/O3

Topic: E.02. Somatosensation – Touch

Support: IIT Gandhinagar Internal Funds

Title: Human Category Learning in Vibrotactile Perception: Role of Rule-Based and Information Integration Strategies

Authors: S. K, N. FATHIMA, *L. LAZAR;
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Abstract: Categorisation of complex stimuli into discrete groups is a fundamental feature across all sensory modalities. In the touch system, vibrotactile stimulus is a complex stimulus, with multiple features like amplitude, frequency, duration, etc., forming a single percept. To categorise such stimuli, features can be combined using rule-based (RB) and integrative (II) strategies. The COVIS model, originally developed for visual and auditory modalities, proposes a dual-system account of category learning, involving an explicit RB system and an implicit II system. In this study, we examined the role of these two strategies in a vibrotactile categorisation task where the category boundary varied according to RB or II strategies. Participants (N=60)

were asked to categorise vibrotactile stimuli randomly into two groups (A or B) based on their own judgment of stimulus properties. Feedback was given based on category boundary using four strategies: Rule-Based Amplitude (RBA), Rule-Based Frequency (RBF), Information-Integration Positive (IIP), and Information-Integration Negative (IIN). Participants were assigned to one of these four groups, where one feedback strategy was used. They completed 250 trials across four training blocks (with feedback) and one testing block (without feedback). Participants in RBA (88%) and IIN (81%) groups had the highest performance accuracy by the end of training, while RBF (54%) and IIP (60%) performance remained low. Post hoc comparisons revealed clear learning in the RB-A group by Block 3 and signs of late learning in the II-P group by Block 4, while no significant learning was observed across blocks in the RB-F and II-N groups. To investigate the strategies used by participants, we modelled the performance of the participants using a decision-bound model with a ($\pm$)10% angle tolerance for unidimensional fits. RBA and IIN were mostly best fit by General Linear Classifier (GLC) models, indicating an integrative strategy, whereas RBF and IIP were often fit by random or misaligned unidimensional models, reflecting poor rule adherence. Most GLC boundaries fell between the negative diagonal and horizontal axis, with few aligning to the positive diagonal, suggesting an intermediate strategy between RBA (0°) and IIN (135°). In a follow-up no-feedback study, a similar pattern emerged, with RBA and IIN still predominantly fit by GLC models, suggesting continued reliance on integrative strategies even without feedback. Our study shows that participants often preferred to use an information-integrative approach to categorise amplitude and frequency in a complex categorisation task.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

Location: SDCC Halls B-H

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Topic: E.02. Somatosensation – Touch

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Title: Divisive normalization accounts for temporal dynamics in somatosensory cortex

Authors: *L. LI¹, I. BLOEM³, S. BADDE⁴, W. SCHELLEKENS⁵, N. PETRIDOU⁵, M. LANDY^{1,2}, J. WINAWER¹;

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Abstract: Neural responses to sensory stimuli exhibit complex temporal dynamics, including sub-additive temporal summation and response reduction with repeated or sustained stimuli (adaptation). Studies of visual temporal dynamics using fMRI, intracranial EEG (iEEG), and macaque single-unit recordings have converged on the finding that these various temporal phenomena can be accounted for by a gain-control model in which neural responses are divisively normalized with a short lag (Zhou et al., 2019, *PLoS Comp. Biol.*). Here, we investigated whether the same temporal phenomena are observed in the tactile domain. We employed an experimental design and modeling approach comparable to those used in visual studies (Groen et al., 2022, *J. Neurosci.*). We measured somatosensory cortex responses to vibrotactile stimuli using fMRI and iEEG separately. Human participants were presented with vibrotactile stimuli (110 Hz) simultaneously to all five finger pads of the non-dominant hand. For both fMRI and iEEG, we used an event-related design in which each trial had either one stimulus (duration: 50, 100, 200, 400, 800, or 1200 ms), or two 200-ms stimuli (inter-stimulus interval: 50, 100, 200, 400, 800, or 1200 ms). The fMRI results, based on deconvolution analysis of BOLD responses, revealed clear sub-additive temporal summation similar to the responses in visual cortex (Zhou et al., 2018, *J. Neurosci.*). iEEG data, based on analysis of the time-varying broadband envelope (60-190 Hz), confirmed sub-additive summation (one-stimulus trials) and adaptation that declined with interstimulus interval (two-stimulus trials). Divisive normalization models outperformed linear models for both the fMRI and iEEG data. The models fit to the iEEG tactile data show that normalization was delayed relative to the initial response, consistent with results from the visual modality. Moreover, parameter estimates derived from the tactile iEEG data are comparable with those reported in visual iEEG studies (Groen et al., 2022), suggesting a conserved computational mechanism. The consistency between fMRI and intracranial EEG findings and across visual and tactile domains further supports the hypothesis that divisive normalization serves as a canonical neural computation, affecting temporal dynamics similarly across sensory modalities.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

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Topic: E.02. Somatosensation – Touch

Support: NSF grant 1912557
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Title: Predictive and reflective neural representation of behaviorally contacted textures in SI cortex

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Abstract: Neurons in the primary somatosensory cortex (SI) are involved in haptic perception during object manipulation but, given technical difficulties in monitoring physical interactions between the hand and manipulated objects, the nature of information-processing performed by SI neurons and how they represent somatosensory events remain essentially unknown. Locomotion is a behaviorally prevalent form of object-body interactions, more amenable to experimental control. During locomotion, the repeating pattern of proprioceptive input to SI is periodically supplemented by tactile input coming from the volar feet. This tactile input enables perception of the properties of the walking surface, which can be varied experimentally to study how SI represents these properties in the natural behavioral context. In this study, spiking activity of SI neurons with cutaneous receptive fields on the volar side of the contralateral forepaw was recorded in microelectrode penetrations of SI cortex in 2 cats while they walked on textured surfaces of varying ridge orientations. SI activity during walking was evaluated for its representation of this basic property of object surfaces. At each step during locomotion, populations of ventral forepaw neurons recorded in area 3b and in areas 1-2 represented the texture orientation of the walking surface in their firing activity both predictively before and reflectively after the forepaw came in contact with the ground. During the stance period of the stride cycle, firing of area 3b population was reduced, except for an initial burst, relative to the swing period. In contrast, firing of areas 1-2 population was elevated starting 50-150ms before the forepaw contact, peaking at the time of contact, and then gradually declining throughout the stance period. Even during periods of reduced firing, the two populations carried information about the texture orientation in the spatial distribution of firing across each population, with 1/3 of area 3b neurons and 1/2 of areas 1-2 neurons exhibiting significant orientation sensitivity.

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Poster

PSTR169: Stimulus Feature and Neural Coding in Somatosensation

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR169.15/O6

Topic: A.06. Developmental Disorders

Support: Curci Foundation Fellowship

Title: Assessing genetic and developmental shifts in tactile sensory processing-related behaviors from adolescence to early adulthood in mouse models

Authors: *S. K. OBAYASHI¹, E. A. LUMPKIN²;

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Abstract: The ability to process and adaptively respond to sensory stimuli is essential for navigating the natural world; however, deficits in sensory processing and atypical behavioral responses to sensory inputs in childhood are highly comorbid with neurodevelopmental disorders. Sensory seeking is an understudied behavioral phenotype characterized by an intense drive to obtain and vigorously explore sensory stimuli. Although sensory seeking behaviors vary across sensory modalities, many sensory seeking individuals exhibit strong preferences for novel tactile stimuli. To dissect genetic underpinnings of sensory seeking in mice, we developed novel behavioral paradigms to quantify differences in non-social affective touch and tactile exploratory behaviors. Mice from two genetically distinct laboratory mouse strains (C57BL/6J, DBA/2J) were studied to ask whether differences in age, sex, and genetic background drive variability in tactile exploratory behaviors. We found that adolescent (postnatal day 31-34) male C57BL/6J and DBA/2J mice exhibited distinct texture preferences and tactile exploratory behaviors. By contrast, young adult males (7-8 weeks) showed no consistent texture preferences. Furthermore, adolescent female mice exhibited greater variability in both texture preference and texture exploration compared to age-matched C57BL/6J and DBA/2J males. These studies suggest that tactile exploration and tactile seeking behaviors differ between sexes, background strains and developmental time frames. Together, these findings provide a foundation to study the genetic and neural circuit mechanisms that drive novel tactile exploration and seeking behaviors in adolescents.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR170.01/O7

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant 1RF1NS132812-01

Title: High-resolution computational simulation of sound localization neurons in the barn owl

Authors: *J. M. R. FOX¹, B. J. FISCHER², W. M. DEBELLO³, D. FIORAVANTE⁴, M. H. ELLISMAN⁵, J. L. PENA⁶;

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Abstract: The auditory pathways of the barn owl (*Tyto alba*) provide a unique system for studying neural coding and computation underlying hearing and sound localization. In this work, we develop high-resolution, morphologically accurate computational models of neurons in the avian midbrain for which we have broad image and functional data, but where models combining

the two have yet to be implemented and studied. This project contributes to the broader research endeavor, informing our understanding of basic levels of neural computations and the potential prevention and treatment of auditory and communicative disorders in humans.

Recent anatomical studies of space-specific neurons (SSNs) found in the inferior colliculus of the barn owl have used high-resolution electron (EM) and stimulated emission depletion (STED) microscopy techniques to reveal dense arborization and complex dendritic structures called toric spines. While the complex morphology of these structures is hypothesized to support frequency and binaural cue integration, the exact nature of this integration is unknown. We use this imaging data to develop morphologically accurate compartmental models using the Arbor simulation codebase, then optimize the model to be consistent with patch-clamp experiments using simulation-based inference, a combination of Bayesian statistical modeling and machine learning. In this way, we explore and constrain the electrophysiological parameterizations that are consistent with in vitro spiking data. The resulting model is used to infer the integration properties of SSNs, such as linearity or nonlinearity, and thus answer key questions about their nature and role in models of sound localization.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Program #/Poster #: PSTR170.02/O8

Topic: E.05. Auditory and Vestibular Systems

Support: NIH grant 1RF1NS132812-01

Title: Towards a morphological cell type atlas in the barn owl auditory space map

Authors: T. BERNI, *W. M. DEBELLO;
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Abstract: We are using Golgi-Cox stain to assemble an atlas of cell types in the barn owl tectal lobe, with emphasis on the external nucleus of the inferior colliculus (ICX), site of assembly and plasticity of the midbrain auditory space map. The computational hubs within ICX are space-specific neurons (SSNs) whose ultrastructure has been characterized by volume electron microscopy. Diverse labeling methods have identified other cell types; however, their full morphologies are poorly understood. We found, not unexpectedly, that the Golgi-Cox stain labels a diverse population of neurons dispersed throughout the auditory space map. The labeling of most neurons appears complete, with distal dendritic features and typical spines evident. A subset appears to express toric spines which are dendritic protrusions associated with Type I SSNs. The spatial density of labeled cells is ideal for microscopic isolation and digital analysis. We are pursuing two platforms for morphological classification: (1) Neurolucida reconstruction

of dendritic branching patterns for Sholl analysis. (2) Acquisition of image stacks for rendering 3D models that preserve morphological detail and process caliber. This second method will feed a pipeline for compartmental simulation of the different cell types. Long-term goals of the atlas: (1) Determine if there are systematic differences in cell morphology across regions of the map encoding frontal vs peripheral space. (2) Assemble the mesoscale connectome based on inferred connectivity with axons emanating from the input nucleus, the ICCs, labeled by focal tracer injections *in vivo*. (3) Correlate known molecular labels for different cell types with their full morphologies. (4) Determine the ‘functional canonical microcircuit’ as defined by the cohort of cell types activated by a discrete sound, to be determined by retrospective immunohistochemistry for the avian activity-dependent marker, ZENK. (5) Developmental series to sequence maturation of neuronal morphology.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Program #/Poster #: PSTR170.03/O9

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant NS104911
NIH Grant DC007690

Title: Auditory competition or binaural decorrelation? A comparison between midbrain space maps in the barn owl

Authors: *R. FERGER, A. BAE, J. L. PENA;
Neurosci., Albert Einstein Col. of Med., Bronx, NY

Abstract: Natural environments challenge the brain to prioritize the processing of salient stimuli. This is especially difficult for concurrent auditory stimuli because sound waves interact such that the phase of each frequency can be altered prior to arrival at the eardrum. This interaction depends on the relative phase of two signals and is different at each ear for spatially separated sound sources, leading to binaural decorrelation. The barn owl, a sound localization specialist, uses interaural time difference (ITD) as primary cue for sound localization in azimuth. ITD detection relies on binaural correlation and, thus, suffers from binaural decorrelation. However, the owl’s midbrain stimulus selection network (MSSN) is dedicated to representing locations of the most salient stimulus among concurrent stimuli. Previous competition studies using unimodal (visual) and bimodal (visual and auditory) stimuli have shown that relative strength is encoded in the spike response rates. Questions remained concerning competition of concurrent auditory signals.

To this end, we presented diverse auditory competitors (concurrent flat noise or amplitude modulated noise) and recorded neural responses of awake barn owls in subsequent midbrain

space maps, the external nucleus of the inferior colliculus (ICx) and optic tectum (OT, homologue to the mammalian superior colliculus). Other work showed that binaural decorrelation can explain decreased spike response rates in ICx. We expanded the above experiments to use competing stimuli that were spectrally non-overlapping, ruling out binaural decorrelation, but contained enough frequencies across the owls hearing range to be unambiguously localized.

While both nuclei contain topographic maps of auditory space, OT also integrates visual input and is part of the global-inhibitory MSSN. Through comparative investigation, we show that while increasing the strength of a competitor sound decreases spike response rates of spatially distant neurons in both regions, relative strength determines spike train synchrony of nearby units only in OT. Furthermore, changes in synchrony in OT are correlated to gamma range oscillations of local field potentials (LFPs), associated with input from the MSSN. Our results suggest that modulations in spiking synchrony between units are an emergent coding scheme for relative strength of concurrent stimuli, which may have implications for downstream read out. We compare results in both midbrain maps according to the effect of spectrally overlapping and non-overlapping stimuli on spike responses and LFP. This further elucidates the role of the MSSN for selecting the most salient stimulus.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Program #/Poster #: PSTR170.04/O10

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01 DC014950
NIH R21 DC021048

Title: Binaural spectrotemporal representation in primary auditory cortex

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Abstract: It is generally agreed that single-unit activity in the auditory cortex (AC) encodes information about both spectrotemporal and binaural sound features. However, previous research has typically focused on just one of these areas and few have explored the binaural representation of spectrotemporal features. It has been established that some spectral and binaural tuning properties, like best frequency and contralateral-ipsilateral balance, are topographic; that is, anatomically adjacent neurons tend to share these tuning properties. This study aimed to establish a deeper understanding of the topography of joint spectrotemporal and binaural tuning, specifically asking how binaural sound features are processed in the auditory

cortex and if certain binaural parameters are associated with distinct cortical columns. Linear electrode arrays were used to record the activity of 3991 neurons from primary and secondary AC (67 recording sites in 6 awake, passively listening ferrets) during the presentation of two simultaneous natural sound streams, presented +/-30 degrees azimuth from the midline. For each neuron, encoding model analysis was used to fit a binaural spectrotemporal receptive field (STRF), an extension of the traditional, single-stream STRF, to account for responses to two spatially distinct stimuli. We compared three models of binaural encoding: the monaural model collapsed two sounds into a single input spectrogram, the allocentric model treated the two sounds as distinct, parallel inputs, and the HRTF model used the head-related transfer function to compute the sound reaching each ear and used those spectrograms as inputs. On average, the HRTF model was more accurate than the allocentric and monaural models, consistent with a predominantly egocentric representation of sound in A1. Both spectrotemporal and binaural tuning properties were often more similar between neurons in the same cortical column (i.e., the same recording site) than in different cortical columns. In many neurons, we observed different spectral tuning between ipsilateral and contralateral ears. The presence or absence of binaural tuning differences was also correlated within cortical columns. In addition to encoding sound location, the joint encoding of spectro-temporal and binaural sound features may support grouping and stream segregation in complex auditory scenes.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR170.05/O11

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01 DC017466-01
NIH R21 DC022648

Title: Connecting Sensation and Perception: Investigating Auditory Illusions Using a Cryptic Species Complex

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Abstract: The ability to perceive and localize sounds is fundamental to many organisms as it plays a critical role in survival and adaptation in various environments. Auditory perception is vital, especially in facilitating communication within social groups. In humans, the complex process of accurate sound localization enhances spatial awareness. It contributes to the development of communication skills, underscoring the profound impact of auditory processing

in cognitive and social interactions. Auditory illusions such as the precedence effect and Franssen effect reveal how the brain resolves spatial and temporal discrepancies in acoustic input and provide insights into the mechanisms of auditory perception. In the precedence effect, when identical sounds with slightly different onset times are presented from two sources, listeners perceive a single auditory event localized to the leading source. Franssen effect, a variant of the precedence effect, involves a transient fast-rise short-duration tone burst followed by a slow-rise, long-duration tone from the other speaker; listeners perceive the sustained tone as originating from the transducer broadcasting the transient tone. To investigate the neural mechanisms underlying the precedence and Franssen effects, we studied the North American gray treefrog species, *Hyla chrysoscelis* and *Hyla versicolor*, respectively, which exhibit species-specific preferences for acoustic signal features. *H. versicolor* (*Hv*) females strongly prefer calls with slow-rise pulses and typically avoid fast-rise alternatives. We leveraged this natural preference to test for the Franssen effect. We found that female *Hv* approached the transducer broadcasting fast-rise (unattractive) pulses if slow-rise pulses, presented from another loudspeaker, were delayed by 0-10 ms. These results demonstrate, therefore, that *Hv* females *perceive* the slow-rise pulses as originating from the loudspeaker broadcasting the fast-rise pulses, i.e., like humans, *Hv* females experience the Franssen illusion. To identify neural correlates, we conducted *in vivo* extracellular recordings from the anuran inferior colliculus, the auditory midbrain. In a subset of neurons, we observed strong suppression of responses to contralateral slow-rise pulses when ipsilateral fast-rise pulses were temporally advanced, mirroring the behavioral effect. By combining behavioral and neurophysiological approaches, our study reveals how fine-scale temporal processing in the auditory midbrain contributes to spatial perception and demonstrates the utility of anuran models for investigating the neural basis of auditory illusions.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

Location: SDCC Halls B-H

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Program #/Poster #: PSTR170.06/O12

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC020097

Title: The influence of spectrum and modulation statistics on the neural representation of speech in natural background sounds

Authors: *J. P. DION¹, I. H. STEVENSON¹, M. A. ESCABI²;

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Abstract: Separating target sounds from background noise is challenging for people with normal hearing, and especially challenging for people with hearing impairments as well as artificial

speech recognition systems. Why different natural backgrounds mask the perception of speech to varying degrees, and how the brain separates speech from background noise, is not yet fully understood.

Here, we recorded multi-unit activity from the inferior colliculus of head-fixed unanesthetized rabbits passively listening to speech mixed with eleven natural backgrounds (speech babble, bird babble, water, fire, city noise, etc.). Speech was mixed with each original (OR) background at multiple acoustic signal-to-noise ratios (aSNRs). We also presented speech mixed with spectrum-matched (SM) backgrounds that retain the original spectra but have whitened modulations, or modulation-matched (MM) variants that retain the original modulations but have whitened spectra. Using a cross-spectrum shuffling procedure, we separated the foreground- from the background-driven neural responses. The neural signal-to-noise ratio (nSNR) was then estimated and used as a metric of speech coding fidelity.

We find that nSNR depends on background category and statistics. Compared to OR backgrounds, nSNR can increase or decrease for SM and MM backgrounds in a category-dependent manner. This suggests that the original spectra (OR vs. MM) or modulations (OR vs. SM) improve or worsen the neural representation of speech. Interestingly, the impact of background category and statistics was largely independent of aSNR, since increasing aSNR amplified nSNR approximately linearly. We also demonstrate how the background spectrum and modulation statistics affect neural encoding of speech at temporal modulations below 10 Hz, which overlap and potentially mask temporal fluctuations for phonemes, words, and syllables. Spectrum and modulation masking effects were clustered according to background category, and a model of the cochlea and auditory midbrain showed a similar clustering. Finally, human perceptual tasks using the same backgrounds suggest that nSNR correlates with speech recognition accuracy. Collectively, the results demonstrate that spectrum and modulation statistics critical to speech masking are reflected in the population activity of the inferior colliculus. These neural response statistics reflect the coding fidelity for speech and likely contribute to downstream signaling underlying speech perception in real-world noise.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Program #/Poster #: PSTR170.07/O13

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC020097

Title: Predicting auditory midbrain responses to natural sounds with adaptive Gabor spiking receptive field models

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Abstract: Spectro-temporal receptive fields (STRFs) are used in auditory neuroscience to model the time-frequency sensitivity of auditory neurons. Often, STRFs are derived using unbiased synthetic stimuli, such as dynamic ripples, which can easily be estimated using spike-triggered averaging. However, with natural sounds, decorrelation and regularization techniques are needed to remove embedded stimulus correlations that distort the estimated STRFs. Furthermore, nonlinearities and non-stationarities make it difficult to predict neural responses to natural sounds. Neural recordings were obtained from the inferior colliculus of unanesthetized rabbits in response to natural sounds and dynamic moving ripple (DMR). We developed a model-based approach for deriving auditory STRFs and predicting single trial spike trains to these sounds. The model consists of a first and second order nine parameter Gabor STRF (gSTRF; Qiu et al. 2003), accounting for the neuron's linear and non-linear spectro-temporal integration. A four-parameter nonlinear integrate-and-fire (IF) compartment incorporates intrinsic noise, cell membrane integration, and nonlinear thresholding to generate simulated spikes, while a six-parameter adaptive STRF dynamically adjusts the intracellular current to account for slow fluctuations in firing rate. Bayesian optimization was used to fit neural data and derive optimal model parameters. We compared optimal gSTRFs to other approaches such as a generalized linear model. STRFs derived via regression were spectrally smeared, indicating that stimulus correlations were not effectively removed. In comparison, the gSTRF was compact and provided biologically feasible estimations of parameters, such as the neuron's best frequency and temporal modulation. The adaptive STRF improves predictions of firing changes across sounds not captured by the gSTRF. Furthermore, unlike conventional receptive field models, which generate continuous outputs, the model produces and predicts spiking activity with spike timing precision comparable to IC neurons (between ~0.5 -5 ms). Simulations were also performed where the "ground truth" STRF and spiking activity were known a priori. We demonstrate that the gSTRF converges to the original simulation parameters and replicates the spiking activity from the original simulations. This approach allows one to derive auditory STRFs and predict neural spiking activity to natural sounds using functionally interpretable basis functions and spiking model computations. The small number of parameters make exploration of nonlinear and nonstationary effects due to natural sound statistics more feasible.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

Location: SDCC Halls B-H

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Topic: E.05. Auditory and Vestibular Systems

Support: Natural Sciences and Engineering Research Council of Canada
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Title: Moderate noise exposure influences the auditory brainstem response in a frequency-related pattern

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Abstract: Background: Exposure to loud noise results in irreversible outer hair cell damage and a marked elevation of the hearing threshold, while prolonged exposure to moderate noise (MN) typically does not produce significant alterations in hearing sensitivity. Recent studies indicate that MN exposure can result in the impairment of ribbon synapses and the neural plasticity of the central auditory system, i.e., tonotopic map reorganization in the auditory cortex. To date, little is known about the functional alteration in the lower auditory brainstem. This study investigated the immediate changes in neuronal responses along the mouse auditory brainstem following long exposure to pure tone. Methods: Under anesthesia (ketamine and xylazine), twenty C57BL/6 young adult mice, aged 4-7 weeks old, were unilaterally exposed to 1 hour of continuous pure tone (characteristic frequency, CF based on mice's hearing) at 65 dB SPL. Before and after exposure, the auditory brainstem response (ABR) was applied to assess the changes in neuronal auditory response in the brainstem. A paired t-test was used to compare the difference between the ABR recording before and after the exposure. Results: Among the 20 mice, the mean ABR threshold was significantly elevated at CF ($p = 0.008$) and 0.5 octaves above ($p = 0.012$). Nine of the experimental mice showed threshold shift after the exposure, with an average of 6.875 ± 3.48 dB SPL. In the mice with no threshold shift ($n=11$), the Wave I amplitude at the threshold level significantly decreased ($p = 0.008$). The dynamic range measured at CF showed that the responses among 40-60 dB SPL were affected most. At CF, the amplitude of Wave I and Wave II at 60 dB SPL significantly decreased, while Wave V showed no significant change. The individual change of Wave I is consistent with a decrease in amplitude and an increase in latency, while in higher auditory brainstem stages, the variability increased. Conclusions: Our results suggest that exposing mice to 1-hour exposure to pure tone with 65 dB SPL impacts the hearing sensitivity in a tone-exposure related pattern. The signal processing in the auditory nerve and cochlear nucleus is impaired, while the impact may probably be compensated in the inferior colliculus.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

Location: SDCC Halls B-H

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Topic: E.05. Auditory and Vestibular Systems

Support: Simons Foundation Junior Fellow Award 965382
NIH U19 Grant NS107616

Title: Longitudinal monitoring of developmental plasticity in the mouse auditory cortex

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Abstract: The postnatal brain undergoes substantial plasticity to represent features and statistics of the sensory world. For the auditory system, studies in rodents (Zhang et al. 2001, Villers-Sidani et al. 2007, Dorn et al. 2010) and humans (Näätänen et al. 1997) indicate that the postnatal primary auditory cortex changes in response to early acoustic experience. Much work on developmental plasticity in rodents has focused on responses to pure tones and representations of sound frequency, whereas less is known about the development of vocalization processing. Ultrasonic vocalizations are spectrotemporally complex sounds used by rodents in varied social contexts, e.g., distress calls from pups soliciting parental caregiving (Ehret 2005). How and when neuronal representations of auditory cues (from lower-dimensional features like spectral frequency to higher-dimensional auditory objects like vocalizations) first emerge in the postnatal auditory cortex and change with experience is unknown. To date, examining sensory processing across postnatal experience has been technically challenging, thus limiting our understanding of how changes unfold across individual neurons and neuronal cell-types. To address these questions, we perform longitudinal two-photon calcium imaging of hundreds of excitatory and/or inhibitory neurons in the auditory cortex of young mice (N=20), from postnatal day (P) 12 into adulthood. We found that both excitatory and inhibitory neurons in the auditory cortex started responding to tonal stimuli by P13-14 with an initial tonotopic organization that expanded over the next few days. A fraction of neurons gradually changed frequency tuning across days, although overall there was a stable tonotopic representation even at these early ages. Repeated tone exposure during the auditory critical period (P13-16) shifted single-neuron tuning towards the exposed frequency. Compared to lower-frequency tones and down-shifted vocalizations, responses to ultrasonic stimuli (both pure tones and natural vocalization playback) emerged at later ages (>P28) but were quite transient, with many responses disappearing after several days. Ultrasonic vocalization responses initially were observed in neurons tuned to ultrasonic frequencies, but over later development they became independent from ultrasonic frequency tuning. Our results show how varied sensory representations at the single-cell and population levels in the postnatal auditory cortex emerge and change over the course of early-life development.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Title: Vagus nerve stimulation enhances gamma-band auditory entrainment in rat auditory cortical regions

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Abstract: Vagus nerve stimulation (VNS) modulates sound-evoked neural activities in the auditory cortex. In our previous study, VNS enhanced onset auditory-evoked potentials and gamma-band activities in response to click sounds in the rat primary auditory cortex. However, it remains unclear how VNS modulates auditory gamma entrainment to 40-Hz periodic sounds, a neural response that is impaired in neurodegenerative and psychiatric conditions including Alzheimer's disease and schizophrenia. In this study, we hypothesized that VNS would enhance gamma-band auditory entrainment in auditory cortical regions. We investigated the effect of VNS using electrocorticography (ECoG) that covered the auditory and insular cortices of 11 Wistar rats under isoflurane anesthesia. Electrophysiological recordings were performed after implantation of the VNS system. The auditory cortex and insular auditory field in the posterior insula were characterized by auditory-evoked potentials using click stimuli. We presented 500ms rapid click trains at 40 Hz (40 clicks/s) in 300-trial sessions before and more than 3 hours after VNS. Auditory entrainment to the 40-Hz click trains was estimated using inter-trial phase clustering (ITPC) and event-related spectral perturbation (ERSP). We assessed how VNS modulates ITPC and ERSP using analysis of variance. ITPC increased at 40 Hz in the auditory cortex and insular auditory field during 40-Hz click trains compared to baseline. VNS significantly enhanced ITPC at 40 Hz in the auditory cortex and insular auditory field, not in the anterior insula. Additionally, VNS enhanced ERSP at 40 Hz specially in the auditory cortex. These results suggest that VNS can enhance gamma-band auditory entrainment in lower-order auditory cortical regions. VNS may represent a potential therapeutic approach for conditions characterized by impaired gamma-band auditory entrainment.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH K99/R00 DC021581
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Title: Projection-specific processing of infant vocalizations for mouse maternal behavior.

Authors: *A. M. LEMESSURIER¹, G. KAUR², J. PARAISO³, A. AGHA⁴, J. STEPHENS³, R. C. FROEMKE⁵;

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Abstract: How does the brain derive meaning from social vocalizations and drive behavior in response? Vocalizations are temporally complex, requiring integration across multiple time-scales for appropriate contextualization. We hypothesize that corticofugal projections modulate temporal integration in feed-forward auditory circuits to facilitate this. We tested this using an ethological mouse behavior that depends on left auditory cortex. Mothers find and retrieve isolated pups into the nest when pups emit ultrasonic vocalizations (USVs). Virgin females don't usually retrieve pups, but learn after several days of co-housing with a mom and litter. We chemogenetically silenced neurons projecting to inferior colliculus (corticocollicular) or tail of striatum (corticostriatal) during pup retrieval in experts, and found that corticocollicular, but not corticostriatal neurons were key for successful retrieval. We compared encoding of USVs over days of co-housing using 2-photon Ca²⁺ imaging in awake virgins. Corticocollicular neurons showed sustained increases in activity during blocks of USV presentation compared to pure tones, while activity was similar for USVs and tones in corticostriatal neurons (N=8 CC mice, N=7 CS). This was corroborated with in vivo whole-cell recordings from optotagged projection neurons (n=8 CC, n=5 CS neurons). In both groups, we observed delayed responses to USVs, which were larger in magnitude on expert days (N=4 mice per group for tracked neurons). To examine how cortical projections modulate activity across auditory areas with precision for spike timing, we performed simultaneous silicon probe recordings from auditory cortex, inferior colliculus, and thalamus (N=6 mice). A subpopulation of neurons in each area didn't respond to single call syllables but instead integrated over longer sequences. We hypothesize that cortical feedback facilitates temporal integration over multiple syllables, which could enable categorization based on temporal features. To test this we optogenetically silenced corticofugal projections, which altered the timing of call-evoked spikes in some IC neurons.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Topic: E.05. Auditory and Vestibular Systems

Support: DC021692
DRL2319492
DC017797

Title: Divergent Principles of State-Dependence Between Early Brainstem and Central Auditory Circuits

Authors: *H. K. SRIVASTAVA¹, K. BOCHTLER², J. DREW¹, K. X. KIM¹, N. SCARCELLI¹, H. JIANG¹, M. J. MCGINLEY²;
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Abstract: Activity in neuromodulatory systems fluctuates continuously during wakefulness, influencing neural processing broadly across the brain. While state-dependent modulation has been extensively characterized in the auditory cortex and thalamus (e.g. McGinley et al., 2015), its effects on earlier stages of auditory processing remain poorly understood. To address this, we recorded single-unit activity from the dorsal cochlear nucleus (DCN) of awake, head-fixed mice using high-density Neuropixels probes, while simultaneously tracking pupil diameter and locomotion as proxies for neuromodulatory brain state. The DCN is an early brainstem structure that integrates both auditory and non-auditory inputs, representing a critical site for investigating how internal brain state shapes sensory encoding. DCN neurons were classified into putative cell types: fusiform (excitatory projection neurons), cartwheel or vertical cell (two classes of interneurons) based on their responses to tones and broadband noise. Spontaneous firing rates exhibited robust, cell-type specific modulation by pupil-indexed arousal level. Moreover, neuronal synchrony within the DCN varied systematically with pupil size, in a cell-pair type-specific manner, suggesting that internal state not only modulates individual neuron excitability but also affects circuit-level interactions. The effects of pupil size on sound-evoked responses in DCN were comparatively small. In similar recordings in downstream inferior colliculus (IC), a distinct pattern was observed. Here, tone-evoked responses showed an inverted-U dependence on pre-stimulus pupil size, consistent with earlier reports from auditory cortex and thalamus. Furthermore, unsupervised clustering revealed subpopulations of IC neurons with distinct state-dependent patterns and unique response properties. The effects of pupil size on spontaneous activity in IC were comparatively small. These findings demonstrate that early auditory brainstem circuits are dynamically modulated by internal brain state, but with a strikingly different pattern than in IC, thalamus, and cortex. In particular, the DCN shows strong state influence on spontaneous activity and its synchrony, highlighting its role as a critical node in state-dependent auditory processing. Ongoing experiments are assessing the impact of other state measures, such as ear movements, on state-dependent DCN sound processing. McGinley, M. J., David, S. V., & McCormick, D. A. (2015). Cortical membrane potential signature of optimal states for sensory signal detection. *Neuron*, 87(1), 179-192.

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Poster

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC021692

Title: Vertical Stripes in the Spectrogram: Interaction of Rapid Onsets with Sustained Narrow-band Sound Responses in the Inferior Colliculus

Authors: *T. CHEN^{1,2}, H. K. SRIVASTAVA², M. RYAN², H. JIANG², M. J. MCGINLEY²;
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Abstract: Rapid acoustic onsets are a salient feature of many natural sounds including speech and environmental noises like rustling. These abrupt sound onsets cue sound objects and are processed by specialized auditory mechanisms tuned for temporal precision. In particular, octopus cells (OCs) in the cochlear nucleus are especially sensitive to these sharp onsets and provide precisely timed inhibitory input to the inferior colliculus (IC) via the ventral nucleus of the lateral lemniscus (Oertel et al., 2000). Despite this well-defined pathway, and functional importance of rapid onsets in object-segmentation and streaming, how these rapid onsets interact with the ongoing stimuli to shape sound processing in the IC remains unclear. To investigate the nature of this interaction, we presented brief, click-like stimuli with bandwidths varying from 1 to 5 octaves and a range of center frequencies, called ‘clickets’. We examined their impact on tone-evoked responses in the inferior colliculus (IC) across varying temporal and frequency offsets in awake head-fixed mice. A simple PSTH-based linear model revealed sublinear integration of tone and click responses, suggesting suppressive interaction. Modulation of tone responses was strongest when clicks and tones were presented simultaneously, consistent with rapid, precisely timed inhibition. Our findings suggest that rapid acoustic onsets engage precisely timed inhibition in the IC, possibly driven by OCs, leading to sublinear integration and suppression of ongoing tone responses. This interaction is strongest at minimal delays, suggesting a possible feedforward inhibitory mechanism for creating ‘pop-out’ of distinct sound objects. Oertel, D., Bal, R., Gardner, S. M., Smith, P. H. & Joris, P. X. Detection of synchrony in the activity of auditory nerve fibers by octopus cells of the mammalian cochlear nucleus. Proc. Natl. Acad. Sci. 97, 11773-11779 (2000).

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Topic: E.05. Auditory and Vestibular Systems

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Title: Task Utility Modulates Temporal Coherence Encoding via STRF and Non-STRF Neuronal Subpopulations in Auditory Cortex

Authors: *K. YU¹, H. K. SRIVASTAVA², J. M. FINE³, B. Y. HAYDEN⁵, K. JASPE¹, N. SCARCELLI¹, H. JIANG¹, J. A. HENNIG⁶, M. J. MCGINLEY⁴;

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Abstract: Temporal coherence (TC) between frequency channels is crucial for differentiating a target sound from its background. Attention plays a key role in utilizing TC for acoustic object streaming, as seen in classic 'cocktail party' scenarios, where individuals focus on a specific sound source, such as a target speaker, and filter out background noise. In recent work, we found that in a mouse behavioral task model, task utility associated with trials can influence attention-like mechanisms, enhancing detection of TC embedded in tone clouds (de Gee et al., 2024). However, how TC is encoded at the population level in auditory cortex (ACtx), and how attentional state modulates this encoding, remain open questions. According to Krishnan et al., TC is encoded by integrating spectrotemporal features such as continuity, pitch, and spectral grouping. To study this, we recorded neural activity from ACtx in mice performing a sustained attention task with fluctuating task utility. Using flexible spline-based receptive field estimation tools (Huang et al., 2021), we identified neurons whose responses to tone clouds were well-explained by spectrotemporal receptive fields (STRFs) and those that were not. While many neurons were well-predicted by STRFs during tone cloud trials, their predictability decreased during TC stimuli, especially under high utility. Linear discriminant analysis (LDA) showed that decoding accuracy for TC improved under high utility but was primarily driven by a complementary population of non-STRF neurons. To explore this computationally, we trained a reinforcement learning RNN model to solve the TC task using spectrotemporal inputs. The model distinguished tone clouds from coherent signals, and its units developed functional preferences for encoding either spectrotemporal features or coherence-related information, with the latter emerging predominantly in deeper layers and not well-explained by STRFs. These findings suggest that STRF-explainable neurons encode low-order features, while TC representation under attentional modulation involves neurons encoding more abstract properties. Ongoing work applies machine learning to characterize the feature space of non-STRF neurons and how their representations vary with task utility. de Gee, J.W. et al. (2024). Strategic stabilization of arousal boosts sustained attention. *Current Biology*. Krishnan, L., Elhilali, M., & Shamma, S. (2014). Segregating complex sound sources through temporal coherence. *PLoS Computational Biology*. Huang, Z., Ran, Y., Oesterle, J., Euler, T., & Berens, P. (2021). Estimating smooth and sparse neural receptive fields with a flexible spline basis. *bioRxiv*.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Title: Population decoding of pitch across harmonic and temporal cues reveal functionally distinct subpopulations of cortical neurons

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Abstract: Pitch, the tonal quality of sound, is crucial to our experience of musical melody, enhances vocal communication, and helps us focus on one voice in a crowded room. We perceive the pitch of a periodic sound at a single fundamental frequency (F0), and this F0 can be derived from either the regular spacing of harmonic frequencies or the repetition rate of the sound's waveform. While previous studies suggest that auditory cortex may play a key role in processing pitch, it remains unclear how neurons in this region extract F0 from harmonic and temporal features of complex sounds. We performed Neuropixels recordings of large populations of single neuron spiking activity in the auditory cortex of anaesthetised ferrets while presenting a variety of pitch-evoking sounds that varied in harmonic composition and temporal regularity. We found that F0 is linearly decodable from neural population activity across all sound types presented, but these population codes differ depending on the acoustic content of the sound. Some neurons play a key role in encoding F0 across many different sound types, while other neurons are only informative about a sound's F0 when specific temporal or harmonic cues are present. Single neurons with consistent F0 tuning across a variety of pitch cues are often key to population-level F0 encoding across different complex sounds. In these neurons, F0 tuning does not generally correspond to their pure tone tuning. This is recapitulated at the population level, where we find that a linear decoder trained on pure tone responses cannot accurately predict the F0 of complex sounds. This suggests that subsets of auditory cortical neurons may be specialized to represent the pitch of complex harmonic and temporal pitch cues using mechanisms that cannot be predicted from their pure tone frequency preferences.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR170.16/P6

Topic: E.05. Auditory and Vestibular Systems

Support: NSF GRFP 2021327094

Title: Encoding of complex sounds across time in primary auditory cortex

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Abstract: How the brain encodes multiple simultaneous stimuli is not fully understood. When presented with multiple sensory stimuli, single neurons can fluctuate or ‘multiplex’ over time between encoding each individual stimulus (Caruso et al., 2018). In visual areas, the prevalence of neurons that are found to show this fluctuating behavior, termed mixtures, has been shown to differ based on the perceptual binding of the stimuli into separate vs. fused objects (Jun et al., 2022, Schmehl et al., 2024). In the auditory system, how the brain binds sounds into “objects” is not entirely understood, but involves a temporal component (Deike et al., 2012). Here, we investigated this binding using harmonically related sounds. We sought to determine how individual neurons in the auditory cortex encode different combinations of harmonic stimuli and how fluctuating response patterns may relate to perceptual binding.

To test this, we collected 60 single-neuron recordings from the auditory cortex of a rhesus macaque as she passively listened to combinations of harmonics that formed congruent and incongruent stimuli. Congruent stimuli contained tones that were integer multiples of the same fundamental frequency, while incongruent stimuli contained lower and upper tones from two different fundamental frequencies, respectively. We found clear evidence of multiplexing in the auditory cortex in response to both types of stimuli; however, patterns changed as the sounds progressed in time. During the initial 0-100 ms response period, neurons most commonly responded to either the lower or the upper harmonics. During the later 100-500 ms period, neurons instead showed fluctuating activity between encoding the lower vs. higher harmonics. These general patterns occurred regardless of the congruence of the harmonic complex. Together, these results suggest that processing of complex sounds with multiple related harmonic components evolves over time in the auditory cortex. This finding may provide insight into how the segregation of auditory “objects” unfolds across time.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR170.17/P7

Topic: E.05. Auditory and Vestibular Systems

Support: P50MH109429
RO1DC012947
RO1DC019979

Title: Layer- And band-specific multi-unit activity (mua) tracking to song envelope in monkey auditory thalamocortical circuits

Authors: *Q. MEIZHEN, A. BARCZAK, T. M. MCGINNIS, C. E. SCHROEDER, A. W. ROE, M. N. O'CONNELL;

Translational Neurosci. Lab. Div., Nathan S. Kline Inst. for Psychiatric Res., Orangeburg, NY

Abstract: Background: Songs carry hierarchical rhythms—slow phrases (< 4 Hz), syllabic patterns (~ 4-8 Hz), and fine acoustic fluctuations (> 30 Hz). It remains unknown how local populations of spiking neurons (multiunit activity; MUA) across cortical layers and the auditory thalamus track these nested rhythms. Which frequency bands of MUA best encode the instantaneous loudness of a song? **Methods:** We recorded MUA via a linear 23-contact probe spanning primary auditory cortex (A1) and medial geniculate body (MGB) in awake macaques listening to song excerpts. From each recording (N = 13 sessions × 21 usable channels), we extracted ± 0.5 s epochs time-locked to song onset. Continuous Morlet wavelet decompositions (2-150 Hz; 7 cycles) produced time-frequency power (MUA band power) for each channel and epoch. We averaged power across canonical bands—delta (1-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-30 Hz), low-gamma (30-50 Hz), mid-gamma (50-80 Hz), high-gamma (80-150 Hz)—and computed Pearson's r between each band's power time series and the song's Hilbert amplitude envelope (50-8000 Hz, 10ms smoothing) on a per-channel basis. **Results:** Initial results showed strong, band-specific tracking of MUA to the music envelope, but only at certain recording sites and in particular frequency ranges. The most robust tracking occurs in alpha (8-12 Hz) and beta (12-30 Hz) ranges, implying that these intermediate frequencies carry the predominant cortical representation of musical loudness transients. This laminar-wide α/β tracking of instantaneous loudness has not been demonstrated previously in primate MUA during natural music listening. Negative delta-band coupling suggests that slow network rhythms are actively suppressed during loud segments, indicating that slow MUA oscillations were suppressed precisely when the song's amplitude peaked—a novel delta-band anti-tracking phenomenon at the multiunit level. **Significance:** This study is the first to map how different MUA frequency bands across cortical laminae and thalamic sites synchronize (or anti-synchronize) with music's envelope in awake monkeys. These results provide a multiscale neural framework for understanding how local spiking populations parse the hierarchical structure of complex natural sounds—insights that are critical for models of auditory perception, rhythm processing, and predictive coding in the primate brain.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Title: Integrating a biophysical model of the macaque auditory thalamocortical system with a directional and scalable (DiSc) microelectrode array

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Abstract: The nonhuman primate thalamocortical auditory system shares key anatomical and functional similarities with the human system and allows for more invasive experimental access, making it an ideal translational model for studying auditory processing. We developed a biophysical model of the macaque thalamocortical auditory system using NetPyNE and the NEURON simulation environment, extending it to multiple cortical columns to explore wider-area dynamics. Our implementation also used Brainstorm, a widely used platform for MEG/EEG analysis, to simulate recordings from directional and scalable (DiSc) microelectrode arrays, a novel iEEG device we are developing to improve source localization. The model simulates a cortical column as a cylindrical volume of 200- μ m radius and 2,000- μ m depth A1 tissue, with over 12,000 neurons and 25 million synapses, incorporating data on 42 cell-type-specific neuron densities, morphology, and connectivity across six cortical layers. It is bidirectionally connected to the MGB thalamus, including interneurons and core and matrix-layer-specific projections to A1. Each neuron is simulated as a compartmental model with multiple ion channels and standard synapses (AMPA, NMDA, GABAA, GABAB). The model simulates cellular and circuit-level electrical dynamics including local field potential (LFP), current source density (CSD), and multiunit activity (MUA). Prior theory suggests that the large apical dendrites of layer V

pyramidal neurons and layer II/III pyramidal cells are primary contributors to the source/sink patterns in laminar CSD signals. Our model allows us to dissect the roles and contributions from distinct cell types and cortical layers to each recorded signal. We use it to quantify these contributions during simulated auditory input. Modeling DiSc functionality and comparing it to standard laminar electrodes, we predict improved stimulus decoding performance and spatial resolution. Preliminary results suggest DiSc arrays outperform conventional multielectrode arrays in spatial resolution and directional sensitivity. We also present experimental data from macaques (n=4) using DiSc arrays and compare them to model-based predictions. Combining modeling and empirical measurements enables detailed analysis of the cellular sources underlying electrophysiological signals and provides a framework for designing next-generation neural interfaces. We describe and demonstrate how Brainstorm simplifies the ability to merge subject-specific imaging and lead field computations with our biophysical model in NetPyNE to study the system- and cellular-level dynamics of auditory processing.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Title: Decoding Illusory Melody from Electroencephalography Using Backward Temporal Response Functions

Authors: *A. CHOI^{1,2}, I. CHOI², K. LEE¹;

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Abstract: Musical illusions offer a unique lens into the constructive nature of auditory perception. Among them, the scale illusion demonstrates how the auditory system can reorganize dichotically presented pitch sequences into a unified melodic contour that differs from the physical input. While prior neuroscience studies have explored such illusions using event-related potentials (ERPs) or spatial activation patterns, the temporally evolving neural representation of

these perceptual reorganizations remains underexplored. In this study, we aimed to demonstrate the neural dynamics of scale illusion via linear decoding of unified melodic contour from listeners' continuous EEG. We recorded 64-channel EEG data from 27 participants who listened to four variations of the scale illusion: (1) monaural presentation of the original illusion stimulus, (2) monaural presentation of the perceived illusory pitch contour, (3) the original scale illusion presented binaurally, and (4) a timbrally mismatched version of the illusion (piano vs. violin). Temporal response function (TRF) models were trained on the two monaural conditions (Stimuli 1 and 2) and tested on the dichotic conditions (Stimuli 3 and 4). After each trial, participants reported whether they perceived a continuous or fragmented contour. Pitch interval and envelope features were extracted and used as targets for decoding from EEG. In backward decoding, pitch-based models outperformed envelope-based models for Stimulus 3 (illusory, timbrally coherent), with the highest decoding correlation (pitch $r = 0.098$ vs. envelope $r = 0.021$). Decoding accuracy was consistently higher for Stimulus 3 than for Stimulus 4 (timbrally mismatched) across both features ($p < .001$), suggesting that timbral coherence supports neural recoverability of perceptual structure. Moreover, models trained on Stimulus 2 (reorganized percept) predicted Stimulus 3 significantly better than those trained on Stimulus 1 (original input) ($p < .001$), indicating that neural activity aligns more with perceived, rather than physical, pitch contours. These results demonstrate that pitch features more effectively capture the perceptual organization of illusory melodies in backward decoding. The enhanced decoding performance for the perceptually coherent and timbrally matched condition supports the view that the brain tracks internally reconstructed pitch streams over raw acoustic input. This suggests that illusory percepts are not only consciously experienced but also robustly encoded in neural dynamics, offering insights into the cortical representation of auditory illusions.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Title: Identifying cell-type-specific alterations underlying schizophrenia-related deficits in auditory steady-state response and stimulus specific adaptation: insights from a multiscale model of auditory thalamocortical circuits

Authors: *S. MCELROY¹, N. NOVIKOV², A. BALLA³, M. N. O'CONNELL³, D. C. JAVITT⁴, S. A. NEYMOTIN³, S. DURA-BERNAL⁵;

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Abstract: Individuals with schizophrenia exhibit a variety of symptoms categorized as positive, negative, and cognitive. A cognitive symptom extensively studied using electroencephalography (EEG) is sensory processing deficits, particularly in the auditory system. These deficits manifest as abnormalities in event-related potentials and cortical oscillations. In particular, this work focuses on reduced mismatch negativity (MMN) amplitude and decreased power of 40Hz auditory steady state response (ASSR) observed in schizophrenia patients.

To investigate this phenomenon, we have extended our previously developed model of auditory thalamocortical circuits to investigate the source of these schizophrenia-related EEG biomarkers. This model simulates a cortical column containing over 12k neurons and 30M synapses. Neuron densities, laminar locations, biophysics, and connectivity at the long-range, local, and dendritic scale were derived from published experimental data. Auditory stimulus-related inputs to the thalamus were simulated using a phenomenological model of the cochlea. The model reproduced in vivo cell type and layer-specific firing rates, local field potentials, and EEG signals consistent with controls.

To simulate MMN, we decomposed the response into two core components: stimulus-specific adaptation (SSA) and deviance detection. SSA reflects a reduced neural response to frequently repeated stimuli due to synaptic and intrinsic refractoriness and has been linked to mechanisms such as N1 ERP suppression. Experimental studies in rodents have implicated GABA B receptor activity in mediating SSA in both the thalamus and cortex. We tuned GABA B time constants per recent findings, enabling the model to exhibit robust SSA across a range of inter-stimulus intervals. Furthermore, blocking GABA B signaling in the model abolished SSA, emphasizing its critical role.

The model has previously been established to capture the healthy 40Hz ASSR, so to investigate its dysfunction in schizophrenia patients, we used findings in genetics and post-mortem histology to develop a model to recreate a disease state 40Hz ASSR. The most critical changes to the model in reducing 40Hz ASSR power were overall NMDA conductance and the density of NMDA receptors, specifically on parvalbumin-positive interneurons. This work aims to bridge the gap between experimentally determined molecular and genetic changes associated with schizophrenia and the resulting circuit and network behavior that give rise to robust EEG biomarkers.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Topic: E.05. Auditory and Vestibular Systems

Support: NIA R01 AG067073

Title: Acute nicotine enhances frequency-selective responses in human auditory cortex of younger but not older adults

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Abstract: Nicotinic acetylcholine receptors (nAChRs) are densely expressed on inhibitory interneurons in auditory cortex, and signaling through these receptors can sharpen receptive fields by suppressing responses to off-center frequencies. In rodent models, systemic nicotine administration decreases bandwidths and increases amplitudes of tuning curves in primary auditory cortical neurons. In humans, age-related hearing deficits are linked to negative outcomes such as dementia, and so a pharmaceutical manipulation that could improve measures of hearing would potentially serve as an important preventative treatment for this kind of disorder. We tested whether acute systemic nicotine increases the precision of tuning of responses to pure-tone stimuli in human auditory cortex and characterized the age dependence of this effect. Forty healthy, non-smoking volunteers (20 younger adults, 18-35 yr; 20 older adults, 59-83 yr) with normal audiograms each completed two functional magnetic resonance imaging sessions (placebo gum vs. 6-mg nicotine gum; double-blind, counter-balanced, ≥ 48 h apart). During imaging, participants heard 14 pure tones (80-8,000 Hz in 0.5-octave steps, ≥ 30 repetitions of each tone) while performing a loudness discrimination task. For every participant, we estimated voxel-wise responses to each presented frequency with a 14-regressor general linear model and used the combined nicotine and placebo data to define a frequency-selective region of interest in auditory cortex. Tuning precision was quantified for each voxel as $\beta_{\text{peak frequency}} - \text{mean}(\beta_{\text{neighboring frequencies}})$ and was averaged across voxels within the region of interest in each hemisphere. We found that a single moderate dose of nicotine significantly increased tuning precision of auditory cortical responses to pure tones in younger adults, consistent with nAChR-mediated intracortical inhibition models. In contrast, nicotine did not significantly affect precision of frequency tuning of auditory cortex in older adults.

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Poster

PSTR170: Coding of Spatial and Non-Spatial Auditory Features

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Title: Contribution of the Striatum to Central Auditory Processing

Authors: *H. LI¹, J. WEI², F. LIANG³, H. W. TAO¹, L. I. ZHANG¹;

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Abstract: Anatomically receiving convergent inputs from both cortex and thalamus, the striatum is believed to play an important role in central auditory processing and sound perception, as evidenced by its involvement in behaviors related to sound-frequency discrimination. However, fundamental questions remain about how specific auditory information is processed, integrated within the striatum, and transformed into appropriate actions. The caudal striatum, or tail of the striatum (TS), receives the most intense projections from the auditory cortex (ACx) among all striatal regions. Our results suggest that a midbrain structure provides significant bottom-up auditory signals to the TS, influencing its auditory processing. In addition, the TS contributes to auditory spatial processing by integrating binaural information from ascending pathways. This study may offer new insights into the functional role of the striatum in auditory perception.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.01/Q1

Topic: E.06. Vision

Support: NIH Grant 2R01EY009593
NIH Grant 1R01EY037195

Title: Species-specific patterns of receptive field distribution, structure, and size in the visual thalamus

Authors: *Y. MIAO¹, R. DAKWALA¹, U. M. CIFTCIOGLU², A. GORIN², F. T. SOMMER⁴, J. A. HIRSCH³;

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Abstract: Before reaching cortex, visual information from the retina is processed by the dorsal lateral geniculate nucleus (dLGN), where it is influenced by two powerful sources of inhibition--local interneurons and cells in thalamic reticular nucleus (TRN). Historically, as phrased by Francis Crick's "thermostat" hypothesis, TRN was thought to provide a form of global gain control to sensory thalamus. However, increasing evidence (that we describe below) supports Crick's alternative "searchlight" hypothesis, which posits a role in spatial attention. Cells in both dLGN and TRN fire either tonic spikes or bursts; these two firing modes provide parallel channels, each of which is able to carry distinct sensory information to cortex. When bursts

occur, they typically follow sustained hyperpolarizations while tonic spikes are produced when the membrane is relatively depolarized. Previous studies showed that the temporal features that prime bursts in dLGN are stronger than those that evoke tonic spikes. Here we report that this is the case in TRN as well, for both cat and mouse. Our findings suggest that inhibition evoked by bursts from TRN might help prime bursts in dLGN, perhaps promoting responses to salient stimuli. Receptive-field structures in dLGN differ from those in TRN, even as sizes are similar at equivalent positions in visual space, as we showed previously in cat. To determine if this pattern is conserved in mouse, we quantified the receptive-field sizes of cells in murine TRN and dLGN. For the most part, receptive-field sizes were comparable in both nuclei, suggesting that TRN can provide localized, searchlight-like inhibition to dLGN across species. Finally, there are unique specializations in the form vision pathways of cat and mouse that are adapted for their natural habitats. For instance, dLGN and TRN receptive-field sizes scale with eccentricity in cat and there is a proportionally larger amount of tissue devoted to the central visual field (the magnification factor). There is greater diversity among ganglion cells in mouse than cat and these diverse cell types are asymmetrically distributed across different regions of murine retina. To learn how this nonuniform retinal organization maps to visual thalamus, we compared the retinotopic distribution of receptive fields in mouse dLGN and TRN. Our results reveal a nonuniform functional grouping of receptive fields in dLGN, though not in TRN as yet. Ultimately, we will combine results of this work with companion studies of local interneurons to understand how both feedforward and feedback inhibition restructure the signals dLGN sends downstream.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Topic: E.06. Vision

Support: NIH 2R01EY009593
NIH 1R01EY037195

Title: Estimating the size of receptive fields in the early visual pathway

Authors: *R. DAKWALA¹, Y. MIAO², F. T. SOMMER³, J. A. HIRSCH²;
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Abstract: Visual receptive fields are defined not only by their shapes, but also their sizes. The absolute size of a receptive field can serve as a proxy for acuity. In highly visual animals such as a monkey or cat, receptive fields are small in the center of gaze and larger in the periphery.

Similarly, in mice, the average receptive field size is smaller in the binocular than in the monocular zone. Further, the relative size of the receptive field of a presynaptic neuron compared to that of its postsynaptic target has a profound impact on visual processing. Consider the implications for receptive field size in Francis Crick's two hypotheses about the role of the thalamic reticular nucleus (TRN), a GABAergic structure that receives input from relay cells in sensory thalamus and feeds back inhibition in return. The thermostat hypothesis posits that TRN provides a global gain control and implies that receptive fields in TRN are far larger than those of relay cells. In contrast, the searchlight hypothesis proposes a role in spatial attention that predicts that receptive fields of reticular cells and relay cells operate over similar spatial scales. Estimates of receptive field size typically use fitting functions such as 2D Gaussians, which assume similarities in receptive field shape. However, receptive fields are sometimes irregular and even discontinuous. Thus, for an earlier study that compared receptive field sizes in cat TRN and dorsal lateral geniculate nucleus (dLGN), we developed a nonparametric method that estimates the statistical significance of each pixel in the spike triggered average (STA) of the stimulus ensemble to generate a "footprint". Footprint sizes in cat TRN and dLGN were comparable, supporting the searchlight hypothesis.

Subsequently, we used this method for a companion study in mouse TRN and dLGN. We presented a suite of sparse and dense noise stimuli of varied size, duration, and contrast and used the STA recovered from the smallest and fastest effective stimulus to compute each cell's footprint. Receptive field position in visual space and recording site for each cell were also tracked. The vast majority of receptive fields in TRN were similar in scale to those in dLGN, though the mean size was slightly larger.

We are currently exploring how different stimulus choices, and types of analysis affect the quantification of receptive fields. Hence, we are reanalyzing our recordings by selecting datasets obtained with stimulus parameters that better match those used by other laboratories, and comparing results generated by different analysis techniques. Thus, we hope to gain insights into the sources of variation among results obtained by different laboratories.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Topic: E.06. Vision

Support: NIH R01 EY036242
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Title: Burst Spiking in the Lateral Geniculate Nucleus of Alert Macaque Monkeys

Authors: *H. J. ALITTO¹, M. STROUD², M.-L. TRAN², W. USREY²;

²Ctr. for Neurosci., ¹Univ. of California, Davis, CA

Abstract: The lateral geniculate nucleus (LGN) receives direct excitatory input from the retina and relays this information to primary visual cortex (V1), making it the first-order thalamic nucleus of the visual system. Like other first-order thalamic nuclei, the primary function of the LGN is the transmission of sensory information from the periphery to the cortex. Rather than altering the information content of retinal input, the LGN functions as a gate, determining if and how much retinal information reaches the cortex. This gating can be dynamically modulated by a range of non-retinal inputs, including robust feedback from V1 and cholinergic input from the brainstem (e.g., the parabrachial tegmental nucleus). Given its anatomical position and its access to modulation, the LGN is a potentially powerful location to regulate the flow of visual information based on changes in sensory and cognitive demands.

A hallmark of thalamic physiology is the ability to transition from tonic to burst firing mode. These state transitions are mediated by intrinsic membrane properties, controlled by modulatory inputs, and are a powerful way to regulate the flow of information. Although thalamic bursts were once associated with non-REM sleep, it is now recognized that higher-order thalamic nuclei enter burst mode during wakefulness in response to changes in sensory and cognitive demands. Indeed, it has been proposed that thalamic burst mode may be functionally correlated with changes in alpha-band oscillations and may contribute to distractor suppression. Although it has not been shown to be the case in primates, burst mode has also been observed in first-order thalamic nuclei during awake, quiescent periods of smaller mammals such as rodents and lagomorphs.

Here, we investigated the burst firing in the LGN of awake macaque monkeys under a variety of behavioral conditions including passive fixation, covert spatial attention, and quiet rest. Our results confirm that thalamic bursts are uncommon in the alert primate LGN, even during prolonged periods of quiet wakefulness in darkness, with no visual stimulation periods. We suggest that the primate LGN reliably transmits visual signals to cortex whenever the animal is awake, and that burst mode is not a mechanism commonly employed during alert visual processing. This contrasts with findings in both non-primate LGN and higher-order thalamic nuclei, where burst firing appears to play a more active role in information gating.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.04/Q4

Topic: E.06. Vision

Support: NIH Grant P50MH132642

Title: Luminance-dependent size perception is consistent with ON/OFF pathway differences in LGN extraclassical suppression

Authors: M.-L. G. TRAN, H. J. ALITTO, J. S. JOHNSON, *W. USREY;
Ctr. for Neurosci., Univ. of California, Davis, Davis, CA

Abstract: The early visual system, from the retina to primary visual cortex (V1), contains multiple parallel pathways, each carrying a full, retinotopically organized representation of the visual environment. A prominent example is the ON and OFF pathways, which respectively encode positive and negative deflections from the mean luminance. These pathways originate with ON and OFF bipolar cells in the retinal inner nuclear layer and remain segregated through the lateral geniculate nucleus (LGN), before converging as distinct subfields in simple cells of V1. Once thought to simply be sign-reversed versions of one another, it is now recognized that the ON and OFF pathways exhibit key functional asymmetries, leading to unequal neuronal representations of bright and dark elements of the visual environment. We recently reported one such difference in LGN receptive field properties of alert macaque monkeys: extraclassical suppression, a phenomenon wherein responses are reduced by stimuli extending beyond the classical receptive field, is robust in OFF cells but largely absent in ON cells. We hypothesized that this physiological asymmetry could give rise to a perceptual illusion, whereby bright stimuli (encoded by ON cells) appear larger than equally sized dark stimuli (encoded by OFF cells). To test this, we conducted a human psychophysics experiment in which subjects fixated centrally while judging the relative size of two equidistant peripheral stimuli. Consistent with our hypothesis, subjects consistently judged white stimuli as larger than black stimuli, even when the black stimulus was up to 15% larger than the white stimulus. This luminance-dependent size illusion was strongest at high contrast, consistent with the role of contrast gain control in early visual processing. Finally, using a large dataset of ON and OFF LGN cells recorded from alert macaque monkeys, we have modeled these psychophysical results and find that they can be parsimoniously explained by the asymmetric gain control mechanisms present in the LGN.

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Poster

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Title: On-pathway visuomotor deficits in human myopia

Authors: *U. MAHARJAN¹, H. RAHIMI NASRABADI², S. POUDEL³, J. JIN¹, M. W. DUL¹, J.-M. ALONSO¹;

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Abstract: The human eyes are continuously adjusting refractive power to optimally activate the retina. This optimization is disrupted in myopia, which blurs vision at far distance and makes ON retinal pathways weaker, slower, and less sensitive. Here, we demonstrate that, in addition to these sensory deficits, myopic subjects have deficits in ON-pathway visuomotor function during lens accommodation. We measured visuomotor accommodative responses to light and dark stimuli (1.5° , 10-800 cd/m², background: 400 cd/m²) in 20 human subjects (14 females, 22-31 years old; 11 myopes: -0.75 to -6.13 diopters and 24.11 to 26.62 mm of eye axial length; 9 age-similar emmetropes: 22.53 to 24.23 mm of eye axial length). A tunable lens defocused the stimuli seen with one eye (-5 diopters for 2.5 seconds) while the other eye remained occluded. The defocus triggered an accommodative response that constricted the pupils and shifted the occluded eye nasally as if the target was approaching the observer (measured with Tobii pro glasses 3, 50Hz). Our results demonstrate that the excess of refractive power in myopia is accompanied by an excess of accommodative eye vergence (mean $\pm$ standard errors and Wilcoxon tests: $3.54^\circ \pm 0.07^\circ$ for emmetropes vs $5.31^\circ \pm 0.09^\circ$ for myopes, $p = 7 \times 10^{-50}$) and accommodative pupil constriction (0.36 ± 0.01 mm for emmetropes vs 0.43 ± 0.01 mm for myopes, $p = 3 \times 10^{-26}$) that shifts ON/OFF pathway balance towards OFF dominance (ON - OFF eye vergence: $0.08^\circ \pm 0.04^\circ$ for emmetropes vs $-0.36^\circ \pm 0.07^\circ$ for myopes, $p = 2 \times 10^{-17}$; ON - OFF pupil constriction: $0.06 \text{ mm} \pm 0.01 \text{ mm}$ for emmetropes vs $0.03 \text{ mm} \pm 0.01 \text{ mm}$ for myopes, $p = 7 \times 10^{-11}$). Importantly, both accommodative eye vergence and pupil constriction are strengthened by repeated accommodation and the time course of this potentiation is faster in myopes than emmetropes (time to 50% of maximum in myopes/emmetropes: 2.4/4.2 minutes for eye vergence and 0.8/4.2 minutes for pupil constriction, $p < 0.05$). In contrast to the accommodative potentiation, myopia weakened pupillary light reflexes driven by eye blinks (reduction in pupillary reflex triggered by long blinks: $101\% \pm 4\%$ for myopes vs $19\% \pm 2\%$ for emmetropes, $p = 2 \times 10^{-89}$). These results indicate that myopes have an ON-pathway deficit that increases accommodative eye vergence and pupil constriction while reducing the pupillary light reflex. If myopia and the ON-pathway deficit originate from low retinal illumination, our results could explain why myopia increases with activities that maximize pupil constriction such as near work and decreases with activities/treatments that increase illumination and/or pupil size such as outdoor activity, atropine, positive defocus and low contrast.

Disclosures: U. Maharjan: None. H. Rahimi Nasrabadi: None. S. Poudel: None. J. Jin: None. M.W. Dul: None. J. Alonso: None.

Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.06/Q6

Topic: E.06. Vision

Support: NIH Grant R01 EY034086

Title: Contrast sensitivity of ON and OFF retinal pathways in experimental myopia

Authors: *M. SUBEDI¹, U. MAHARJAN¹, S. POUDEL², J. JIN¹, B. DENG¹, D. JAMES¹, J.-M. ALONSO¹, A. BENAVENTE-PEREZ¹;

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Abstract: ON and OFF retinal pathways have different contrast sensitivities and are differently affected by myopia (nearsightedness), a disease that makes ON pathways less sensitive and slower in humans (Poudel et al. 2024). Here, we replicate these findings in juvenile marmosets (*Callithrix jacchus*) with myopia induced by exposing their eyes to defocus with soft contact lenses (starting with -5 diopters and gradually increasing to 60% of refractive error as myopia progresses, 9/15 hours of light/dark cycle, beginning at ~70 days of age and up to one year, 8 marmosets treated with defocus and 5 controls left untreated, multiple longitudinal measures per animal). Retinal responses were recorded in all animals with light-adapted full-field electroretinograms (ERG, Espion Ganzfeld ColorDome stimulator, Diagnosys LLC), under anesthesia (glycopyrrolate, acepromazine, and ketamine), and with dilated pupils (1% cyclopentolate). Gold wire electrodes were placed on the cornea to record retinal responses evoked by 0.2 s flashes against a 500 cd/m² background (0-1000 cd/m² in 50 cd/m² steps). ON responses were evoked by flash intensities above background (>500 cd/m²), and OFF responses by flash intensities below background (<500 cd/m²). Contrast response functions were fitted with Naka-Rushton functions and the best fits ($R^2 > 0.9$, $n=51$) were used to extract luminance contrast at half maximum response (C50), exponent (n), and response latency. Our cross-sectional results demonstrate that, as in humans, response latencies are longer in ON than OFF pathways (28.2 ± 2.1 for ON vs 24.1 ± 1.7 for OFF, $p: 5.1 \times 10^{-10}$, Wilcoxon tests). We also demonstrate that the response latency of ON pathways increases with myopia making eye axial length significantly correlated with both the OFF/ON latency ratio ($r: -0.35$, $p: 0.013$) and OFF-ON latency difference ($r: -0.38$, $p: 0.006$). Moreover, we reveal new correlations not reported in humans that further demonstrate a loss of ON pathway sensitivity in myopia. Marmoset eye axial length was correlated with the OFF/ON C50 ratio ($r: -0.42$, $p: 0.002$), OFF-ON C50 difference ($r: -0.4$, $p: 0.004$), OFF/ON exponent ratio ($r: -0.45$, $p: 0.001$), and OFF-ON exponent difference ($r: -0.39$, $p: 0.004$). These cross-sectional results demonstrate that humans and marmosets have similar ON-pathway deficits in myopia, and show similar changes in ON/OFF pathway balance with myopia progression. They also indicate that marmosets can be a powerful translational model to study longitudinal changes in ON and OFF pathway function, both before myopia onset and throughout its progression.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Topic: E.06. Vision

Support: Peter and Yayi Pezaris
Don Good
Michael Gersh
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NIH EY027888
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Title: Single-cell transcriptomic analysis of macaque LGN neurons reveals novel subpopulations

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Abstract: The primate lateral geniculate nucleus (LGN) has long been described as comprising three major cell types, magnocellular (M), parvocellular (P), and koniocellular (K) neurons, each with distinct anatomical and physiological characteristics. However, evidence from electrophysiology studies suggests greater functional heterogeneity within these populations than the classical view. To explore this potential diversity, we analyzed publicly available single-nucleus RNA sequencing data from 1,309 macaque LGN neurons. Using high-resolution clustering and differential gene expression analysis, clustering analyses identified neuronal subpopulations within the M, P, K cell populations that were transcriptionally distinct: two M, two P, and three K cell types. To select parameters for clustering, we used brute-force grid search across Seurat settings, evaluating cluster consistency with silhouette scores and modeling results via generalized additive models to determine optimal values. While M and P subtypes exhibited limited transcriptomic distinction, we found strong molecular signatures in one P subtype characterized by elevated expression of structural and metabolic genes, suggesting higher activity or larger cell size. The greatest heterogeneity was observed among K cells. One K subtype showed enriched expression of gap junction proteins, possibly implicating a role in thalamic burst synchronization. Another K subtype expressed numerous ion channels and neuromodulatory receptors, suggesting enhanced excitability and modulation by histamine and endocannabinoid systems. These findings highlight unexpected diversity among LGN neurons and propose novel molecular distinctions that may represent specialized roles in visual processing. This work lays the groundwork for future studies linking transcriptomic subtypes to physiology and anatomy, and questions the canonical M-P-K framework toward a more nuanced cellular taxonomy of the primate visual thalamus.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Support: LABEX CORTEX ANR 11 LABX 0042
INSERM IRP CORTICAL_CONNECTOME
ANR-24-CE37-5022-CONNECTOME
ERC-2023-Adv 101142153 PREDICTION

Title: Differential cortical and subcortical inputs to retinotopic subdivisions of macaque areas V1, V2 and V4

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Abstract: Background: Human and non-human primate visual cortex are organized in a framework where retinotopic specializations of the early visual cortex are transcribed across hierarchical levels allowing decoding of faces and objects in separate higher-order areas with distinct foveal and periphery dominance. However, studies of early visual cortex have often been limited to central visual field representations and lacked extensive quantitative analysis across eccentricities. In order to study the differences in the connectivity of retinotopic subdivisions (RSDs), we performed 35 retrograde tracer injections in the RSDs of areas V1, V2 and V4. Connection weights from cortical and subcortical structures to each injection site were quantified by calculating the fraction of labeled neurons (FLN), which constitutes the cortical and subcortical connectivity profile for each injection (Markov et al. 2014).

Results: 1. The differential connectivity of dorsal and ventral visual streams to individual RSDs demonstrates dorsal stream is preferentially connected to far periphery lower visual field, and the ventral stream to upper and center visual fields. 2. Multi-dimensional scaling (MDS) analysis of cortical connectivity profiles revealed clearly segregated clusters projecting to central, paracentral, and far-peripheral RSDs. 3. Differences in subcortical inputs to individual RSDs are found across a wide range of nuclei, including many beyond those traditionally associated with visual processing. 4. MDS analysis of subcortical connectivity profiles revealed clearly segregated clusters projecting to central, paracentral, and far-peripheral RSDs. 5. Theoretic graph analysis shows RSDs shape the intra-cortical network resulting in specialized information flow.

Conceptual significance: These results show that in the early visual cortex there are profound connectivity changes with eccentricity. The observed cortical connectivity changes support Previc's (1991) ecological theory of vision (Previc 1990). The observed subcortical connectivity changes within a given cortical area warn against a corticocentric vision of brain networks.

References

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Previc FH. 1990. Functional specialization in the lower and upper visual fields in humans: Its ecological origins and neurophysiological implications. *Behav Brain Sci*. 13:519-575.

Disclosures: Z. Luo: None. Y. Hou: None. M. Wang: None. S. Horvát: None. M. Poo: None. C. Dehay: None. K. Knoblauch: None. M. Ercsey-Ravasz: None. J. Vezoli: None. Z. Shen: None. H. Kennedy: None.

Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.09/Q9

Topic: E.06. Vision

Title: Projection Strategies of the lateral geniculate nucleus (LGN) in Primate: From Single-Neuron Reconstructions to Population-Level Connectome

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Abstract: The pathway from the lateral geniculate nucleus (LGN) to the primary visual cortex (V1) represents a key component of the visual system, with its laminar and columnar organization providing a fundamental framework for visual processing research. To investigate mesoscale projection principles, we propose employing single-neuron reconstruction techniques in macaque. The VISoR2 (Volumetric Imaging with Synchronized on-the-fly-scan and Readout) pipeline comprises five key phases: (1) dual-AAV sparse labeling, (2) serial thick-sectioning and tissue clearing, (3) high-throughput volumetric imaging, (4) computational 3D reconstruction, (5) single neuron reconstruction and region-of-interest (ROI) parcellation. By calculating the laminar distribution patterns of projection strengths of single LGN neurons in V1, we classified these neurons into five categories. Among them, the neurons of the Magnocellular & Parvocellular pathways (Group B & C) basically conform to the traditional definition. LGN neurons exhibit extensive thalamo-cortical projections beyond V1, including targets in visual area V2 et al. LGN also sends direct projections to the claustrum. We conducted a population-level analysis of LGN neuronal projection patterns. Along the superior-inferior axis of LGN, neurons exhibit a topographic mapping in V1. Through systematic examination of both naturally organized neuronal ensembles and abstracted grouping-based combinatorial models, we proposed a laminar and columnar organization revised model of LGN projections in V1. Mesoscopic connectome analysis reveals heterogeneous projection patterns of LGN neurons and their population-level organizational architecture.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.10/Q10

Topic: E.06. Vision

Support: NIH Grant 7K99EY034699

Title: Targeting primate pulvinar projections: a neurosurgical and electrophysiological approach

Authors: *A. R. ANDREI¹, D. MIKULEK¹, J. O. SZABLOWSKI², V. DRAGOI³;

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Abstract: The multimodal pulvinar is largest nucleus in the primate thalamus and is prolifically connected to the entire cortical mantle. The visual pulvinar receives driving input primary visual cortex, and projects to higher areas throughout the dorsal and ventral visual processing streams. The pulvinar is thought to be critical for coordinating activity across these distant cortical areas, but exactly how this occurs is unclear. Pharmacological and thermal silencing of the pulvinar leads to impairments in attention and neglect of the contralateral hemifield, suggesting a key role in perception. Elucidating cortico-thalamo-cortical coordination via the pulvinar requires causal control of pulvinar-projecting cortical neurons. Previously, these circuit elements have been difficult to isolate because the cortical cells that project to the pulvinar are intermingled with neurons that project elsewhere. Here, we present two approaches by which to selectively target cortico-pulvinar projections for optogenetic manipulation in task engaged macaque monkeys. The first approach involves direct injections into the pulvinar. The injection geometry is first optimized ex vivo, to identify the needle orientation and bevel angle that produces an injection volume whose 3D shape matches the individual animal's pulvinar. We use an MR and CT guided neuro-navigation procedure to precisely locate the needle tip in the center of the lateral pulvinar for surgical optogenetic viral injections. The viral construct (AAVrg-CaMKII-ChR2) is then slowly infused into the parenchyma. The second approach uses MR-guided focused-ultrasound (fUS) combined with microbubble injection to focally disrupt the blood brain barrier (BBB) over the targeted deep brain structure. Immediate MR after fUS confirms opening of the BBB, followed up by histological evaluation of Evans Blue penetration in gray matter at the target location. Successful fUS can be followed up with a systemic viral injection, which will penetrate the brain at the site of BBB-opening. These methods allow for optogenetic identification and causal manipulation of the cortical neuron population that projects to the pulvinar. After 6 weeks for viral expression electrophysiological recordings and optogenetic stimulation begins from pulvinar-projecting cortical areas, such as V1. Current-source density estimates (CSD) are used to localize neural activity to specific cortical layers. Pulvinar-projecting neurons are identified by their location in infragranular layers, and their rapid (<2ms) response to light.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR171.11/Web Only

Topic: E.06. Vision

Title: Identifying effective neuronal connectivity in the rat lateral geniculate nucleus (LGN) from spike train data

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Abstract: The lateral geniculate nucleus (LGN) is conventionally regarded as a passive thalamic relay between the retina and primary visual cortex. However, growing evidence suggests that its neuronal populations engage in higher-order visual information processing. To explore this possibility, we recorded neural activity from the LGN of six adult female Albino rats. Animals were anesthetized, and a 4×4 mm craniotomy was performed over the right LGN. A 32-channel silicon microelectrode array recorded extracellular activity for approximately 26 minutes in a darkened room, with a 13-inch screen positioned tangentially to the left eye at a distance of ~ 15 cm. The visual stimulus was a 4×8 -pixel checkerboard in which four randomly selected pixels flickered ON for 200 ms, followed by 300 ms OFF; 32 distinct patterns were presented in pseudorandom order, each repeated 100 times. Spike trains were extracted for each neuron, and their tuning curves were analyzed to estimate receptive fields, evaluating how individual neurons responded to the stimuli. Cross-correlation analysis was performed to infer effective connectivity, and trial-specific adjacency matrices were used to construct directed graphs depicting excitatory and inhibitory connections. We trained support vector machine (SVM) classifiers to distinguish between all possible pattern pairs using three representations of population activity: raw spike trains, spike counts, and connectivity matrices. Across animals, mean classification accuracy for the top 10 stimulus pairs was highest when using connectivity features (mean = 0.86), followed by spike counts (mean = 0.79) and spike trains (mean = 0.75). Effective connectivity outperformed the other representations in five out of six rats (Wilcoxon signed-rank test, $p < 0.05$), suggesting that incorporating network-based features enhances decoding performance. Statistical significance was corroborated using t-tests, yielding complementary results. Tuning curve and receptive field analyses revealed that individual neurons did not consistently prefer the most accurately classified patterns, suggesting that improved decoding arose from emergent population-level dynamics captured through connectivity. These findings support the hypothesis that interactions among LGN neurons encode information about visual stimuli, consistent with a computational role for the LGN beyond simple signal relay. Overall, our results underscore the value of connectivity-based representations in understanding sensory population coding and inform future applications in visual prosthetics.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Topic: E.06. Vision

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Title: Subcortical Encoding of Numerosity: Evidence from Deep Neural Network Modeling of the Mouse Lateral Geniculate Nucleus

Authors: M. GAMAL¹, *S. ELDAWLATLY^{2,3};

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Abstract: Numerosity, defined as the visual ability to perceive and quantify discrete items within a scene, is traditionally associated with high-level cortical processing areas. In this study, we challenge this conventional view by examining whether the lateral geniculate nucleus (LGN), an early subcortical structure historically considered a simple relay station in visual pathways, encodes numerosity. We explore this hypothesis by employing goal-driven deep neural networks (DNNs), specifically VGG16 and ResNet50, to model mouse LGN neural activity recorded during natural scene viewing from the Allen Brain Observatory's Visual Coding Neuropixels dataset.

Our models were trained as encoding models of LGN firing, where each DNN network layer served as a feature extractor from natural images, feeding into neuron-specific readout layers optimized to predict actual recorded LGN spike counts. This method allowed us to systematically evaluate how effectively different network layers represented LGN neural responses. We found novel evidence that numerosity, typically considered a higher-level visual feature, is encoded in LGN neural activity. Our results reveal that intermediate layers of these DNNs, typically associated with encoding more complex visual features, significantly outperform early layers in predicting numerosity from LGN responses. This finding indicates that intermediate network layers, which correlate with cortical regions processing mid-level visual features, also capture sophisticated visual representations at subcortical stages. To comprehensively assess numerosity encoding, we employed synthetic image datasets designed with controlled complexity levels. Results from these artificial stimuli experiments reinforced our finding from natural scenes that numerosity is encoded in LGN firing. Furthermore, we demonstrate that an ensemble model combining predictions from both early and intermediate layers achieved superior neural prediction accuracy while robustly capturing numerosity, suggesting a nuanced interaction between low- and mid-level visual processing pathways within the LGN.

This study provides novel evidence that the LGN encodes high-level visual features such as numerosity. It also highlights the utility of goal-driven DNNs not only as powerful predictive tools but also as exploration mechanisms to uncover complex neural encoding strategies. Our

findings advocate for revising the simplistic view of subcortical visual processing, underscoring a sophisticated and integral role for the LGN in the visual perception hierarchy.

Disclosures: M. Gamal: None. S. Eldawlatly: None.

Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.13/Q12

Topic: E.06. Vision

Support: Leo M. Davidoff Department of Neurological Surgery, Albert Einstein College of Medicine

Title: Demonstrating visual percepts in mice via lateral geniculate nucleus stimulation: a model for visual prosthesis development

Authors: *W. S. KEMBALL-COOK, E. R. BADER, E. N. ESKANDAR, N. J. KILLIAN; Neurosurg., Albert Einstein Col. of Med., Bronx, NY

Abstract: Electrical stimulation of the lateral geniculate nucleus (LGN) is a promising therapeutic approach for restoring vision in individuals with blindness. Stimulation of the visual stream evokes discrete percepts of light called “phosphenes,” which form the basis of artificial vision. However, there are no commercially available LGN prostheses, and testing prototypes in humans is costly. We investigated whether mice could perceive phosphenes induced by LGN stimulation, establishing a safe, cost-effective preclinical model for testing microelectrode arrays. Mice (N=2) were stereotactically implanted with a stimulation electrode in the dorsal LGN. We designed a head-fixed classical-conditioning task in which water-restricted mice learned to associate a visual stimulus with a delayed sucrose reward. During pre-training, 500 ms flashes of light were presented on an LED screen, followed by a 500 ms delay before reward delivery. This reliably elicited anticipatory licking during the delay. Once this association was learned, optical cue trials were randomly interleaved with electrical stimulation trials (22 μ A, biphasic pulses at 100 Hz for 500 ms). After three sessions, mice underwent bilateral optic nerve transection (ONT) to model advanced blindness. We anticipated that after ONT, anticipatory licking would persist only for stimulation trials. Before ONT, mice showed robust anticipatory licking to both optical cues (84%, 242/288 trials) and electrical stimulation (89%, 278/312 trials). 2-13 days post ONT, responses to stimulation remained high (88%, 263/298 trials), while responses to optical cues (6%, 17/282 trials) dropped significantly (chi-square test of independence, $p < 0.001$). To test whether mice can differentiate phosphene patterns, we implanted an additional mouse with a 32-channel recording/stimulation electrode. Receptive fields (RF) were derived by computing the cross-covariance of the high-pass filtered local field potential envelope with a stimulus movie. RF centroids were mapped to individual channels and clustered in visual space to yield two distinct LGN stimulation patterns. One pattern was always

rewarded, while the other was never. The mouse was trained for six days with the two stimulation patterns. Anticipatory licks were significantly higher for the rewarded pattern (median = 2 licks/stim) than the unrewarded pattern (median = 0 licks/stim) across the last four days of training (Wilcoxon rank-sum test, $p < 0.001$). These results suggest that mice can perceive and discriminate artificial percepts evoked by LGN stimulation, supporting their use as a viable preclinical model for testing subcortical visual prostheses.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Topic: E.06. Vision

Support: NEI R15EY036226
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Title: Thalamic encoding of visual experience during early development in zebrafish

Authors: *E. HORSTICK^{1,2};

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Abstract: During early development environmental input has a substantial role in determining long term neural function. Critical periods (CP) are discreet developmental windows where the environment has profound impact on structural and functional changes to neural circuits, a form of experience dependent plasticity. The visual CP is a well-established developmental window where visual experience is required for normal visual function. Impaired visual experience during the CP can lead to amblyopia and potentially lifelong vision impairment. Cortical mechanisms instructing visual CP plasticity are well established. Conversely, subcortical thalamic mechanisms have only recently been described and remain incompletely understood. This work investigated thalamic mechanisms underlying visual CP plasticity using an innovative zebrafish model that provides neuron level resolution of thalamic responses in vivo. We can use the zebrafish model to connect experience, neurophysiology, and behavior in single animals to understand how visual input modulates visual processing in the brain. Using the zebrafish model, we provided asymmetric visual experience during a visual CP. We found two populations of thalamic neurons that encoded visual experience and resulted in reciprocal functional asymmetries. These thalamic functional asymmetries correlate to visual experience and match the directional performance of a visuomotor behavior. This functional asymmetry was not present in other visual processing areas. Through targeted multiphoton ablation, we determined

that these thalamic regions functionally dictate the identity of motor bias, and optogenetics stimulation demonstrated that the activation of these neurons was sufficient to drive motor behavior. We also show that the AMNs are inhibitory, and inhibitory signaling controlled the timing of visual plasticity and thalamic neuron encoding of visual experience. Last, we show that inhibitory modulation is dependent on GABRA1 containing GABA signaling. This work has developed a thalamus-centric model to understand neuron level subcortical changes imposed by visual experience during a visual CP.

Disclosures: E. Horstick: None.

Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.15/Q14

Topic: E.06. Vision

Support: SNSF 212255

Title: Frequency-dependent effects of optogenetic activation in the lateral geniculate nucleus in the tree shrews

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Abstract: The lateral geniculate nucleus (LGN) plays the role of a relay between the retinal visual input and further processing in the visual cortex, which makes this central thalamic region a good target for visual prosthesis. Optogenetic activation of the LGN is a potential way to restore vision. Here we conduct the experiments on tree shrew, a close relative of primates, whose visual circuits share significant homology with those of primates. Recently, our lab have shown the optogenetic activation of CamKII-ChR2 in LGN can be detected by tree shrews(1). Here, we examined optogenetic activation of hSyn-ChR2 in LGN to activate a broader population of neurons to explore the frequency-dependent effects of optogenetic activation in LGN. To validate the activation effects, we performed electrophysiological recordings under anesthesia and discrimination tasks in behaving animals. First, we injected tree shrews with the AAV-hSyn-ChR2 virus in the LGN. Then we recorded both unit activity and local field potential responses using Neuropixel probes in primary visual cortex (V1), which is the downstream region of LGN in the primary visual pathway. Our preliminary analyses suggest that V1 can be reliably activated by optic fiber light stimulation in LGN with different frequencies (1, 5, 10, 15, 20, 30, 40Hz), both the single neuron and LFP level. In parallel, we have trained the tree shrews on a visual flicker discrimination task, in which they get juice rewards during S+ conditions (i.e. 20Hz flicker) but not during S- (e.g. 5Hz flicker) conditions on a variable interval schedule. Consistent with our previous findings, tree shrews can learn to discriminate visual flicker. Our ongoing experiments aim to determine whether tree shrews can also discriminate between

optogenetic stimuli that are temporally modulated at the same frequencies used in the visual discrimination experiments. Our findings extend previous knowledge about how visual circuits can be activated by optogenetic stimulating in LGN and how do the tree shrews use such activations to guide their behavioral performance. References:1. Jing Wang, Hamid Azimi, Yilei Zhao, Melanie Kaeser, Pilar Vaca Sánchez, Abraham Vazquez-Guardado, John A Rogers, Michael Harvey, Gregor Rainer (2023) Optogenetic activation of visual thalamus generates artificial visual percepts eLife 12:e90431 . Available from: <https://doi.org/10.7554/eLife.90431>

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Poster

PSTR171: Visual Pathways: Subcortical Structures

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR171.16/Q15

Topic: E.06. Vision

Support: NIH-NINDS U01NS122040

Title: Development of cell type-specific viral tools for tree shrew midbrain circuits

Authors: *A. KIPCAK, A. ERISIR;
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Abstract: The lack of cell type-specific viral tools is a major limitation for species without established transgenic lines to study neural circuit anatomy and function. Most existing tools are developed in mice and are not readily applicable to higher-order mammals such as the tree shrew. This constraint is particularly pressing for evolutionarily conserved brain structures like the superior colliculus (SC), where conserved cell types exist but remain poorly understood due to limited molecular access. To address this gap, we focused on Wide Field Vertical (WV) neurons of the tectopulvinar pathway. These neurons integrate retinal and cortical inputs via large dendritic arbors and are involved in motion detection and freezing behavior. Previous work identified Nephronectin (NPNT) and Cerebellin 2 (CBLN2) as potential markers of WV neurons in mice. Here, we show that CBLN2 - but not NPNT - is a conserved marker of WV neurons in the tree shrew. Comparative analysis of the CBLN2 locus across mouse, tree shrew, and human revealed a 1.8 kb conserved region in the 5' UTR. This sequence was cloned into an AAV vector upstream of a GFP reporter (AAV-tsC2Pro-GFP). Following injection into adult tree shrew SC, the AAV labeled CBLN2⁺ cells with high specificity and sensitivity verified by RNA-FISH. Labeled cells displayed characteristic WV morphological features and projected to the pulvinar. We also validated the effectiveness of this promoter to target WV neurons in mouse SC, demonstrating its cross-species applicability. To enable intersectional strategies, we developed a bicistronic version of the virus that expresses Cre recombinase. This represents the first example of a viral tool derived from the tree shrew genome for cross-species, cell type-

specific targeting. Our results also provide a foundation for extending this approach to additional conserved cell types in the SC and other brain regions.

Disclosures: A. Kipcak: None. A. Erisir: None.

Poster

PSTR171: Visual Pathways: Subcortical Structures

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Topic: E.06. Vision

Support: NIH Grant R01EY025267
Walt & Lily Disney Award for Amlyopia Research Grant

Title: Morphological Characterization of Monocularly- and Binocularly-Innervated Neurons in the Mouse Superior Colliculus

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Abstract: The superior colliculus (SC) is a major retinorecipient nucleus that regulates ethologically critical behaviors. The SC is directly innervated by contralaterally and ipsilaterally projecting retinal ganglion cells (contra- and ipsi-RGCs) that terminate in distinct layers. Despite this arrangement, recent studies suggest that SC neurons can exhibit multiple modes of binocular modulation and that binocular vision is required for appetitive and defensive SC-driven behaviors in mice. However, little is known about the circuitry underlying binocular processing in the mouse SC. To bridge this gap, we sought to define the neuronal populations innervated by contra- and/or ipsi-RGCs. We injected trans-synaptic AAV1-Cre and AAV1-Flp intraocularly in separate eyes and Cre- and Flp-dependent reporters in the SC. Reporter signal was amplified and cell-specific markers labeled by immunohistochemistry, followed by collection of confocal images on cleared tissue, 3D reconstruction, and quantification of reconstructed cells. Out of a total of 353 reconstructed neurons, 40.6% were innervated solely by contra-RGCs (SC_{contra}), 39.1% solely by ipsi-RGCs (SC_{ipsi}), and 20.3% were innervated by both (SC_{binoc}). Unexpectedly, we found cells from each of these populations distributed across the entire rostro-caudal and medio-lateral axes of the SC. Morphological analysis revealed that SC_{ipsi} neurons had smaller somas than either SC_{contra} or SC_{binoc} cells, but no differences in dendritic architecture. Interestingly, while we identified morphologically distinct populations of SC neurons, consistent with previous studies, each could be identified in SC_{contra}, SC_{ipsi}, and SC_{binoc} populations. Taken together, these data suggest that SC neurons innervated in distinct patterns may have overlapping visual tuning properties, such that eye-specific information could be multiplexed onto distinct neuronal subtypes.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.18/R1

Topic: E.06. Vision

Support: NEI Grant 3R01EY025627-07S1

Title: Role of Visual Experience and FMRP in Cortico-Collicular Refinement in a Mouse Model of Fragile X Syndrome

Authors: *G. SHARMA;

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Abstract: Fragile X syndrome (FXS) is caused by reduced expression of fragile X messenger ribonucleoprotein (FMRP) and is commonly comorbid with sensory processing deficits. Yet, the etiology of underlying circuit disruptions driving sensory dysfunction in FXS remain poorly understood. Previously, we demonstrated that visual circuitry in the superior colliculus (SC) was disrupted in a mouse model of FXS (*Fmr1*^{-y}). Specifically, inputs from layer 5 neurons in the primary visual cortex (L5V1) were disorganized and misaligned with retinal ganglion cell inputs. However, when these deficits arise remain unclear. Previously we demonstrated that spontaneous activity during the second postnatal week is required for visual map alignment. To determine if FMRP is required in this process, we labelled L5V1 neurons at different developmental stages and analysed termination zone (TZ) organization in the SC. Surprisingly, we found that L5V1 projections refined normally between postnatal day 8 (P8) and P12 in *Fmr1*^{-y} mice, akin to controls, suggesting that FMRP is dispensable for initial refinement. However, beginning at P15 and continuing through P21, TZs were significantly larger in *Fmr1*^{-y} mice, suggesting a failure to maintain circuit organization. Given the timing of the disruption, we reasoned that visual experience may play an important role in circuit maintenance in the SC, which is disrupted in *Fmr1*^{-y} mice. Indeed, we observed an increase in TZ size in wild type (WT) mice visually deprived beginning at P11 compared to sham controls. Of note, this plasticity was confined to a critical period, as deprivation beginning at P21 did not induce changes in TZ size. Consistent with previous studies, we observed increased TZ size in *Fmr1*^{-y} sham controls, which were larger than those of deprived WT mice. Intriguingly, visual deprivation in *Fmr1*^{-y} mice resulted in a mild rescue of L5V1 disorganization, suggesting visual experience disrupts maintenance, perhaps due to altered downstream FMRP signalling. Taken together, these data suggest that both visual experience and FMRP play critical roles in the maintenance of visual circuitry in the SC, which may utilize both distinct and common mechanisms. Elucidating these mechanisms will provide important insights into sensory processing deficits characteristic of FXS and the development of targeted therapeutic strategies.

Disclosures: G. Sharma: None.

Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.19/R2

Topic: E.06. Vision

Support: NIH Grant EY034004

Title: Identifying the structure and function of retinotectal retinal ganglion cells across species.

Authors: *A. M. RUDZITE¹, M. O. BOHLEN³, M. A. SOMMER², G. D. FIELD⁴;
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Abstract: The superior colliculus (SC), a major retinal target, plays a pivotal role in attention, decision-making, and sensorimotor integration. While the SC is hypothesized to receive input from more retinal ganglion cell (RGC) types than any other brain area in both rodents and primates, the diversity and functional roles of these inputs remain unresolved, particularly in primates. This gap limits our understanding of how evolution influences SC circuits and their relevance to neurodevelopmental disorders, such as attention deficit hyperactivity disorder (ADHD). Here, we map the morphological and functional diversity of SC-projecting RGCs in rats and rhesus monkeys, enabling cross-species comparisons of this conserved visual pathway. We introduce projection targeting with phototagging, a cross-species approach that integrates retrograde viral constructs with large-scale multielectrode array (MEA) recordings. This method enables simultaneous classification of RGC structure, functional characterization (e.g., receptive fields, response dynamics to visual stimuli), and projection mapping, circumventing reliance on transgenic animal models. In both species, SC injections of rAAV2-retro constructs delivered a fluorescent marker to RGCs for morphological identification and the red-shifted opsin ReaChR for optogenetic tagging to enable physiological identification. Retinas were harvested post-survival, and retinotectal RGC visual responses were measured *ex vivo* using MEAs. Subsequent immunolabeling and confocal imaging linked these functional properties to morphological identities. In rats, we optimized viral strategies to catalog SC-projecting RGCs, resolving their morphological diversity and visual response properties. Translating this framework to macaques, we identified novel primate RGC projections (e.g., large-smooth cells) and confirmed predicted types (e.g., parasol cells). For many primate RGCs, we established the first structure-function correlations and discovered an uncharacterized wide-field type absent from existing atlases. We have developed a pipeline to both determine retinotectal projecting cell types and to match their morphology and physiology to build an atlas of RGC types across species. This resource is crucial for understanding how visual input influences SC-dependent behaviors and for elucidating their contributions to attentional disorders.

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Poster

PSTR171: Visual Pathways: Subcortical Structures

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Program #/Poster #: PSTR171.20/R3

Topic: E.06. Vision

Title: Characterizing midbrain visual- and auditory-related activity during reversible inactivation of the primary visual cortex of rhesus macaque monkeys

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Abstract: Using a short-latency, reflexive oculomotor phenomenon, we recently discovered that spatially uninformative sounds can activate otherwise dormant visual-motor pathways bypassing the primary visual cortex (V1). Here, we aimed to better understand how this might happen. We first recorded from superior colliculus (SC) neurons (two monkeys) with either intact or focally inactivated V1 (muscimol microinjection; 1.5-2.5 μ L; 10 mg/1mL). We presented a 0.2 deg radius disc (black; 100% and 20% contrast) within the neurons' receptive fields (RFs) and randomly interleaved trials in which we paired the visual stimulus onset with a bilateral sound pulse (50 ms; 1 kHz). This sound pulse was neither informative about the visual stimulus location nor spatially aligned with RFs. In the first set of tasks, monkeys fixated centrally and ignored the stimuli. With intact V1, SC neurons showed little to no response to sound alone, yet visual response strength and latency were variably modulated in multisensory trials. Such multisensory integration was also evident in local field potentials (LFPs), with evoked responses to multisensory stimuli being enhanced and distinct from those elicited by unimodal stimuli. With inactivated V1, SC visual responses in targeted layers were largely abolished, both at the single unit and LFP levels. However, adding spatially uninformative sounds unmasked a relatively weak visually-evoked, and contrast-dependent, LFP response, not attributable to sound alone. Interestingly, these effects were amplified in an active oculomotor task, where monkeys executed guessed, visually guided saccades toward the visual target. Namely, there were some SC visual responses, even without sounds, and some neurons displayed visual tuning properties when sound was added. Moreover, SC motor responses retained their visually-driven sensory tuning properties, which were also modulated by sound presence. Finally, we sampled some inferior colliculus (IC) neurons. With intact V1, when IC neurons exhibited visual responses, they showed clear multisensory integration, even without having sound-only responses; however, LFP visually-evoked responses were predominantly driven by sound. With inactivated V1, IC single-unit and LFP responses resembled those in SC: though the IC visual responses were

virtually abolished during fixation, they were partially restored in an active oculomotor task (even without sounds), and they were enhanced by sound presence. These results underscore the distinct SC and IC roles in multisensory integration, and they support a potential involvement of both structures in visually-guided behavior when V1 is compromised.

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Poster

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Topic: E.06. Vision

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Title: Unilateral inactivation of the superior colliculus modulates bilateral activity and biases sensory choices

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Abstract: [Introduction] Mouse superior colliculus (SC) plays a key role in selecting actions guided by sensory cues. A longstanding hypothesis is that SC helps select actions thanks to competitive mechanisms that operate within and across hemispheres. We thus hypothesized that inactivating SC unilaterally would suppress contraversive choices and increase activity in the contralateral SC. [Methods] To test this, we first unilaterally inactivated the left SC in mice performing the International Brain Laboratory's biased visual discrimination task. Head-fixed mice (n=10) were trained to turn a steering wheel to report the side (left or right) on which a visual stimulus appeared, with stimulus location probabilities varying across blocks. We expressed the inhibitory opsin halorhodopsin (eNpHR3.0) via AAV injections in the left SC and delivered 561 nm light through an optical fiber. To examine the neural effects of inactivation, we suppressed left SC activity during passive viewing while recording from both SCs using Neuropixels probes. Across 25 sessions in 8 mice, we recorded 35,879 units, of which 8,893 passed basic quality criteria. [Results] Consistent with our hypothesis, unilateral optogenetic manipulation in the lateral part of SC suppressed contraversive choices, and increased ipsiversive choices (n=5 mice). Our electrophysiology recordings revealed laser stimulation modulated neuronal activity across hemispheres: 920 units showed significant suppression, and 633 units were significantly activated. The suppressed population typically exhibited high baseline firing rates, which were strongly reduced during laser stimulation. Conversely, the activated population

had lower baseline firing rates and increased activity during inactivation. These effects were observed in both hemispheres, consistent with intercollicular interactions. However, most suppressed neurons were located near the optical fiber tip, and those activated in the opposing hemisphere, as expected from the hypothesis of intercollicular competition. [Conclusions] Mouse SC does play a causal role in visual discrimination. Moreover, intercollicular competition is present in vivo and is likely to modulate SC output during decision-making.

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Poster

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Title: Optic Flow Representation by Thalamic Laterodorsal Nucleus Encodes Turning Direction in Spatial Navigation

Authors: *J. J. HUANG¹, Z. LI⁵, Y. ZHANG², K. SU³, B. PENG⁶, M. B. SEO⁴, L. I. ZHANG³, H. W. TAO⁷;

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Abstract: Vision is essential for navigation, but how the brain transforms visual signals into navigational cues remains unclear. The laterodorsal nucleus of the thalamus (LD), with strong connections to visual and navigation-related regions, is well positioned for this function, yet its role has been largely unexplored. In mice, we found that LD neurons exhibit strong direction selectivity, with a dominant preference for horizontal, temporal-to-nasal motion in the contralateral visual field—mirroring optic flow during contraversive turning. In freely moving animals, LD ensembles were preferentially activated during contraversive than ipsiversive turns in a vision-dependent manner, enabling the encoding of turning direction. Optogenetic activation or suppression of LD during learned navigational tasks selectively biased turning decisions in accordance with its directional tuning. These findings suggest that LD converts visual motion

into egocentric turning cues, contributing to spatial cognition and memory. Thus, LD may serve as a critical hub linking vision to navigation.

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Poster

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Topic: E.06. Vision

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Title: Investigating photoreceptor-specific modulation of amygdala activity as a mechanism for light-induced effects on affective state

Authors: *A. DEDIGAMA ACHARIGE^{1,2}, A. NAMESNA², T. HOUSTON², A. E. ALLEN², R. STORCHI², T. BROWN², N. MILOSAVLJEVIC³;

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Abstract: Light exerts widespread effects on physiology and behaviour that extend beyond its visual functions. Non-visual effects of light, including regulation of mood and affective state, are well-documented, yet the neural substrates and mechanisms mediating these effects remain incompletely defined. The amygdala, a central structure in affective processing and mood regulation, receives visual input through both indirect pathways, via the visual cortex and superior colliculus, and sparse, direct input from the retina, specifically from melanopsin-expressing intrinsically photosensitive retinal ganglion cells (ipRGCs). The functional relevance of these visual inputs to amygdala physiology remains to be fully elucidated. To address this, we employed *in vivo* extracellular electrophysiology in head-fixed anaesthetised red cone mice (*Opn1mwR*), genetically engineered to express human L-cone opsin in place of mouse M-cone opsin, allowing us to leverage silent substitution techniques for precise, photoreceptor-targeted stimulation. We designed and validated polychromatic light stimuli that selectively targeted melanopsin, rods and individual cone opsins, in the *Opn1mwR* mouse visual thalamus before applying the same to define photoreceptor contributions to light-responsive neurons within the medial and central amygdala subnuclei. In the amygdala, we found 20% of units (40/205; n = 9 mice) exhibited significant light-evoked activity, with the majority showing melanopsin-dominant sustained-ON responses (24/40) followed by responses classified as slow-ON (7/40), transient-ON (5/40) and OFF (4/40). Notably, several units demonstrated cone-specific tuning (16/40), including colour opponent responses (10/16), S-cone (3/16) and L-cone preference (3/16), indicating that the amygdala receives a more diverse visual input than previously

assumed. Our preliminary data using electrophysiological experiments in mice under freely moving conditions show that ~30% of amygdala units responded to white flash visual stimuli, suggesting that movement and/or anaesthesia influence amygdala physiology as previously reported. Our results provide the first functional evidence that the amygdala integrates photoreceptor-specific input, supporting a novel pathway by which light may directly influence affective brain states. These findings expand models of light-mood interactions by identifying the amygdala as a key node for integrating visual and emotional information. They highlight a potential pathway for light-driven modulation of mood, with future research aimed at determining the behavioural relevance of this sensory-limbic coupling.

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Poster

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Title: Functional Characterization of Visual Axonal Activity in the Mouse Corpus Callosum

Authors: *A. N. MALOY¹, S. NISHIMOTO^{2,3}, A. FUNAMIZU^{2,3}, M. WATANABE¹;
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Abstract: Decoding sensory and cognitive states from brain activity is a foundational goal of neuroscience and BCI research. Most invasive recording approaches rely on cortical gray matter, limiting scalability and writing capacity while requiring multiple probes across brain regions. We investigated the feasibility of decoding visual information from the corpus callosum (CC), a compact interhemispheric tract, using Neuropixels probes in mice. This region is typically avoided due to its saltatory, low-amplitude nature of axonal spikes, but new high-density recording and analytical techniques now allow exploration. Adult C57BL/6J mice were implanted with headplates and underwent craniotomy over the splenium of the CC. Neuropixels 1.0 probes were inserted through the retrosplenial cortex to a depth of ~3 mm, and full-field high-contrast drifting gratings (8 directions, 500 ms) were presented in pseudorandom order while photodiode signals synchronized stimulus onset and neural data. Spikes were extracted and curated using Kilosort 4.0 and Phy, then sorted by trial and stimulus direction. Multiple units localized to the presumed CC exhibited stimulus-locked responses to stimulus onset. These waveforms were consistently positive in polarity, low in amplitude, and localized to few

recording sites, consistent with the spatially constrained propagation of axonal spikes. Additional units recorded deeper along the probe showed direction-tuned or suppressive responses consistent with midbrain visual response properties. Together, these findings provide evidence that direction-selective axonal signals can be recorded from the corpus callosum and may support a centralized decoding architecture.

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Poster

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Title: Hierarchical functional processing of threat learning within pulvinar divisions in humans

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Abstract: The thalamus is gaining recognition for its role in fear conditioning, particularly highlighting the pulvinar's involvement in processing visual threats. However, the distinct contributions of individual pulvinar subdivisions to this process remain poorly understood. We investigated the functional relationships among the anterior, medial, inferior, and lateral pulvinar subdivisions during fear conditioning. We analyzed the fMRI data of 293 participants who underwent Pavlovian fear conditioning. We compared activation to conditioned stimuli (CS+, neutral visual object paired with electric shock) and control stimuli (CS-, unpaired) using trial-wise RM-ANOVAs, network modeling, and mediation analysis. The trial-wise analyses showed increased activation induced by CS+ during trial 1 in the medial, inferior, and lateral pulvinar (all $p_{FDR} < 0.05$), suggesting earlier sensory processing of CS+ in these divisions. The anterior pulvinar exhibited a delayed BOLD response starting in trial 2 ($p_{FDR} < 0.05$), a response consistent with associative learning. Network modeling showed direct lateral-to-anterior pulvinar connections and indirect pathways from lateral and inferior divisions to the anterior pulvinar via the medial pulvinar. Additionally, the medial pulvinar exhibited the highest centrality values (reflecting a region's influence in the network), indicating a potential hub role of this division in associative threat learning. Based on these findings, we hypothesize that the activation in the

medial pulvinar mediates the functional relationships between the inferior and lateral divisions with the anterior pulvinar. We tested this using a mediation model analysis and evaluated the model's robustness using cross-validation sub-samples. The sample ($N = 293$) was randomly divided into three groups. Each sub-sample was used to test the model, while the remaining groups served as a training phase. This resulted in six mediation model iterations. To strengthen generalizability, we confirmed the findings in an independent sample ($N = 114$). In both samples, the medial pulvinar mediates threat information from the inferior and lateral divisions to the anterior pulvinar (all $p < 0.05$ and path coefficients 95% CIs excluded zero). These findings support a functional hierarchy within the pulvinar, with specialized roles of each division during threat learning. The medial pulvinar (connected to deep superior colliculus (SC) layers, attention, and memory) integrates sensory input from the inferior and lateral pulvinar (linked to retinorecipient superficial SC layers) and relays it to the anterior pulvinar for higher-order processing.

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Poster

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Title: Population Receptive Field Properties of the Human Visual Claustrum Zone

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Abstract: The claustrum is a thin, bilateral sheet of grey matter between insula and putamen that stands out by its high interconnectivity with almost the entire cortex. Despite continuing research in humans and animals, its functional role remains largely unknown. In the present study, we explored the topographic organization of the recently described human visual claustrum zone. We performed a population receptive field (pRF) analysis on the 7T retinotopy dataset of the Young Adult Human Connectome Project ($N = 181$; Benson et al., 2018), comparing the claustrum with established pRF properties of the lateral geniculate nucleus, the primary visual cortex, and the higher-level topographic maps of the dorsal and the ventral stream. We confirmed that the human visual claustrum shows several key topographic properties, including a significant representational bias towards the contralateral visual field, which was however

weaker compared to other topographic maps. Similar to the properties found in other mammals, we also demonstrated that the human claustrum exhibits an overrepresentation of the visual periphery compared to other areas as well as a positive linear relation between pRF size and eccentricity. Moreover, the human claustrum displayed a positive eccentricity gradient along the anterior-posterior axis, with more anterior regions representing more peripheral visual field locations, thereby deviating from the findings in other mammals. This study is the first to characterize the topographic organization of the visual claustrum zone in humans, highlighting similarities to animal models as well as uniquely human properties.

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Poster

PSTR172: Category-Selective Cortical Visual Processing

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Title: Cortical face selectivity extends far into the visual periphery

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Abstract: Visual recognition is limited in peripheral vision relative to that of central vision by low acuity and more complex effects like crowding. Yet we can identify important stimuli, like faces, when presented relatively far from the center of gaze. However, both facial recognition and the neural mechanisms that support it have mostly been studied in central vision and the near periphery — rarely outside 20 degrees from the fovea. Here, we combined targeted neuronal population recordings from cortical face patches in macaque monkeys, naturalistic stimulus synthesis, and an advanced stimulus projection system to investigate the strength and feature selectivity of neuronal face preference across nearly the entire visual field. The stimulus apparatus consists of a projector, spherical mirror, and hemispheric dome screen allowing projection of visual stimuli up to an eccentricity of 90 degrees. We implanted microwire brush arrays in three fMRI-identified cortical face patches in two macaque monkeys: The anterior medial face patch in inferotemporal cortex, the perirhinal face patch, and the prefrontal orbital face patch. Stimuli consisted of natural face and nonface object images. We created scrambled stimuli corresponding to each natural image using an image synthesis algorithm that disrupted

complex object features while retaining low- and mid-level features. These scrambled stimuli are known to drive similar responses to that of the originals in early visual cortex, and under some circumstances to match the peripheral appearance of natural images. During recording, the two monkeys fixated a spot directly ahead while we briefly flashed images at different visual field positions up to 80 degrees eccentricity. We found that the face selectivity of neuronal populations in all macaque face patches was present for stimuli presented at locations far into the visual periphery, sometimes beyond 50 degrees eccentricity, although selectivity was generally weaker than when stimuli were presented centrally. Further, although some face selectivity remained for scrambled stimuli in the responses of neurons in the anterior medial face patch, we found little evidence that face selectivity in peripheral vision can be accounted for by lower-level visual features. This result contrasts with perceptual studies showing that appearance can be matched between natural images and their scrambled counterparts presented in the periphery, and indicates that cortical face patches maintain highly selective responses to faces presented far in the visual periphery.

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Title: Structural and functional organization of social perception networks in the temporal cortex of human and macaque

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Abstract: The temporal cortex mediates social perception across primate species and shows distinct organizational patterns between humans and macaques. In humans, face-selective regions include the fusiform face area (FFA) in the ventral temporal cortex and regions within the superior temporal sulcus (STS). In contrast, macaques possess several face-selective patches within the STS but lack a more ventral face area, raising questions about the functional correspondence of social perception networks between species. We investigated the neural basis

of social perception in three macaque monkeys (2 *Macaca mulatta* and 1 *Macaca fascicularis*) using high-resolution functional MRI (fMRI) and the Human Connectome Project (HCP) style data acquisition and analysis. Categorical visual stimuli (face, body, object, place) were presented during ferumoxytol-weighted fMRI acquisition using a 3T MRI scanner and a 24-channel multi-array RF coil designed for nonhuman primates (NHP). The data were processed using an NHP version of the HCP pipeline, mapped onto the cortical surface, and analyzed with a general linear model using FEAT (FSL) for category-related signals and temporal independent component analysis for resting state networks. The results were compared to human HCP data. Significant face-related signals were found within the bottom and ventral bank of the STS, which encompassed face patch AF, MF, ML and AM, AL, and PL, respectively, as reported in previous literature. Body-related signals are also shown within STS, whereas object and place-related signals in a wide area of the inferior temporal cortex. These category-selective activation patterns in the macaque suggest that a face patch in area TEa on the ventral bank of the STS (face patch AL) corresponds to the human FFA, whereas macaque face patches in the dorsal bank and fundus of STS (face patch AF, MF, and ML) correspond to human STS face-related areas. These findings suggest that the concentrated macaque STS face-processing network differentiated into two spatially separated streams in humans: the ventral fusiform areas and the lateral STS areas. The gap between these two streams in humans encompasses the middle temporal gyrus including areas of the default mode network and central executive network, whereas the corresponding region in macaques occupies a smaller STS fundus region weakly connected to putative macaque homologues. We propose that the evolutionary expansion and differentiation of temporal cortex face-processing networks in humans, coupled with the middle temporal area enlargement and integration into higher cognitive networks, underlie the emergence of uniquely complex human social behaviors.

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Title: Effect of Task on Body Selectivity in the Macaque Middle and Anterior Superior Temporal Sulcus

Authors: *G. GHAMKHARI NEJAD¹, A. BAHRAMI¹, A. BOGNÁR¹, A. MUKOVSKIY², M. GIESE², R. VOGELS¹;

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Abstract: Previous studies of body representations in the macaque Superior Temporal Sulcus (STS) focused on responses during passive fixation, and thus it is unknown how task context influences body representation in the STS. In this study, we determined whether body pose encoding in the ventral bank of the middle (mSTS) and anterior STS (aSTS) is modulated by task context by comparing neural responses and selectivity across two tasks that differed in the behavioral relevance of body pose. Two male macaques were trained on a pose categorization task, where they categorized body pose of a monkey avatar across variations in viewpoint and size, and a target detection task, in which they made a saccade to a randomly positioned target following presentation of the same stimuli, which were now task-irrelevant. Acute neural recordings from the mSTS were conducted using 24-channel Plexon V-probes, with task conditions alternating in blocks. Across all reliably responsive and selective units, the mean firing rate for the preferred stimulus (determined separately for each task) did not differ significantly between the tasks. Training a linear support vector machine classifier to decode pose and view using the neural responses of 75% of the trials from one task yielded similar classification accuracies for independent test trials from the same or the other task—suggesting highly similar body representations for the two tasks. Nonetheless, analysis of behavioral response latencies showed pose-related differences between the two tasks. These results suggest that body pose selectivity of body-responsive mSTS units is not modulated by task demands for well-visible body stimuli and the tasks used here. Subsequently, we increased task difficulty and reduced pose visibility by partially occluding the monkey avatar (40% occlusion) by a random dot pattern. Recordings in mSTS of one monkey showed a significantly increased response to the preferred stimulus for the pose categorization task, compared to the target detection task. Recordings in aSTS also showed a significantly increased response in the pose categorization task, although with a smaller effect size. In mSTS, the median pairwise dissimilarity in population responses to different poses and viewpoints was greater in the categorization task than in the detection task, while it remained nearly identical in aSTS. Decoding accuracy of pose and viewpoint was higher in the categorization task than in the detection task in both mSTS and aSTS. These data show that both the response and selectivity for body poses and viewpoints are enhanced in the macaque STS when the latter stimulus properties are task-relevant and the body poorly visible.

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Title: What will you look at next? The neural processes of eye-movement guidance to objects revealed by intracranial electroencephalography

Authors: *A. ALREJA¹, M. J. BORING², M. WARD⁵, M. RICHARDSON⁶, C. E. SCHROEDER⁷, T. J. ABEL³, A. S. GHUMAN⁴;

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Abstract: We move our eyes to look at things: a cup of coffee, your phone, your daughter's face, etc. However, our understanding about the neural guidance of eye movements is shaped largely by studying where we are going to look next. Therefore it remains unclear how our brain guides our eyes to things in our environment ("what" we are going to look at next). Thus, while many studies have examined the role of the dorsal "where" pathway in guiding eye movements, the role of the ventral "what" pathway in eye movement guidance remains relatively unexplored. We addressed this gap with simultaneously recorded intracranial electroencephalography and eye tracking in individuals with epilepsy during free viewing of scenes as well as during unscripted natural social interactions in the real world. In both paradigms, brain activity from prior to the onset of saccades to objects could be used to predict the category of object participants looked at next - even after controlling for spatial locations of eye movements. Prediction of what a person was going to look at next was enabled not only by brain activity from areas of parietal cortex traditionally associated with eye movement guidance but also category selective regions of ventral temporal cortex. The influence of parafoveal responses to the object of the next fixation was examined by comparing saccades traversing greater than 5 degrees of visual angle to smaller saccades. Prediction accuracy did not diminish for these larger saccades, suggesting that parafoveal preview was not why ventral temporal cortex predicts what people are going to look at next. Preliminary results indicate predicting the object category of the next fixation may involve theta band activity in category selective ventral visual cortex, putatively related to interactions with theta frequency activity in hippocampal regions involved in visual navigation. These results suggest ventral temporal cortex is involved in guiding what to look at next, and interactions between ventral temporal cortex, hippocampus, and parietal cortex may guide where to look for that object.

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Title: The contribution of motion and static features to dynamic body responses in macaque middle and anterior Superior Temporal Sulcus

Authors: *A. BAHRAMI, A. BOGNÁR, G. GHAMKHARI NEJAD, R. VOGELS;
KU Leuven, Leuven, Belgium

Abstract: fMRI studies in monkeys show stronger activation to movies of moving monkeys than to still images in the macaque Superior Temporal Sulcus (STS; Bognar et al., 2023). Single-unit recordings in the ventral bank of the anterior STS also suggested that both motion and static features contribute to dynamic body selectivity, and that motion features predicted dorsal bank STS neurons' selectivity for dynamic bodies better than static features (Raman et al., 2023). In this study, we examined how motion and static features contribute to dynamic body selectivity in units of the more posterior ventral bank middle STS (MSB), in addition to those of the anterior ventral bank STS. Based on the presence of random dot motion responses in the middle but to a lesser extent in anterior STS (Bognar et al., 2025), we predicted a stronger contribution of motion to middle STS than anterior STS units. We targeted the fMRI-defined middle (MSB) and anterior STS (ASB) body patches in two male rhesus monkeys using 16-channel V-probes. We presented 19 one-second-long natural movies of an acting monkey and 10 snapshots (300 ms duration) from each movie. To assess the sensitivity to snapshot sequence, we also presented time-reversal versions of each movie, randomly interleaved with the original ones and the 190 snapshots. In both regions, the response selectivity to the body movies could be predicted from the snapshot responses, indicating a contribution of static features to the movie responses. However, after the initial transient, the average response to reversed movies was significantly larger than to the original ones in both MSB and ASB. Although this response difference may arise from a higher familiarity with the original movies, it nonetheless indicates that neurons in both regions show sequence sensitivity. In MSB—but less so in ASB—the response differences among dynamic movies correlated with the differences in velocity pattern, computed using an optical flow algorithm, among the movies; this correlation was stronger for reversed than for original movies. The opposite pattern was present when correlating the response difference with Convolutional Neural Network (AlexNet and ResNet50) features: a higher correlation for ASB than MSB, and higher for the original compared to the reversed movies. These data suggest a stronger motion contribution to the selectivity for dynamic bodies in the middle compared to anterior STS regions. However, in both STS regions, static features contribute to the selectivity for moving bodies.

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Poster

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Topic: E.06. Vision

Title: Representational geometry of human ventral temporal cortex is insufficiently categorical to fully account for human categorical judgements

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Abstract: The representational geometry of human ventral temporal cortex (VTC) is thought to support categorization by maximally separating object representations in late stages of the visual hierarchy. Here, we test whether this separation fully matches that of human categorical judgments or if further readout from VTC is required. We created stimulus sets that smoothly interpolate between object endpoints in their V1-like visual features but exhibit a sharp object identity boundary. These stimuli were synthesized by interpolating between latent representations in a diffusion model. We then measured the perceptual and representational geometries of each image set by calculating *categorical index values* (CIVs), which quantify how categorical each geometry is. For each interpolation set, we measure both perceptual (categorization task) and representational (measured BOLD responses) similarity matrices (RSMs), and fit them as linear combinations of two ideal RSMs: one V1-like (smooth interpolation), and one categorical (sharp boundary). CIVs are calculated for each geometry as the relative weight of the categorical model, ranging from 0 (smooth) to 1 (categorical). Perceptual CIVs were near 1 (mean 0.95 ± 0.049 std), indicating human observers perceived sharp category boundaries in the interpolations. Participants ($n = 7$) performed a categorization task classifying each image as one of the two endpoint objects. Using these data we fit psychometric functions to estimate the perceptual distance between images in each interpolation, computed full RSMs from those estimated values, then used those RSMs to compute perceptual CIVs. Like human perceptual judgments, the choice layers of various visual neural networks were also highly categorical (mean CIV = 0.98 ± 0.042 std). However, the neural networks achieve this geometry through readout from representational layers, not representational alignment: the last representational layers of the networks, before the linear readouts, were substantially less categorical than the final readout layers (mean CIV = 0.42 ± 0.18). Measurements in human visual cortex revealed that, similar to neural networks, VTC representational geometry was markedly less categorical than perceptual judgements (mean 0.35 ± 0.19), suggesting that human visual perception adopts a similar strategy as neural networks in achieving full categorical perception through read-out rather than full representational alignment. Our results suggest that VTC only partially adapts representational geometry for categorization. This partial adaptation may allow for flexibility to accommodate many different types of judgements that one might make.

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Poster

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Title: The cellular basis of human face categorization in the fusiform gyrus

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Abstract: Humans have an outstanding ability to rapidly and automatically recognize sensory stimuli in their environment such as faces. Although face-selective population-level neural activity has been recorded for decades with neuroimaging or (intracranial) electroencephalography, the cellular basis of this impressive human face categorization ability remains largely unknown. To address this gap in knowledge, we recorded cellular neural activity inside the human middle Fusiform Gyrus (mFG) ('Fusiform Face Area', FFA) of eight epileptic patients implanted with hybrid macro-microelectrodes during an automatic face categorization task. Within a rapid 6 Hz stream of variable non-face objects, natural images of faces were presented periodically every fifth image (1.2 Hz) during 70-s stimulation sequences. Across all individual brains tested over several independent recording sessions, this frequency-tagging stimulation objectively identified a very high proportion (317 out of 466 units identified; 68%, $p < 0.05$) of neurons discharging at 1.2 Hz in the FFA, i.e., face-selective neurons. Notably, half of this face-selective population consisted of neurons responding exclusively to faces (i.e., no 6 Hz response). Additionally, we observed a tight correspondence between increase/decrease in BOLD activity and neuronal firing: while single-units recorded in the lateral mFG showed a selective increase to faces, neurons localized in the medial mFG decreased spiking activity selectively to faces. Cellular activity subtending face categorization showed a consistent time-course across individual neurons and brains, remarkably in line with onset times (~100 ms) and duration (~300 ms) obtained with the same stimulation mode at higher levels of physiological recordings. Overall, these observations provide new insights into the cellular mechanisms underlying human face categorization.

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Poster

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Title: Generative modeling tools for characterizing human higher visual cortex

Authors: A. LUO¹, *M. M. HENDERSON², S. PARK², M. J. TARR², L. WEHBE²;
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Abstract: Characterizing the fine-grained functional organization of human higher visual cortex remains a significant challenge. Traditional neuroimaging experiments are limited in the number of stimuli they can sample, which may bias results toward particular stimulus attributes. In prior work we developed a novel data-driven tool, termed “BrainDiVE” (Luo et al. 2023, NeurIPS), which addresses these challenges by synthesizing images optimized to activate specific brain regions. BrainDiVE leverages pretrained image diffusion models guided by gradients from an image-computable fMRI encoding model. Here, we validated BrainDiVE experimentally by generating images that targeted several functional regions of interest (i.e., images predicted to maximally activate those areas), and showing them to human participants (n=12) in a new fMRI study. We found that the synthesized images elicited robust and specific responses in the predicted target regions, yielding significantly higher measures of category selectivity relative to natural images. This validates BrainDiVE's ability to capture neural selectivity in human ventral visual cortex. Furthermore, we demonstrated fine-grained experimental control by differentially activating two face-selective regions—the occipital face area (OFA) and fusiform face area (FFA)—suggesting, as reflected in the BrainDiVE images, that they encode distinct aspects of faces. These findings provide new insights into the representational structure of category-selective regions and establish a novel paradigm for targeted exploration of neural selectivity in human visual cortex. More generally, our approach offers a powerful tool for investigating the functional organization of visual cortex at a fine-grained level, exceeding the capabilities of traditional methods across multiple dimensions.

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Poster

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Topic: E.06. Vision

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R01NS109487
T32EB014855

Title: Semantic Decoding of Naturalistic Movies using High-Density Diffuse Optical Tomography

Authors: *W. FEHNER¹, M. FOGARTY¹, A. BAJRACHARYA⁴, Z. E. MARKOW², D. WILHELM¹, J. TANG⁵, A. HINES³, J. TROBAUGH³, A. G. HUTH⁶, J. P. CULVER¹;
¹Radiology, ²Biomed. Engin., ³Washington Univ. in St. Louis, St. Louis, MO; ⁴Yale Univ., Saint Louis, MO; ⁵Computer Sci., ⁶The Univ. of Texas at Austin, Austin, TX

Abstract: Introduction: Visual semantics link to language and enable the retrieval of object and action categories without language input. fMRI studies indicate shared cortical representations of vision and language (Popham et al., 2021). This connection provides a chance to study language disorders, such as stroke-induced aphasia, where visual semantics may bypass damaged language areas. fMRI pioneered semantic mapping with natural stimuli (Huth et al., 2012), but its scan environment presents logistic challenges. We present High-Density Diffuse Optical Tomography (HD-DOT) as a surrogate for fMRI semantic mapping. While earlier HD-DOT studies utilized motion energy wavelets for model-based decoding (Markow et al., 2023), this study applies a semantic model, with weights and accuracy extending beyond the primary visual cortex.

Methods: Six subjects completed 3 HD-DOT sessions (4.5 h), featuring localizer and movie clips (120 mins training, 10 repeats of 9-min test clips). Each second was labeled with 1,708 semantic features. A voxelwise L2-regularized linear regression model was fit using bootstrapped cross-validation for hyperparameter selection. Model accuracy was assessed by correlating predicted and actual voxel time courses. For semantic decoding, we conducted winner-takes-all clip identification using the most predictive voxels (top 10%). Bootstrapping for best voxel selection was repeated 10 times during model validation. **Results:** Figure 1 shows successful semantic encoding and decoding, with high prediction accuracy extending beyond primary visual areas. Model weight RMS values were higher in similar regions. Four subjects exhibited positively skewed accuracy distributions, indicating strong model fits. For all subjects, clip ID decoding was consistently above chance and frequently high across clip segments, supporting the robustness of semantic representations in DOT data. **Conclusion:** The ability to capture rich semantic representations positions HD-DOT as a promising alternative to fMRI for naturalistic semantic brain mapping of clinical populations.

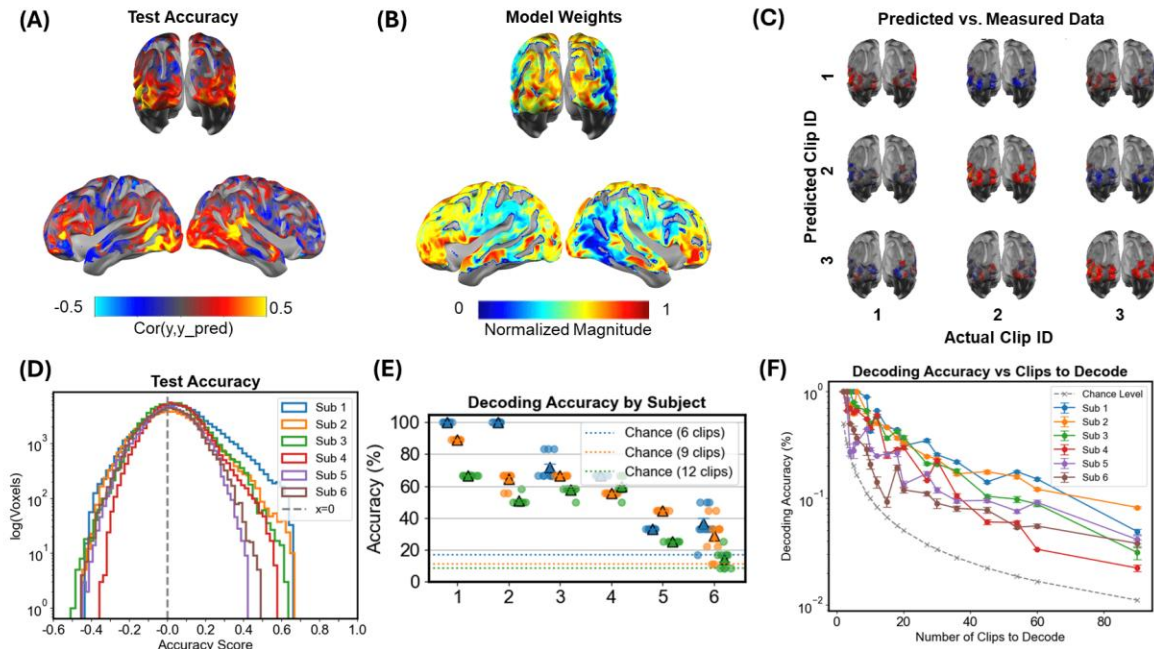


Figure 1 | Semantic encoding model and clip decoding. The semantic encoding model predicts voxel-level brain activity from the semantic features of a naturalistic movie stimulus. Model weights were estimated using L2-regularized linear regression. **(A)** Voxelwise model accuracy maps (Pearson correlation between predicted and actual responses) evaluated on held-out test data for Sub 1. **(B)** Spatial distribution of normalized weight magnitude (RMS) for Sub 1. **(C)** Temporal correlation matrices between predicted and measured voxel responses for the predicted movie clip (on-diagonal) and other (mismatched) clips (off-diagonal), shown for Sub 1. Test data was divided into three 3-minute clips. Decoding was constrained to the top 10% of best-performing voxels, determined during model validation. **(D)** Histograms of model accuracy across all voxels for all subjects. **(E)** Decoding accuracy across sessions and subjects. Scatter plots show decoding accuracy for 10 bootstrap repetitions, grouped by subject. Large markers and error bars represent the mean decoding accuracy $\pm$ SEM. Colors indicate the number of clip segments used for decoding. **(F)** Decoding accuracy vs number of clips to decode. The 9 min of test data (averaged over 10 repeats) was divided into 2 (270 s) to 90 (6 s) clip segments for decoding.

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Poster

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Federal Ministry for Health SSTeP-KiZ BMG: ZMWI1-2520DAT700. 3
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Title: A multi-view video, motion capture dataset and pipeline for 3d macaque animation

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Abstract: The investigation of the neurocomputational mechanisms of the visual processing of bodies in primates is less developed than that of face processing. This is partly explained by the difficulty in constructing highly controlled stimulus sets. Realistic computer animation models of non-human primates (NHPs) are hardly available, because marker-based full-body tracking of these species is often impossible, and because markerless tracking with sufficient accuracy for computer animation has been an unsolved problem. Due to the lack of large amounts of training data, many established high-quality markerless tracking approaches used for humans are not applicable. Existing behavioral tracking approaches for NHPs would require large numbers of hand-labeled 2D keypoints to make them suitable for realistic computer animation. Furthermore, existing avatar models cannot be easily adapted to different monkey individuals.

METHODS/RESULTS: We have addressed these challenges by devising a novel large macaque video and motion capture database, which includes more than 750 recorded actions of rhesus macaques. Actions are labeled using categories defined by an ethogram that is derived from behavioral research. Our data set includes accurate 3D tracking data, prepared for driving skeleton models in 3D animations, and is generated by a novel multi-view tracking approach that includes silhouette and 2D keypoints for surface tracking, producing accurate joint-angle estimates with fewer keypoints. Therefore, the dataset comprises the corresponding synchronized multi-view RGB videos, 2D keypoint trajectories, silhouettes, and colored surface models. The associated software allows the animation of individual-specific highly-realistic avatars with the recorded motions, rendering them in arbitrary views. **DISCUSSION:** This new data set and the associated algorithms lay the basis for highly controlled experiments that investigate the representation of dynamic bodies in NHPs with exact stimulus control, e.g. for experiments in electrophysiology or functional imaging. The developed method can be readily transferred to generate 3D dynamic avatars of other species.

Disclosures: L. Martini: None. A. Bognár: None. R. Vogels: None. M.A. Giese: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.01/S4

Topic: E.08. Multisensory Integration

Support: DFG Grant EXC 2050/1 – Project ID 390696704

Title: Adult age differences in attentional modulation of cortical activity during visuo-proprioceptive integration in virtual environments

Authors: ***K. KARAN**^{1,2}, **K. KANG**³, **J. LIMANOWSKI**^{4,1}, **S.-C. LI**^{1,2};

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Abstract: This study investigated the impact of aging on multisensory integration, specifically visuo-proprioceptive integration with a virtual reality (VR) setup. As adults age, their capacity to process and integrate sensory information, particularly visual and proprioceptive cues, undergoes significant changes. We recruited older (OA; $N = 45$, range = 60-75) and younger adults (YA; $N = 40$, range = 18-35) to complete a visuo-proprioceptive phase matching task in VR, while brain hemodynamic responses were measured using functional Near-Infrared Spectroscopy (fNIRS). Participants wore a data glove to match the size of a target dot with their hand movements, focusing either on the virtual hand (VH) displayed on the screen (visual modality) or their actual hand (proprioceptive modality), thereby engaging attentional processes related to integrating vs ignoring conflicting sensory input. In half of the trials, a visuo-proprioceptive incongruence was introduced through a 750 ms delay in VH movements. Our results indicate that OA exhibited greater movement deviations when confronted with incongruent stimuli only, as shown by a linear mixed-effects model with a significant age $\times$ attention $\times$ congruency interaction ($F(1, 249) = 18.73, p < .001$, including post-hoc analyses): This suggests a decline in OA's ability to resolve conflicts between visual and proprioceptive information. Further analyses on oxygenated hemoglobin (HbO) levels revealed distinct patterns of brain activity in OA, indicating that aging influences how the brain processes temporally incongruent multisensory input. Significant main effects of attention, congruency, and age were found in regions associated with visual and somatosensory functions, including the visual cortex ($p < .000$), supplementary motor area (SMA, $p < .005$), and right superior parietal lobule (rSPL, $p < .000$). Three-way interaction effects were observed in the superior parietal lobule, somatosensory, motor, and visual cortices, with OA showing reduced cortical activity compared to YA while attending to the VH under incongruence. Increased movement deviations and altered cortical responses in OA suggest a reduced ability to resolve visuo-proprioceptive conflicts, contributing to age-related declines in sensorimotor adaptation. These neural changes can lead to slower reaction times, increased susceptibility to distraction from intersensory conflicts, and reliance on less optimal cues, ultimately impairing sensorimotor adaptation and coordination in OA. Understanding these age-related differences is crucial for optimizing VR, ensuring they are effective and immersive for users across age groups.

Disclosures: **K. Karan:** A. Employment/Salary (full or part-time): TU Dresden, CeTI. **K. Kang:** A. Employment/Salary (full or part-time): University of Leicester. **J. Limanowski:** A. Employment/Salary (full or part-time): University of Greifswald. **S. Li:** A. Employment/Salary (full or part-time): TU Dresden, CeTI.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.02/S5

Topic: E.08. Multisensory Integration

Support: Medical Research Council (UK) Grant MR/Y004000/1

Title: Multisensory Integration in Heading and Scene-Relative Object Motion Estimation

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Abstract: Both vestibular and visual signals contribute to our ability to: (i) estimate instantaneous direction of self-movement (heading); (ii) compensate for reafferent sensory input from self-movement to detect and assess movement of other scene elements (Scene-Relative Object Motion; S-ROM). Multiple studies (e.g., Gu et al., 2007; Yakubovich et al., 2020) suggest that these sensory signals are integrated near-optimally during heading estimation, consistent with Maximum Likelihood Estimation (MLE; Ernst & Banks, 2002), where weights assigned to each sensory input are scaled by reliability to maximize precision of the resulting estimate. Although Macneilage et al. (2012) provided evidence for visual-vestibular integration in S-ROM estimation, whether this is optimal remains unclear. Here, we investigate optimality of visual-vestibular integration in heading and S-ROM tasks within the same participants. In both tasks, participants experienced three self-movement conditions: visual only - stationary participants viewed optic flow simulating forward self-movement via a head-mounted display; non-visual only - participants were physically moved on a 6-DOF motion platform with no visual motion input; combined - participants experienced both physical movement and simultaneous visual self-movement cues. In the heading task, interleaved adaptive staircases varied the angle of translational observer movement on each trial (in a range $\pm 16^\circ$ from straight ahead), and participants reported perceived self-movement direction relative to straight ahead. In the S-ROM task, participants moved along an oblique ($\pm 30^\circ$) trajectory and judged the scene-relative direction of a probe object with movement controlled by interleaved adaptive staircases. In both tasks, psychometric functions linking physical to perceived direction (of the self in the heading task and the probe in the S-ROM task) yielded bias and precision (reliability) measures. We then tested each participant's parameters for consistency with MLE integration. Preliminary results (N=7) in the heading task align with prior findings, with 6 of 7 participants showing MLE-consistent behaviour. In the S-ROM task, we also find consistent evidence for MLE-like sensory integration. This work is part of the ongoing STudy to Assess and Reduce Dizziness Using

Sensory Theory (STARDUST). Based on this preliminary work, we will assess potential deviations from MLE as a contributing factor to dizziness symptoms in individuals with a Functional Neurological Disorder thought to affect sensory integration.

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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.03/Web Only

Topic: E.08. Multisensory Integration

Support: JSPS KAKENHI Grant JP23H00076
JSPS KAKENHI Grant JP20H05801
JSPS KAKENHI Grant JP23K18980

Title: Age-related changes in hand position perception: A Bayesian causal inference approach

Authors: N. KURODA¹, Y. SATO², S. HARADA³, R. TERAOKA⁴, *W. TERAMOTO³;
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Abstract: Hand position perception relies on the integration of visual and proprioceptive inputs. While previous studies suggest that older adults depend more on visual cues than younger adults, the computational mechanisms driving this shift remain unclear. This study applied a Bayesian causal inference (BCI) model to disentangle sensory reliability, causal prior, and integration strategy. Using a video-projection setup, we introduced spatial mismatches between visual and proprioceptive hand positions. Participants reached a target with their hidden hand immediately after the visual hand image disappeared, allowing us to infer perceived hand position from reaching errors. Experiment 1 included an embodiment phase to promote ownership of the visual hand, while Experiment 2 omitted it to assess age-related differences in causal prior. Both younger and older adults exhibited systematic reaching errors, with larger absolute errors observed under greater visual-proprioceptive mismatches. Older adults showed stronger visual influence than younger adults. BCI modeling revealed that aging is associated with reduced proprioceptive reliability and a heightened bias toward assuming a common cause for sensory signals. These findings highlight age-related changes in multisensory integration and demonstrate the value of BCI modeling in understanding perceptual differences across the lifespan.

Disclosures: N. Kuroda: None. Y. Sato: None. S. Harada: None. R. Teraoka: None. W. Teramoto: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.04/S6

Topic: E.08. Multisensory Integration

Support: NHMRC 105508

Title: Proprioceptive judgements made with the hand and the jaw - two distinct but functionally related body parts

Authors: *M. E. HEROUX¹, L. ROBERTSON², G. FISHER⁵, A. A. BUTLER³, S. C. GANDEVIA⁴;

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Abstract: Proprioception is often assessed with low-level (LL) judgements, those made within a single proprioceptive frame of reference. However, there are also high-level (HL) judgments, which involve central transformations between two frames of reference (e.g. visual and proprioceptive). It is unknown whether these central transformations are similar across body parts. This study focuses on the jaw and hand, two functionally linked body parts (e.g. feeding). We compare LL and HL judgements that require participants to grasp or bite objects of different sizes. Thirty adults (13 males; mean age 34 SD 8 y) performed four proprioceptive tasks: 1) LL hand (grasp-to-grasp), 2) HL hand (grasp-to-vision), 3) LL jaw (bite-to-bite), and 4) HL jaw (bite-to-vision). Participants adjusted a hidden object (LL) or visual line (HL) to match the perceived width of the stimulus object. Accuracy (mean absolute error, MAE), precision (R^2), and central calibration parameters (slope, intercept) were computed. Mean [95% CI] differences were computed for pre-planned contrasts: difference between a) HL and LL tasks (hand and jaw), b) hand and jaw tasks (LL and HL). Correlation coefficients were calculated to estimate key relationship. LL judgements were more accurate than HL ones at the jaw (mean different in mean absolute error: 0.15 mm [0.09 to 0.20]) and the hand (0.20 mm [0.12 to 0.27]). There was no difference in the precision of judgements between jaw LL and HL (mean different in R^2 : -0.04 [-0.09 to 0.02]). However, for the hand, judgements were more precise in the LL task (0.06 [0.03 to 0.09]). Compared to the jaw, precision was greater at the hand in both the LL (0.08 [0.04 to 0.13]) and HL tasks (0.06 [0.02 to 0.09]). Overall, there were differences between the hand and the jaw, which indicate the brain does not apply the exact same central calibration to transform coordinates from a proprioceptive frame of reference to a visual frame of reference across different body parts. Moreover, the consistency that was present within participants highlights the personalised nature of HL proprioceptive judgements.

Disclosures: M.E. Heroux: None. L. Robertson: None. G. Fisher: None. A.A. Butler: None. S.C. Gandevia: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.05/Web Only

Topic: E.08. Multisensory Integration

Title: Sensory Processing Deficits as an Individual Difference Associated with Anxiety and Depression

Authors: *C. KOCH, E. DEL VALLE;
Psychology, George Fox Univ., Newberg, OR

Abstract: This study was conducted to examine the relationship between subclinical levels of sensory-related processing, including visual acuity, color vision, dry eyes, and hearing, and anxiety and depression. Participants, 220 college students, completed visual acuity, color vision, dry eyes, and hearing screening measures. They also completed the Trait Anxiety Inventory Questionnaire (TAIQ), GAD-2, PHQ-2, and Epworth Sleepiness Scale. The scores from the screeners were standardized and combined into one sensory processing score so that those variables could be examined individually and collectively. The sensory processing composite score was significantly correlated with depression (PHQ-2) and both trait (TAIQ) and state (GAD-2) anxiety. Sensory processing was a significant predictor of trait anxiety ($F(2, 207)=15.42, p<.001$). This finding suggests that sensory-related processing may be an important individual difference associated with emotional states and overall trait anxiety. However, the individual sensory processes were correlated with the composite score, with r 's ranging between .58 and .63, and the internal reliability of the composite score was .47. Therefore, differences in sensory processing ability may be important to consider when examining anxiety and depression, but additional research is necessary to develop a better measure of overall sensory processing based on simple screening measures.

Disclosures: C. Koch: None. E. Del Valle: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.06/S7

Topic: E.08. Multisensory Integration

Title: Distinct brain co-activation patterns in patients with persistent perceptual postural dizziness (PPPD)

Authors: *C. CONCETTI¹, I. LOZZI^{2,1}, S. AYBEK RUSCA¹;

¹Dept. of Movement Sci. and Neurosci., Univ. of Fribourg, Fribourg, Switzerland; ²Dept. of Neuroscience, Biomedicine and Movement, Univ. of Verona, Verona, Italy

Abstract: Background: Persistent Perceptual Postural Dizziness (PPPD) is a subtype of Functional Neurological Disorders (FNDs), a spectrum of disorders leading to various neurological symptoms due to neural networks dysfunction in the absence of an identifiable brain lesion, at the interface of neurology and psychiatry. PPPD patients experience chronic dizziness and unsteadiness impacting everyday life. These are thought to stem from a disruption in higher-order integration of visual and vestibular signals, rather than from vestibular dysfunction. This disorder is one of the most common causes of chronic dizziness but has been recognized only recently and no resolutive treatment is currently available. **Objectives:** The aim of this study is to better characterize brain activity alterations in PPPD patients and their relationships to gait and postural outcomes, stress markers, and neuropsychological risk factors, known to play a role in the pathophysiology of other FNDs. **Methods:** 20 PPPD patients and 20 age- and gender-matched healthy controls (HC) were recruited. PPPD patients were diagnosed by a multidisciplinary team in the Center of Dizziness of the Inselspital Bern, Switzerland, according to ICD-11 criteria. Participants underwent a resting state fMRI recording, gait and posture assessments, and saliva sampling. Data from 2 PPPD patients had to be excluded (due to MRI acquisition quality), yielding a final sample of 18 PPPD patients and 20 HC. The fMRI dataset was preprocessed using a standard pipeline and analysed using a co-activation patterns (CAPs) approach. **Results:** Our preliminary analysis shows that PPPD patients have distinct brain-wide CAPs with respect to controls, with a decrease in co-activation of the caudate nucleus and the insular cortex with patterns involving the default mode and limbic networks. Differently from other FNDs, we find no alteration in rTPJ patterns. Brain signatures of multi-sensory integration and motor control will be further explored, together with the relationship between brain CAPs with features of posture, gait, stress, and neuropsychological risk factors (analysis ongoing). **Conclusion:** This study offers a characterization of brain functional alterations at rest in PPPD patients with a novel, dynamic connectivity approach, possibly a signature of altered high-level motor control. It also investigates the relationship of altered brain CAPs with clinical manifestations of the disease and suspected risk factors. Although limited by its sample size, it offers one of the widest samplings of multi-modal data in the PPPD population, shedding light on its similarities and differences to the wider FNDs category.

Disclosures: C. Concetti: None. I. Lozzi: None. S. Aybek Rusca: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.07/S8

Topic: E.08. Multisensory Integration

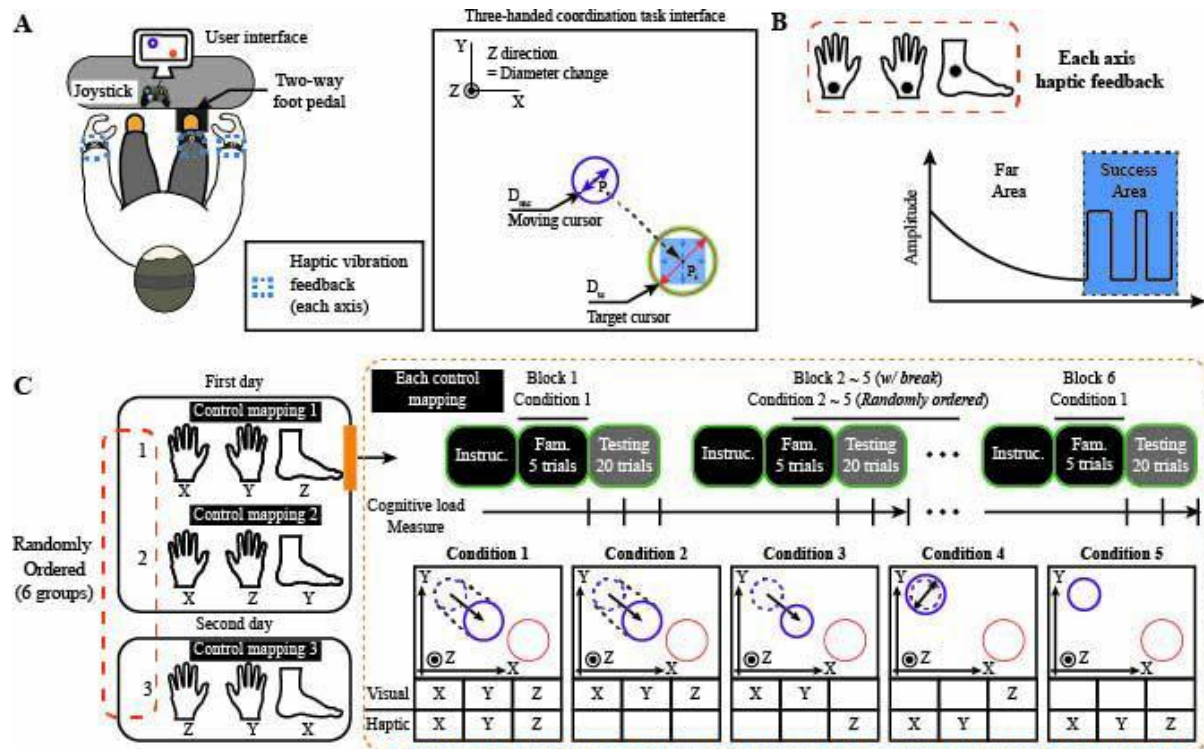
Support: NSF Grant 1934792

Title: Sensory substitution of haptic feedback for visual information in multi-limb coordinated tasks

Authors: *K. HONG¹, A. KANAPSKYTE², H. GOWDA⁵, W. M. JOINER³, L. M. MILLER⁶, J. S. SCHOFIELD⁴;

²Dept. of Biomed. Engin., ³Dept. of Neurobiology, Physiol. and Behavior, ⁴Dept. of Mechanical and Aerospace Engin., ¹Univ. of California, Davis, Davis, CA; ⁵Dept. of Electrical and Computer Engin., Univ. of California, Davis, Davis, CA; ⁶Univ. of California Davis, Davis, CA

Abstract: Humans coordinate multi-limbs that rely on motor commands between the brain and limbs, while seamlessly integrating sensorimotor information. Somatosensory information allows for coordination without constant reliance on visual information. As additional limbs and task complexity is increased, challenges may arise in effective task performance and maintaining coordination across limbs. Haptic feedback has shown potential in improving coordination. Our sensorimotor system is theorized to assign relative weighting to vision and haptics based on their reliability, and spatial-temporal characteristics for tasks. A notable gap remains in understanding multisensory integration when haptic information may be substituted to relieve a task with high visual demand. Also, little is known about the extent to which this substitution can support multi-limb coordination tasks. To solve this gap, we conducted an experiment investigating how sensory feedback can be incorporated in a multi-limb coordination task. To explore this, we conducted an experiment in which 25 participants performed a multi-limb coordination task using a virtual cursor-to-target task. Participants controlled the cursor with both upper limbs and one lower limb. We systematically varied visual and haptic feedback. We assessed task performance measures, including a cognitive workload. Our findings indicate that haptic feedback can effectively substitute for one degree of visual information during our task. We found no significant difference between conditions where all visual cues were presented in the task and the condition where one visual feedback was replaced by haptic feedback; however, we found significant decrements in performance when haptics substitute for visual information beyond this level. These results suggest that haptic feedback can, to an extent, serve as a viable alternative to visual feedback in complex multi-limb tasks. Our current findings highlight the potential of sensorimotor integration to enhance human-machine interaction in assistive technologies and other applications.



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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.08/S9

Topic: E.08. Multisensory Integration

Support: NIH Grant 5R01NS065395
NIH Grant 5U01NS113339

Title: Stereoelectroencephalography reveals neural signatures of multisensory integration in the human superior temporal sulcus during audiovisual speech perception

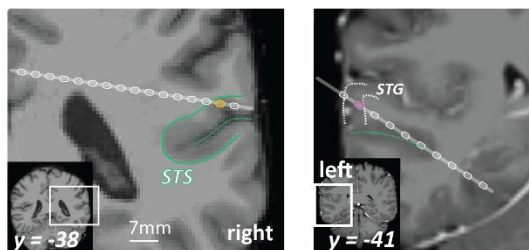
Authors: Y. ZHANG¹, *J. F. MAGNOTTI², X. ZHANG², Z. WANG², Y. YU², K. DAVIS², S. A. SHETH¹, D. YOSHOR², M. BEAUCHAMP²;

¹Baylor Col. of Med., Houston, TX; ²Univ. of Pennsylvania, Philadelphia, PA

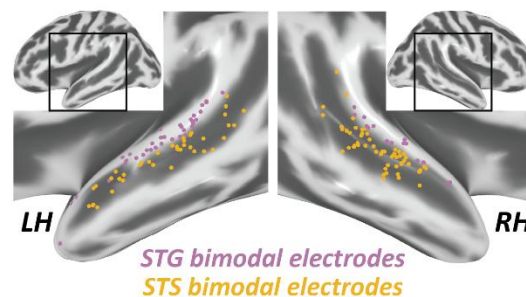
Abstract: Human speech perception is multisensory, integrating auditory information from the talker's voice with visual information from the talker's face. BOLD fMRI studies have implicated

the superior temporal gyrus (STG) in processing auditory speech and the superior temporal sulcus (STS) in integrating auditory and visual speech, but as an indirect hemodynamic measure, fMRI is limited in its ability to track the rapid neural computations underlying speech perception. We directly recorded neural activity in the STG and STS in 42 epilepsy patients implanted with stereoelectroencephalography (sEEG) electrodes. Patients identified single words presented in auditory, visual and audiovisual formats with and without added auditory noise. Seeing the talker's face provided a strong perceptual benefit, improving perception of noisy speech in every participant (42% average improvement). Neurally, a subpopulation of bimodal electrodes concentrated in mid-posterior STG and STS showed short latency responses to auditory speech (71 ms) and visual speech (109 ms). Significant multisensory enhancement was observed in STS bimodal electrodes: compared with auditory-only speech, the response latency for audiovisual speech was 40% faster and the response amplitude was 18% larger. In contrast, STG bimodal electrodes showed neither faster multisensory latencies nor significant response enhancement. Surprisingly, STS response latencies for audiovisual speech were significantly faster than those in the STG (50 ms vs. 64 ms). This suggests the possibility of a parallel pathway model in which the STG plays the primary role in auditory-only speech perception, while the STS takes the lead in audiovisual speech perception.

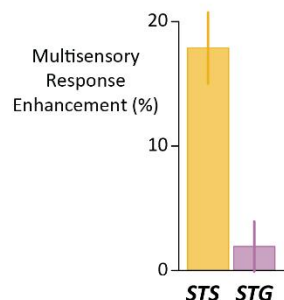
Using stereo EEG we find contacts in STS or STG



Find contacts that respond to both auditory-only and visual-only speech



STS bimodal electrodes show multisensory response enhancement (AV amplitude greater than A-only) and multisensory latency enhancement (AV faster than A-only speech)



Disclosures: Y. Zhang: None. J.F. Magnotti: None. X. Zhang: None. Z. Wang: None. Y. Yu: None. K. Davis: None. S.A. Sheth: None. D. Yoshor: None. M. Beauchamp: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.09/S10

Topic: E.08. Multisensory Integration

Title: Generalization of Learning Arbitrary Audiovisual Associations via Low-Level Features

Authors: ***A. MACHADO**¹, C. CHANG³, M. T. WALLACE²;

²Psychology, ¹Vanderbilt Univ., Nashville, TN; ³Electrical and Computer Engin., Vanderbilt University, Santa Clarita, CA

Abstract: Audiovisual integration supports higher cognitive functions such as language and object recognition, yet how cross-modal associations are formed remains poorly understood. This study introduces a controlled behavioral paradigm to investigate how low-level sensory features—such as spectral structure and geometric complexity—support the learning and generalization of arbitrary audiovisual pairings. Ten adult participants (7 female, 3 male; ages 22-60) completed a multi-phase task using novel auditory and visual stimuli. Shapes varied in polygonal structure and jaggedness; tones varied in fundamental frequency and harmonic richness. Participants completed either four or five blocks: (1) an initial free-pairing block to assess baseline mapping tendencies; (2) a passive exposure block (in a subset of participants); (3) an active learning block with feedback; (4) a second free-pairing block with novel stimuli; and (5) a final test block with novel pairings. Participants showed increasing accuracy during active learning and maintained high performance when tested on novel pairings, indicating successful generalization (Cohen's $d = 0.59$). Accuracy was higher when matching shapes to sounds than vice versa, suggesting an asymmetry in audiovisual retrieval. Accuracy also increased with greater perceptual distance between target and distractor stimuli. Perceptual distance was defined based on systematic variation in low-level features: increasing polygonal complexity for shapes and decreasing fundamental frequency with sparser harmonics for sounds (e.g., $F_0 = 246$ Hz vs. 130 Hz). These results suggest that structural differences facilitated both learning and generalization. Importantly, participants who experienced both passive and active exposure showed higher test-phase accuracy than those with active exposure alone, suggesting that passive learning may enhance the acquisition and generalization of arbitrary audiovisual associations. Together, these results demonstrate that in the absence of semantic meaning, humans can rely on perceptual regularities to form and extend cross-modal mappings, with structural similarity guiding this learning process.

Disclosures: **A. Machado:** None. **C. Chang:** None. **M.T. Wallace:** None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.10/S11

Topic: E.08. Multisensory Integration

Support: NIH R01 NS129703

Title: Multimodal sensory-motor transformations for speech

Authors: *A. MAJUMDAR¹, A. EARLE-RICHARDSON², G. A. GRANT^{2,3}, B. FRAUSCHER^{4,1,3}, D. G. SOUTHWELL^{2,1,5,3}, G. B. COGAN^{2,1,4,3,6},

¹Biomed. Engin., ²Neurosurg., ³Compr. Epilepsy Cent., ⁴Neurol., ⁵Neurobio., ⁶Ctr. for Cognitive Neurosci., Duke Univ., Durham, NC

Abstract: Auditory and motor systems are tightly coupled in speech perception and production through sensory-motor transformations. During production, auditory feedback supports real-time monitoring and error correction, while the motor system is thought to contribute to perception by engaging articulatory representations of heard sounds. Since speech primarily engages the auditory system, these sensory-motor transformations may be mediated by a specialized auditory circuit rather than a general system for all modalities. Despite this hypothesis, visual cues such as images or written words can also elicit spoken responses, suggesting that visual input may access overlapping or parallel pathways to support speech production. Therefore, it is possible that speech-related sensory-motor circuits may be partially multimodal, but the extent and nature of this overlap remain unclear. We hypothesized that sensory-motor speech circuits differ by modality, with auditory-to-motor pathways serving as the primary route. To test this, we recorded intracranial EEG from 22 subjects (mean age = 36, 11 female) during epilepsy monitoring for surgical intervention as they performed a delayed multimodal repetition task. A set of words was presented in 3 input types: auditory words, visual images, and visual text. Behavioral analysis revealed no significant differences in speech onset latency across the input types. Electrodes with significant increases in high-gamma power (70-150 Hz) relative to a pre-stimulus baseline were identified using cluster-corrected permutation tests and were classified by type (sensory, motor, or sensory-motor) and by specificity as either modality-common (responsive to auditory *and* visual input) or modality-specific (responsive to auditory *or* visual input). We found significantly more auditory-specific sensory-motor than visual-specific electrodes suggesting a distinct auditory-motor pathway. The relative scarcity of visual-to-motor specific electrodes suggests that visual input may engage fewer direct pathways and may influence speech at a higher level rather than direct sensory-to-motor mapping. Interestingly, while sensory-motor electrodes were broadly distributed across frontoparietal and temporal regions, auditory-specific sensory-motor electrodes appeared more frequently in the temporal cortex, and visual-specific ones were more distributed across frontoparietal areas. These results suggest that while both auditory and visual inputs can drive speech production, auditory pathways may hold a privileged role, with visual information engaging sensory-motor circuits through more distributed routes.

Disclosures: A. Majumdar: None. A. Earle-Richardson: None. G.A. Grant: None. B. Frauscher: None. D.G. Southwell: None. G.B. Cogan: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.11/S12

Topic: E.08. Multisensory Integration

Support: NIH 2T32DC010775-11

Title: Multisensory cognitive benefits of video gaming: working memory and pattern separation across sensory and memory domains

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Abstract: This study investigates the multisensory cognitive benefits of video gaming, focusing on working memory (WM) and pattern separation abilities. Building on previous research on WM capacity and function (Baddeley, 2003; Luck & Vogel, 1997; Awh et al., 2007; Cowan, 2008), we employ a novel experimental paradigm combining multisensory n-back and visual mnemonic-similarity tasks to explore how gaming expertise influences these cognitive functions. Our experiment utilizes a cross-sectional design, comparing non-gamers, novice, intermediate, competitive, and professional gamers on innovative cognitive assessments. We hypothesize that expert gamers will demonstrate superior performance on both tasks, building on findings of enhanced visual attention and WM in action video game players (Green & Bavelier, 2003; Colzato et al., 2012). Furthermore, we extend this investigation to auditory cognition, addressing gaps in previous research (Boot et al., 2008; Stewart et al., 2020). The multisensory n-back task presented participants with simultaneous visual and auditory stimuli, requiring them to identify matches occurring n items back in either modality (letters or notes). This task thus assessed the participant's capacity to maintain and manipulate information from multiple sensory channels concurrently. Participants also completed unimodal visual or auditory n-back tasks for comparison. The mnemonic similarity task (MST), adapted from previous studies (Stark et al., 2021; Kirwan & Stark, 2007; Stark et al., 2013), evaluated participants' ability to distinguish between highly similar visual stimuli, testing fine-grained pattern separation using visual stimuli with varying degrees of similarity. Participants also completed an extensive online questionnaire assessing gaming experience and related sensory-motor expertise. We found significant differences across gaming groups in both n-back and MST performance. N-back tasks showed improved sensitivity (d-prime) and lower reaction times as gaming expertise increased, while MST revealed higher scores in lure discrimination and recognition. These findings indicate

variations in working memory, reaction speed, and pattern separation abilities across gaming groups, suggesting a potential link between gaming expertise and cognitive performance. These findings help to elucidate the relationship between gaming expertise and cognitive performance across sensory modalities, potentially informing the development of targeted cognitive training programs and rehabilitation strategies for various sensory and cognitive impairments (Ally et al., 2013; Stark et al., 2023; Brewer et al., 2012).

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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

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Program #/Poster #: PSTR173.12/T1

Topic: E.08. Multisensory Integration

Support: NRF2023R1A2C2007289

Title: Pitch-brightness crossmodal correspondence modulates perceptual selection of the Necker cube

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Abstract: Crossmodal correspondences (CMCs) refer to associated stimulus pairings across different sensory modalities, such as bright visual stimuli paired with high-pitched sounds, and dark visual stimuli paired with low-pitched sounds (Melara, 1989). A previous study demonstrated that CMCs can bias the initial perceptual selection of a bistable stimulus based on figure-ground reversals: the Rubin's face/vase (Zeljko et al., 2021). However, it remains unclear whether such effects of CMC can be generalized to other types of bistable perception. This study used the Necker Cube, which is a bistable stimulus based on perspective reversals. A Necker cube was shown with the edges of one face in either bright (43.76 cd/m²) or dark gray (23.53 cd/m²), and the remaining edges in the opposite luminance, against the mid-gray background (34.12 cd/m²). During the task, participants (N = 13) indicated which face appeared to be in front using a 2-AFC keypress. Each keypress elicited one of the three auditory stimuli: a high-pitched sound (1800 Hz), a low-pitched sound (600 Hz), or no sound. The tones lasted for 300 ms. Participants were instructed to release the key when their perceptual state changed, and the duration of each perceptual dominance was measured. Dominance durations were normalized by dividing each sound condition's durations by the mean 'no sound' duration for the corresponding brightness condition. The data were first analyzed using a 2 (pitch: high, low) × 2 (brightness: bright, dark) factorial design. Based on the crossmodal congruency, the results were then examined by comparing the congruent (high-bright, low-dark) and the incongruent (high-

dark, low-bright) conditions. While the interaction between pitch and brightness was not statistically significant ($p = .108$), normalized dominance durations in the congruent condition were significantly longer than those in the incongruent condition ($p = .031$). This effect was stronger for dark than for bright edges, and stronger for low- than for high-pitched sound. These findings suggest that crossmodally congruent stimuli not only enhance perceptual salience but also contribute to the perceptual selection. Such results may build on findings about the effects of eye fixation in Necker cube perception, where the face nearest fixation is typically seen as front (Ellis, 1978); CMCs may help sustain dominance by increasing the duration of attentional or ocular fixation on a given interpretation.

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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

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Program #/Poster #: PSTR173.13/T2

Topic: E.08. Multisensory Integration

Support: UNAM-PAPIIT IN221324
CONACYT 263377

Title: Phase Synchrony During a Visuospatial Task Involving Different Auditory Stimuli

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Abstract: It has been observed that after listening to Mozart's Sonata for Two Pianos K. 448, accuracy increases in tasks that require different cognitive abilities such as visuospatial skills. This effect persists for 10 to 15 minutes and it is unclear whether the effect is the same if the music is presented before or during the task, or which brain networks are involved in these conditions. Therefore, we investigated the phase synchrony behind the multimodal processing of music and visuospatial reasoning. We recorded 51 participants (mean age: 24 years, range: 21-30 years; 25 men, 26 women) divided into three groups: 1) Pre-Music, the group solved the visuospatial task immediately after listening to the music, the sonata K 448 and a control piece (Wagner's opera Lohengrin). 2) During-Task, participants solved the task while listening to the music (Mozart / Wagner). 3) No-Music, participants executed the task without the influence of music. The music was presented counterbalanced with a 15-minute rest period between them. Electroencephalographic (EEG) recordings were analyzed while performing the task; after removing artifacts, the phase synchrony obtained through Hilbert transform was compared among groups and conditions. Differences in the distribution of the instantaneous phases were analyzed using permutation tests. Behavioural data revealed an effect of Mozart's music,

reflected in decreased reaction times only when performing the task while listening to Mozart in comparison to Wagner ($p = 0.007$) and when the Mozart music was presented before the task ($p = 0.045$) (Wilcoxon Signed-Rank Test for paired samples and the Rank-Sum Test for independent ones). No differences were observed in accuracy. Phase synchrony revealed a network in the right frontal and temporal areas in the alpha frequency band when listening to sonata K 448 during the task, compared to listening to the music before. This may be related to an increase in attentional inhibition of irrelevant stimuli. In contrast, listening to Wagner while solving the task generates a long-range network across the left hemisphere in theta and alpha frequencies, shifting to the right in low beta. It could be attributed to a global brain integration. Moreover, comparing solving the task while listening to Wagner versus Mozart showed a more synchronized frontal network in high beta frequency, which may be associated with more neural resources in executive processing. Overall, our evidence suggests that the multisensory integration of visuospatial task execution and music listening simultaneously resulted in a higher cognitive load while listening to Wagner than to Mozart.

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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

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Program #/Poster #: PSTR173.14/T3

Topic: E.08. Multisensory Integration

Title: McGurk perception in 165 humans tested in-person and 165 artificial neural networks

Authors: *H. MA, Z. WANG, X. ZHANG, J. F. MAGNOTTI, M. BEAUCHAMP;
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Abstract: The McGurk effect is a multisensory illusion induced by pairing certain incongruent auditory and visual syllables, such as auditory "ba" with visual "ga" (AbaVga). A deeper understanding of the McGurk effect has been hampered by a paucity of computational models. Recent advances in artificial neural networks (ANNs) have produced ANNs with human-like language abilities, such as AVHuBERT (Audiovisual Hidden-unit Bidirectional Encoder Representations from Transformers), which transcribes speech into text using both heard (auditory) speech and visual information from the face of the talker. AVHuBERT was trained on congruent audiovisual speech, so we set out to examine whether AVHuBERT also experienced the McGurk effect when presented with incongruent audiovisual speech. When humans are presented with AbaVga, there is substantial variability in the reported percepts. The most frequent responses are "da" (the illusory fusion percept) and "ba" (the auditory component of the stimulus). For the same McGurk stimulus, different individuals report different percepts, and for different McGurk stimuli, different individuals report different percepts. Averaged across 12 different McGurk stimuli, 165 humans reported an average of 37% McGurk percepts, with a

range from 0% to 100%. To model human variability, we created 165 variants of the pre-trained AVHuBERT ANN by adding Gaussian noise to the learned weights in the transformer layers. Then, we presented each variant with the same 12 McGurk stimuli presented to human observers. For each stimulus, a variant provided 20 possible transcriptions, ranked by their likelihood, and the initial syllable of each transcription was used to calculate the percentage of "ba" or "da" responses for that stimulus for that variant. Across variants, the mean McGurk percentage was 39%. This was not significantly different from the human percentage ($p = 0.3$) using an unpaired t-test. AVHuBERT variants, like human participants, showed high levels of variability in McGurk responses, although the range was compressed (15% to 70%, vs. 0% to 100% for humans). There was variability across the 12 McGurk stimuli for both human participants (17% for the weakest stimulus to 58% for the strongest stimulus, averaged across participants) and AVHuBERT variants (19% for the weakest stimulus to 64% for the strongest stimulus, averaged across variants) but the correlation in stimulus strength between participants and variants was not strong ($r=0.34$, $p = 0.28$).

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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

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Program #/Poster #: PSTR173.15/T4

Topic: E.08. Multisensory Integration

Support: NSF Career Award 1847891
NIH Award R90DA060340-02S1

Title: Split-belt walking adapts the active perception of symmetric walking while preserving sensitivity to inter-leg speed difference

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Abstract: The human motor system adapts our actions to counteract changes in the environment (e.g., walking on different terrains) or in our bodies (e.g., growth). Motor adaptation relies on sensory information to compare expected and actual sensory consequences of movement. While motor adaptation is well studied, less is known about sensory adaptation. Previous studies have assessed sensory adaptation through active perception tasks, where participants reported perceived speed differences between their legs. We hypothesized that participants would adapt their perception of the environment following sustained external perturbations. To test this,

seventeen young neurotypical adults (11 females) walked on a split-belt treadmill, where one leg moved faster than the other, for approximately 40 minutes. To quantify perception during walking, we used two-alternative forced choice tasks (a decision-making task) during both baseline and split-belt walking. At each perceptual trial, participants had up to 8 seconds to indicate which leg was perceived as slower, while experiencing small speed differences ranging from 50 to 450 mm/s. Each of the nine speed differences was repeated 10 times. We modeled participants' choices and extracted two aspects of speed perception during steady-state walking in the baseline and split-belt conditions: (1) the point of subjective equality (PSE), i.e., the speed difference perceived as symmetric; and (2) the just noticeable difference (JND), i.e., the smallest speed difference detected accurately 75% of the time. We found that only the point of subjective equality was significantly different between baseline (0.18 ± 16.49 mm/s) and split-belt (289.44 ± 30.08 mm/s) walking ($p < 0.001$), whereas the just noticeable difference was not (Baseline: 49.96 ± 25.19 mm/s; Adaptation: 46.69 ± 15.04 mm/s; $p = 0.263$). These findings suggest that sustained external perturbations shift individuals' perception of symmetric walking speeds toward the external disturbance, but do not affect their sensitivity. Future studies should investigate whether perceptual processes not only accompany but also influence how humans adapt to and retain new motor patterns during locomotion.

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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

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Program #/Poster #: PSTR173.16/T5

Topic: E.08. Multisensory Integration

Support: RO1EY036172
90REGE001

Title: Vestibulo-ocular Reflex in Central Vision Loss

Authors: *A. VISHT¹, A. VELISAR³, B. A. ROSENGREN⁴, N. M. SHANIDZE²;

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Abstract: Age-related macular degeneration (AMD) is the leading cause of vision loss in industrialized countries and, when present in both eyes, can lead to central visual field loss (CFL). This loss of foveal vision significantly impacts mobility and quality of life, increasing the risk of falls. While much is known about the visual implications of the disease, less is known about how loss of vision and loss of the fovea interacts with the aging vestibular system. Prior

work (González et al., 2018) reported increased variability and directional asymmetries in vestibulo-ocular reflex (VOR) gain during active, sinusoidal head rotations in individuals with CFL. While the mean gains also appeared higher in CFL, no significant difference was reported. They also observed a right-left gain asymmetry, consistent with the oculomotor reference shifting to an eccentric preferred retinal locus (PRL) from the non-functional fovea. Whether similar changes emerge during passive rotations remains unknown. In this preliminary study, we tested VOR gain during passive yaw rotations in total darkness using a motorized, chair-fixed setup designed to isolate reflexive VOR responses. We tested one participant with CFL (F, 84) and two older controls (2M, 71-76). All participants had no history of vestibular deficits. Eye and head movements were recorded using an EyeSeeCam Sci binocular eye tracking goggles (250 Hz/eye). The head was immobilized relative to the chair, so the head and body rotated in tandem. The participants underwent velocity step rotations in yaw applied randomly at two speeds (90°/s, 120°/s) in clockwise (CW) and counterclockwise (CCW) directions. The CFL participant had greater (CFL: mean gain = -0.76; Controls: mean gain = -0.54) and more variable VOR gains (across speeds and directions, CFL: range = 0.29; Controls: mean range = 0.08) and greater directional asymmetry in gain between CW versus CCW steps (CFL: CCW/CW = 1.32; Controls: CCW/CW = 0.94). Notably, the asymmetry was consistent with the participant's PRL location to the left of the fovea, with her having smaller leftward than rightward VOR responses. Binocular coordination also appeared more variable in the participant with CFL. Data collection is ongoing. If these findings extend to future participants, results suggest that central vision loss alters core vestibular reflexes, even under conditions that isolate brainstem-level VOR activity. The data also provide further evidence of PRL re-referencing as an oculomotor anchor.

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Poster

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Topic: E.08. Multisensory Integration

Support: NIH Grant R01HD111546

Title: Examining construct validity between the sensory profile 2 and sensory processing measure 2 in children under age 4 years.

Authors: *J. SHAHID¹, M. MONTGOMERY², R. PERERA³, J. S. THOMAS², S. DUSING⁵, V. W. CHU⁴;

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Abstract: Background:

The Sensory Processing 2 (SP2) and the Sensory Processing Measure 2 (SPM2) are two widely used tools in pediatric rehabilitation for identifying sensory related challenges in children. However, limited studies have examined their construct validity, especially in children under age 4.

Objective: To evaluate the construct validity between SP2 quadrants, sensory and behavioral scores and SPM2 subscales scores by analyzing the correlation.

Method: The cross sectional study involved 128 children, including children born full term and preterm under age 4 years while children with neurological diagnosis were excluded. The mean age of the participants was 28 months. SP2 and SPM2 scores were collected from parents, and Pearson correlation coefficients were computed to find the relationship between scales.

Results: Significant correlations were observed across multiple aligned domains between SP2 and SPM2, indicating moderate to strong correlations. High correlations with significant P value ($r > 0.6-0.7$, $p\text{-value} < 0.05$) were observed between sensory domains of SP2 and SPM2 for visual (0.625), auditory (0.788), and touch (0.63). Moderate correlations ($r = 0.4-0.6$, $p\text{-value} < 0.05$) between sensory domain of SP2 movement with SPM2 body awareness (0.51) and balance (0.510), SP2 oral and SPM2 taste and smell (0.478) and SP2 social emotional and SPM2 social participation (0.49) suggest these scales measure the same constructs while having slight differences in focus. SPM2 sensory total T score was significantly high correlated with SP2 quadrants (avoiding (0.79), sensitivity (0.69), and registration (0.73)) and SP2 sensory sections (general (0.65), auditory (0.691), touch (0.64), body position (0.63)), and SP2 behavioral sections (behavioral (0.63) and conduct (0.77)).

Conclusion: The findings support the construct validity—particularly convergent validity—of the SP2 and SPM2 in assessing sensory processing in young children. Strong correlations in aligned sensory domains (e.g., auditory, visual, and tactile processing) suggest that both tools effectively capture core aspects of sensory processing. Moderate correlations in areas such as movement, oral processing, and social participation reflect conceptual differences in domain focus, highlighting the complementary nature of the two measures. Using the SP2 and SPM-2 in younger children may support early identification of sensory processing issues that contribute to difficulties in behavioral regulation and developmental coordination.

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Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

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Program #/Poster #: PSTR173.18/T7

Topic: E.08. Multisensory Integration

Support: NIH Grant R01HD111546

Title: Sensory processing differences in premature and full-term children under age 4 using SP2 and SPM-2 classifications

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Abstract: Background: Sensory processing is critical for motor development, emotional regulation, and adaptive behaviour in early childhood. Sensory processing difficulties are thought to be prevalent in infants born premature, the ability to quantify, describe or compare these challenges is limited by a lack of clarity on the most appropriate assessment tool. The Sensory Profile 2 (SP2) and Sensory Processing Measure (SPM2) are standardized assessment scales to identify sensory processing difficulties across multiple domains.

Objective: The study aimed to describe and compare the classification patterns of sensory processing differences between children born preterm (PTC) and full-term (FTC) under the age of 4 using two standardized tools, the SP2 and the SPM-2.

Method: A cross-sectional study was conducted involving 93 children under age 4, 52 FTC, and 41 PTC children. The mean age of the participants was 28 months. Parents completed the SP2 and SPM-2 questionnaires about their child, administered under the supervision of the research investigator. SP2 classification was merged into typical, moderate ("more than" and "less than"), and severe ("much more than" and "much less than"). Frequency counts for classification were analyzed across each domain using cross-tabulation, and the group differences (preterm vs. full-term) were tested separately for SP2 and SPM-2 using the Pearson chi-square test.

Results: For SP2 across all quadrants, sensory and behavioral categories, the majority of children in both groups were rated as "typical." For the sensitivity category, 92% of full-term children were classified as "typical" compared to preterm (75%). 14.6% of premature children were rated as "moderate" as compared to the control (7.7%), and 7.3% of preterm children were classified as "severe", while no full-term children were classified as severe. The chi-square p-value for sensitivity is approaching significance ($p = 0.07$). For SP2 sensory categories, more preterm children were classified as "severe" in auditory (4.9%), visual (4.9%), touch (4.9%), movement (7.3%), oral (4.9%), and behavioral (9.8%) compared to full term who didn't score severe for the same categories. Chi-square analyses for all these SP2 and SPM-2 domains were not statistically significant ($p > 0.05$).

Conclusion: The findings suggest that the SP2 may be identifying more children with sensory processing differences than the SPM-2 in preterm and full-term children under age 4. However, without a gold standard for comparison, it remains unclear whether this reflects greater sensitivity or over-identification. This ongoing study will collect additional data to better examine these trends.

Disclosures: J. Shahid: None. M. Montgomery: None. O. Rolin: None. J.S. Thomas: None. R. Perera: None. S. Dusing: None. V.W. Chu: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.19/T8

Topic: E.08. Multisensory Integration

Support: Nancy Lurie Marks Family Foundation

Title: Identification of personalized targets for longitudinal treatment effectiveness using standardized digital biometrics of motor learning in the context of Cerebral Palsy and the Feldenkrais Method

Authors: *T. BERMPERIDIS¹, E. B. TORRES², J. VEGA LEIVA¹;

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Abstract: Cerebral Palsy is often difficult to detect by observation alone. Early detection would help families choose therapies that could help neuromotor development and enhance motor coordination and motor learning from early infancy. However, there is currently a gap in therapies that serve this purpose in infancy. There is also a shortage of outcome measures permitting the assessment of therapy effectiveness over time, particularly in therapies that are designed to combine clinical settings with continuation of the therapies (by the parents) at home. In this work, we offer a new platform for mobile assessment, to longitudinally track the progress of the outcomes of the Feldenkrais Method (FM) as a form of therapy in young infants (up to 3 months old) and young children (3-9 years old) with cerebral palsy (CP). FM evokes awareness of self-generated bodily motions and enhances interactions with the therapist thus evoking in the child a sense of motor autonomy and motor control. The settings of this therapy are both at the clinic, with the therapist, and at home, with the parents. We record video data remotely with the use of video cameras and a smartphone app (at 30Hz). We then employ pose estimation methods to obtain the bodily skeleton with 25 positional nodes and through forward and inverse kinematics mapping, estimates of the joint angle trajectories, to track both the motions of the end effectors and those of the internal joint. By combining kinematics modeling, stochastic analysis, nonlinear dynamics and information theoretical approaches, we uncover standardized parameter spaces revealing maximal changes over time and informing the evolution of potential targets for treatments. We leverage causal correlation analysis and facial and body maps to determine lead-lag patterns in synchronous face-body and clinician-child interactions. We then derive indexes of motor agency balancing quantities defining ranges of motor autonomy and motor control. By identifying the most relevant biometrics revealing the longitudinal rates of change, this study aims to improve identification of personalized and dynamically evolving targets for treatment, and early detection of CP and other disorders of neuromotor development.

Disclosures: T. Bermperidis: None. E.B. Torres: None. J. Vega Leiva: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

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Program #/Poster #: PSTR173.20/T9

Topic: E.08. Multisensory Integration

Support: New Jersey Department of Labor - Innovation and Research Fellowship Program
Nancy Lurie Marks Family Foundation

Title: STEM 2 Autonomy: Empowering autism through scientific research and digital technologies

Authors: *M. ELSAYED¹, E. B. TORRES²;

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Abstract: Many therapeutic approaches with purported benefits to autistic children are advertised to parents and families without proper assessment of treatment effectiveness. Because the causes of Autism Spectrum Disorder are multilayered, dynamically inter-related, and evolving in highly nonlinear, multi-dimensional ways, it is important to develop approaches capable of tracking the effectiveness of such treatments. Current methods are static, linear, and one-dimensional. Because they are based on behavioral observation and detached from any physiological underpinnings of what is observed, these methods miss important opportunities to offer proper support to the person, the caregivers, and the therapists. Our goal is to help fill this gap by investigating how therapeutic approaches influence the autonomic and the peripheral nervous systems through new assessments of cardiac, facial, and motor signals in highly scalable, dynamic, and non-invasive ways. These new multi-layered techniques help evaluate the systems' dynamics and offer new ways to support both the child receiving the therapy and the therapist/caregiver helping the child. We combine brief and simple-to-use assays that leverage commercially available biosensing technologies to assess the individual's actions in naturalistic environments such as homes, schools, and clinics. These methods featuring our *Lab in a Box* © are paired with a statistical platform for the individualized analysis of behavior providing standardized objective outcome biometrics that can be tracked daily and longitudinally. They help us ascertain true ranges of the person's physiological states (relative to the population ranges) and produce standardized population scales. Our work is revealing, for the first time, changes in autonomic reactivities/imbances and peripheral responses that are clinically relevant to any therapy. In over 100 individuals and over thousands of sessions, we perform optimal parameter identification to uncover those maximizing information on the moment-to-moment states and providing parameter ranges across multiple cohorts of participants on the autism spectrum. With unprecedented precision, our integrative, multi-sensory, and multi-layered personalized approach offers new avenues to ultimately aid in the improvement and continuous support of the nervous systems' autonomy and in the objective tailoring of treatments according to individual needs.

Disclosures: M. Elsayed: None. E.B. Torres: None.

Poster

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Program #/Poster #: PSTR173.21/T10

Topic: E.08. Multisensory Integration

Support: The Nancy Lurie Marks Family Foundation

Title: Standardized digital biometrics for somatic-sensory-motor control, co-regulation and support of agency in partnering communication methods for non-speakers

Authors: *E. B. TORRES¹, J. VEGA LEIVA²;

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Abstract: Autistic children who are non-speakers have profound motor control issues that impact their communication and language acquisition through traditional means. While research on augmented and supported communication is very scarce, research on the motor control, dysregulation and coordination issues that this community faces is absent. Over decades, methods such as Facilitated Communication, Rapid Prompting Method, Spell to Communicate, among others, have become popular among parents and self-advocates as they offer a way to communicate with these families. Common to all these methods is the need to control the bodily degrees of freedom (DOF) and particularly, those involved in the type of eye-hand coordination required to point to letters on a letter board, or to characters on a keyboard, etc. Another aspect of these methods involves the coordination of two bodies in motion, one of which supports the student and provides a shared space with the communication partner. Understanding both the individual's motor control, coordination and learning needs, and those of the shared space with the partner is critical to creating standardized technology supporting the needs of this community and filling the current research gap. We examine here several data sets obtained from individuals as they communicate while supported by the communication partner. To that end, we use a combination of wearable systems, computer vision methods and Virtual Reality data (Polhemus 240Hz, Polar sensors 250Hz, APDM inertial measurement units 128Hz, Face and Open Pose estimation from video 30Hz). We introduce new models of motor control involving the recruitment of task-relevant and task-incidental manifolds in systems with redundant DOF within the computation of motion dynamics and moment-to-moment-evolving stochastic patterns. Using this modelling framework of the empirical data, we provide indexes and parameter ranges of dysregulation, coordination and dyadic interactions commonly present across all existing communication partnering methods. Our preliminary results suggest a compact set of biometrics amenable to objectively track the support of the person to help regulate the somatic-sensory-motor systems, alleviate cognitive loads and to create a balance between motor control and motor autonomy. This platform provides an index of the person's states of agency throughout interaction to help advance the methods towards independent communication. We discuss our

results in the context of creating a formal research program for reproducible outcomes needed to transition these methods to schools and formal educational settings.

Disclosures: E.B. Torres: None. J. Vega Leiva: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.22/T11

Topic: E.08. Multisensory Integration

Support: Nancy Lurie Marks Family Foundation

Title: Characterizing embodied and spatial cognition in an implicit motor learning task

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Abstract: Spatial exploration involves complex coordination between cognitive mapping and motor control, yet most studies examine these processes separately using paradigms that provide explicit instructions or visual guidance. This creates a gap in understanding how humans naturally coordinate multi-joint movements in spatial tasks requiring problem solving and self-discovery of goals. Our work seeks to characterize the embodied nature of spatial learning where movement patterns emerge from the interaction between motor constraints and environmental discovery. In this work, healthy adults perform spatial exploration using unconstrained arm movements. Participants search for hidden 3D targeted volumetric regions of varying difficulty in peripersonal space using combined external visual and proprioceptive feedback, with no prior knowledge of target location, size, or shape. A 4-sensor system (Polhemus Liberty, 240Hz) tracks the complete kinematic chain (shoulder, upper arm, forearm, fingertip) throughout exploration and subsequent phases of demonstration of the motorically perceived shape. Participants discover success via binary video-based visual feedback when the fingertip enters the target zone and a media play videos/sounds. We quantify exploration efficiency, motor coordination patterns, and individual strategy differences using a combination of kinematic/geometric modeling, empirical characterization of stochastic patterns and movement dynamics. We provide a characterization of motion in multiple space-time coordinates involving the geometry of both extrinsic end effector and intrinsic joint angle coordinates, along with probabilistic energy landscapes of arm movement dynamics. Our goal is to understand higher level cognitive states at the intersection of motor self-perception emerging from control coordination strategies and self-emergent systems' solutions towards the types of self-discoveries: exploration, attempting to understand the entire shape vs exploitation, only attempting to discover the initial feedback. Statistical analyses examining strategy stability across sessions and shapes is presented to unveil possible relationships between kinematic

features and task performance as a function of shape difficulty. This paradigm will establish a novel framework for investigating embodied spatial cognition by revealing how motor coordination patterns reflect individual differences in spatial exploration strategies. The findings seek to bridge motor control and spatial cognition research.

Disclosures: J. Vero: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.23/T12

Topic: E.08. Multisensory Integration

Support: Nancy Lurie Marks Family Foundation Career Development Award

Title: Multimodal Detection of Stress and Anxiety in U.S. Military Recruiters: Affective Facial Analysis and Heart Rate Variability Monitoring

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Abstract: Military recruiters operate under sustained occupational stress, yet few studies have examined their physiological and facial stress indicators in real time. This study investigates stress and anxiety in U.S. military recruiters using a multimodal approach that integrates the tracking of affective facial behavior with monitoring autonomic function. To that end, we will use our Lab in the Box© kit. This kit includes apps for brief video acquisition, HRV registration, IRB consenting, and analytics to report immediate results. Evidence from previous work in our lab demonstrates the effectiveness of using facial micro-expressions and heart rate variability (HRV) metrics included in this kit to track states of stress and pain. Here, we will leverage that research model to perform remote recordings of U.S. military recruiters to characterize their stress states in real-time. To acquire the face data, we will use a smartphone app (collecting brief 5-second-long videos) at rest pre- and post-interview. To acquire the HRV data, we will use a combination of biosensors that will enable us to test our biometrics across different platforms (Polar H10, Apple Watch, and MC10 Bio stamp) and acquire data continuously while timestamping it prior to, during, and after the interview. We will recruit at least 30 participants, ranging from 24-38 years of age, and deploy our study at different recruitment sites under IRB approval. Data streams will be synchronized using timestamp markers, and participants will complete the State-Trait Anxiety Inventory (STAI) and the Montreal Cognitive Assessment (MoCA) pre- and post-tasks to assess subjective stress and related cognitive load. Based on our preliminary research, we can use facial micro-motions and HRV signatures as proxies of stress. In addition, we can map the subjective scores reporting stress levels onto the digital data. We will identify the parameters maximizing information as the person transitions from a resting

baseline state prior to experiencing the recruitment interviews to states of stressful interactions during and after the recruitment interviews. The combined facial and physiological biometrics for real-time stress detection in field-relevant populations has cognitive and military psychology implications. They may explain how occupational stress disrupts attention, emotion regulation, and executive function. This work will contribute to embodied cognition models and open new lines of inquiry on developing early intervention strategies to sustain recruiter readiness and resilience.

Disclosures: J. Ramos: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.24/T13

Topic: I.02. Perception and Imagery

Support: Australian Government Research Training Program (RTP) Scholarship
Monash University Electrical and Computer Systems Engineering
Supporting, Manufacturing, Assisting Research and Teaching team

Title: Evaluating wrist-worn vibrotactile feedback for enhanced directional guidance in users with visual impairments

Authors: *C. KIM¹, J. ARGANARAS¹, Y. WONG^{1,2};

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Abstract: Although vision typically guides directional perception, visually impaired individuals navigate using alternative sensory cues. Wrist-worn vibrotactile systems are promising, yet how stimulus parameters affect direction perception remains poorly understood. We developed a wrist-worn vibrotactile device featuring eight motors and tested two configurations: 4-motor (90° spacing) and 8-motor (45° spacing). Directional feedback was provided through single (one motor), dual-sequential (two motors sequentially), or dual-simultaneous (two concurrently) modes. In dual modes, vibration durations were scaled logarithmically by proximity to the target (e.g., at 10° offset: closest motor ~780 ms, adjacent ~425 ms). Ten sighted and four visually impaired participants completed six blocks of 50 trials, alternating between the 4- and 8-motor layouts. Within each block, feedback modes were randomized. Sighted participants responded visually via mouse; visually impaired via joystick. Measures included motor recognition accuracy (match between stimulated motor and the one closest to the response), angular error (difference between target and response angles), and response time. Recognition accuracy was significantly higher for 4-motor (0.91±0.01) than 8-motor layouts (0.72±0.03; n = 14; β=-0.15, p<0.001, linear mixed-effects). Angular error differed significantly by feedback mode (linear mixed-effects, p<0.002): lowest in single (15°±2), intermediate in dual-sequential (27°±3),

highest in dual-simultaneous ($29^{\circ} \pm 1$). This pattern was clearer in sighted participants ($p=0.067$) but varied among visually impaired users. Regional analysis (wrist divided into quadrants) showed lower errors in lower-left ($21^{\circ} \pm 2$) compared to upper-right ($24^{\circ} \pm 4$) quadrants among sighted participants ($n = 10$; Friedman test, $\chi^2=9.76$, $p=0.021$). Recognition accuracy was slightly but not significantly higher in lower (0.77 ± 0.02) versus upper regions (0.74 ± 0.02 ; $n = 14$; Wilcoxon test, $p=0.23$). Response times significantly differed by feedback mode (Friedman tests; sighted: $\chi^2=10.36$, visually impaired: $\chi^2=10.00$; both $p<0.01$), shortest in single and longest in dual-sequential. Post-task feedback indicated that visually impaired participants preferred simpler feedback (4-motor, single-mode). These findings demonstrate that low-density motor layouts and simple feedback enhance directional perception on the wrist, supporting their use in tactile interface design. They offer insight into how spatial information can be effectively conveyed through the skin, potentially improving independent mobility and safety for visually impaired individuals.

Disclosures: C. Kim: None. J. Arganaras: None. Y. Wong: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.25/T14

Topic: E.08. Multisensory Integration

Title: Coloring cognition: evidence from functional near-infrared spectroscopy that synesthetic associations act as elaborative rehearsal mechanisms in working memory for grapheme-color synesthetes

Authors: *A. G. BRISTER¹, E. A. BOURASSA-PRICE²;
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Abstract: Grapheme-Color Synesthesia is a perceptual phenomenon where individuals involuntarily and consistently associate specific colors with non-colored graphemes. Prior research suggests synesthetes demonstrate enhanced working memory (WM) efficiency toward their synesthetic stimuli; however, the mechanism behind this advantage remains unclear. This study investigated whether these associations function as a priming mechanism or as an elaborative rehearsal strategy, and how they interact with distraction during WM tasks. Ten synesthetes and ten nonsynesthetes completed a screening battery assessing the number, strength, and automaticity of synesthetic associations. They then completed a visuospatial WM task involving 6, 8, or 10 graphemes briefly presented around a screen, with accuracy measured by recall of a target grapheme's location. Functional near-infrared spectroscopy (fNIRS) captured BOLD responses in the left hemisphere for seven synesthetes and nine nonsynesthetes. Tasks were presented under three conditions: (A) all graphemes uniquely associated with different synesthetic colors, (B) two graphemes sharing a color association (one being the target), and (C)

an incongruent distractor colored in the target's synesthetic hue. Results showed no performance change across conditions for synesthetes, which rejected the priming hypothesis. fNIRS data showed that synesthetes had increased BOLD response in the superior parietal lobule, area V3, supramarginal gyrus, anterior prefrontal cortex, superior and middle temporal gyri, and Broca's area during the B task, as well as increased BOLD response in areas V1, V3, and superior parietal lobule during section C. These findings support the conclusion that synesthetes use their color associations as an elaborative rehearsal strategy rather than for priming. These associations enhance WM encoding and resilience to distraction by enriching cognitive representation and allowing for conflict resolution to interact with working memory, rather than facilitating rapid target detection.

Disclosures: A.G. Brister: None. E.A. Bourassa-Price: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.26/T15

Topic: E.08. Multisensory Integration

Title: Cue-dependent audiovisual motion judgments are statistically optimal but visually biased

Authors: *A. J. TIESMAN¹, R. RAMACHANDRAN², M. T. WALLACE¹;

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Abstract: The ability to perceive and respond to multisensory motion cues is essential for survival, where relevant cues often span multiple sensory modalities. However, it remains unclear whether naturalistic motion perception relies on a statistically optimal integration of both auditory and visual motion, and how much each modality contributes to a unified motion percept. Here, we explored the combination of auditory and visual motion information under auditory-cued, visual-cued, and audiovisual-cued multisensory conditions using random dot kinematograms and amplitude-modulated broadband white noise. Using a 2-AFC task, participants (n=50) reported motion direction across varying levels of motion strength, allowing us to extract sensitivity to changes in motion direction. By comparing sensitivities across different cueing conditions, we found that multisensory motion provided different levels of behavioral benefit, depending on the sensory modality cued. Using maximum likelihood estimation, we examined the relative reliabilities of the auditory and visual motion cues and found that subjects rarely equally weigh both, with performance showing large heterogeneity. However, these relative reliabilities were predictive of multisensory performance across different cued conditions; vision provides more reliable motion information (Δ ; JND=2.2, $p=0.001$), and visual bias, or an increase in visual reliability relative to auditory reliability, increases motion direction sensitivity in our task ($p=0.0205$). Our results support that humans perform statistically

optimal, but visually biased, judgments on motion direction and that perceptual decision making for our task seems to be modulated by both attention (via cueing) and sensory information. This work will guide future neurophysiological studies on the behavioral and neural correlates of audiovisual motion perception in humans and nonhuman primates, as well as enhancing perceptual quality in immersive environments.

Disclosures: A.J. Tiesman: None. R. Ramachandran: None. M.T. Wallace: None.

Poster

PSTR173: Multisensory Integration, Sensorimotor Learning, and Perception Across the Lifespan

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR173.27/T16

Topic: I.02. Perception and Imagery

Support: NIHR01MH126000

Title: Personalization and network specificity of cerebellar TMS in schizophrenia

Authors: E. JONCAS¹, E. PAYNE², M. NYE³, I. DEMO¹, E. LEE¹, R. O. BRADY, Jr.³, M. A. HALKO⁴, *R. U. PARLIKAR¹;

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Abstract: Background Cerebellar transcranial magnetic stimulation (TMS) may serve as an adjuvant therapy for psychosis symptoms, most recently we have shown improvements in negative symptoms (Brady et al 2019). Historically, cerebellum TMS has not utilized functional neuroanatomy for targeting, and the precision of TMS to the cerebellum is unclear. A classical view of the cerebellum as solely involved in motor computations has been updated with the discovery of rich non-motor connectivity including the default, dorsal attention, frontoparietal control and ventral attention networks. We sought to assess cerebellar TMS magnetic field effect within individually defined networks of the cerebellum. **Methods** Imaging data from schizophrenia and schizoaffective participants (n=27) in a double-blinded trial of cerebellar TMS (NCT05343598) was used. Individualized resting-state connectivity fMRI maps of the cerebellum was computed for 7 canonical networks (Yeo et al 2011; Buckner et al 2011). Individualized TMS simulations were computed in SimNIBS with real-world subject-specific coil placement and intensity determination. **Results** The peak stimulation effect (99th percentile) for each network in each subject was computed. There was an overall network effect (p<0.001) demonstrating cerebellar TMS selectively targets networks. The strongest effects were found on default (44.4%), limbic (37%) and frontoparietal control (11.1%) networks. Cerebellar brain network organization was found to be similar in the patient sample to previously published large-sample organization. **Conclusions** For personalized TMS, it is important to consider the targeted

network, as well as the potential off-target network effects. Our findings demonstrate that cerebellar TMS has the strongest field effect on non-motor, cognitive and affective networks within the cerebellum. These results suggest cerebellar TMS may be ideal for schizophrenia symptoms unaddressed by pharmacological treatments, and effects may vary by individual network topology.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR174.01/U1

Topic: F.03. Basal Ganglia

Support: NIH Grant R01NS123516
PEW Latin American Fellow
State of California

Title: Spiking of Identified Striatal Parvalbumin Interneurons Reveals Specific Contributions to Action Suppression and Execution.

Authors: *M. DUHNE¹, C. ZHENG², J. D. BERKE³;
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Abstract: The dorsolateral striatum (DLS) plays a critical role in motor control, but exactly what this role is and how it is achieved by DLS circuitry remains unclear. DLS spiny projection neurons (SPNs) receive extensive glutamatergic drive from cortex and thalamus, yet SPNs are typically quiet except for an orderly sequence of sparse firing during movement. This functional silence reflects a combination of SPN intrinsic properties and extrinsic GABAergic inhibition - in particular from nearby parvalbumin-expressing (PV+) interneurons. Despite a range of studies monitoring presumed PV+ cells *in vivo*, exactly how they shape SPN activity during behavior is not clear. Here we recorded from optogenetically identified DLS PV+ neurons (n = 28) in awake adult rats (n = 3) as they performed a trial-and-error decision-making task (n = 24 sessions). As part of this task, rats maintain their noses within a central port (for 500-1500 ms) until a Go cue indicates they should move leftward or rightward to an adjacent port. Surprisingly, identified PV+ cells did not correspond to the narrow-waveform, fast-firing cells that we and other groups have long assumed were PV+. During the hold period, ~80% of identified PV+ neurons showed sustained elevation in firing. During this time, optogenetic inhibition of PV+ neurons increased premature movements, consistent with a role for PV+ in restraining actions. Following the Go cue, PV+ neurons decreased firing, but then fired in a rapid sequence - similarly to SPNs - selectively during contralateral movements. Unexpectedly, unilateral inhibition of PV+ neurons

after the Go cue slowed movement and reduced contralateral choices - consistent with some role in movement production, not simply restraint. We hypothesized that inhibiting PV+ enables afferent excitatory inputs to drive activity of the “wrong” SPNs, interfering with the formation of context-appropriate movement-potent SPN ensembles. Recordings from SPNs confirmed that PV+ inhibition unmasks aberrant, task-related firing of SPNs that are normally quiet during contralateral movements. Together, our results suggest that inhibition by striatal PV+ interneurons serves both to broadly restrain premature actions, and to precisely sculpt the formation of functional SPN assemblies during movements.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR174.02/U2

Topic: F.03. Basal Ganglia

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AMED JP23bm1323001
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AMED JP24wm0625501

Title: Striosome circuitry activation inhibits striatal dopamine release and locomotion in mice

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Abstract: The mammalian striatum consists of two distinct anatomical compartments: the island-like striosomes and the surrounding matrix. The striosome compartment is classically defined by strong expression of the mu opioid receptor (MOR). Both compartments contain two major types of spiny projection neurons (SPNs): dopamine receptor D1 (D1R)-expressing direct pathway SPNs (dSPNs) and dopamine receptor D2 (D2R)-expressing indirect pathway SPNs. Previous studies have suggested that abnormalities in striosomal neurons may contribute to movement disorders such as X-linked recessive dystonia-parkinsonism (DYT/PARK-*TAFI*) and Huntington's disease. However, the functional roles of the striosome compartment in motor control and dopamine regulation remain poorly understood. The aim of this study is to elucidate

the role of striosome compartment in locomotion and dopamine dynamics in freely moving mice. We targeted MOR-expressing striosomal neurons using the MOR-CreER mouse line, which expresses tamoxifen-inducible Cre recombinase under the control of the MOR promoter. By injecting a Cre-dependent adeno-associated virus (AAV) vector into the dorsal striatum of male MOR-CreER mice followed by tamoxifen administration, we predominantly labeled D1R-expressing dSPNs within the striosome compartment. Using this model, we introduced Gq-coupled designer receptors exclusively activated by designer drugs (DREADDs) into unilateral striosomal dSPNs. Chemogenetic activation of unilateral striosomal dSPNs resulted in a significant reduction in contralateral rotations and overall locomotor activity. Next, we employed wireless fiber photometry with a genetically encoded dopamine sensor to monitor dopamine dynamics in freely moving mice. Upon ipsilateral activation of striosomal dSPNs, both the mean dopamine signal and the frequency of dopamine transients in the dorsal striatum were markedly reduced. Furthermore, the suppression of mean dopamine levels and transient frequency correlated with ipsilateral rotational bias and decreased average locomotor speed, respectively. These findings demonstrate that a subset of striosomal dSPNs suppresses both locomotion and dopamine release, in contrast to the broader population of dSPNs, which facilitate contralateral movement and locomotion upon unilateral activation. Our results highlight a distinct role for striosomal MOR-expressing neurons in motor control and dopamine regulation, suggesting that their dysfunction may contribute to the pathophysiology of movement disorders.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR174.03/U3

Topic: F.03. Basal Ganglia

Title: Impact of dendritic morphology on the generation of glutamate-mediated dendritic plateau potentials

Authors: ***S. MITRA**¹, W. W. LYTTON², S. D. ANTIC³, R. A. MCDOUGAL⁴;
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Abstract: The striatum integrates excitatory inputs from the cortex and thalamus and outputs inhibitory signals to the thalamus and other subcortical structures via the basal ganglia. The striatum also receives strong dopaminergic innervation from the substantia nigra pars compacta; degeneration of the input dopaminergic input contributes to the hypokinesia observed in Parkinson's Disease (PD). Around 95% of the striatum is composed of GABAergic cells known as Spiny Projection Neurons (SPNs) or Medium Spiny Neurons (MSNs). Around half of these

SPN's exclusively present D1 type metabotropic dopaminergic receptors (D1Rs) while the other half exclusively present D2 type receptors (D2Rs). The D1R cells are involved in the 'go' or direct pathway, promoting motor movement, the D2R cells are considered to be part of the 'no go' pathway or indirect pathway, inhibiting motor movement. In anesthetized model animals, MSN's have been observed to display a cyclic state of depolarization from a somatic resting membrane potential of a 'DOWN state' of about -85 mV to a relatively depolarized -55mV 'UP state'. Evidence indicates similar regenerative dendritic plateaus exist in dendrites. It is hypothesized that the 'UP states' and plateaus create a spatiotemporal window allowing for integration of input information. Understanding of the generative mechanisms of these states is severely limited. Identifying molecular and biophysical factors could help decide targets for the treatment of PD. The morphology of cells, along with channel and receptor distributions determine the electrophysiological and chemical properties of neurons. Here we investigate the role played by the morphologies of the MSN's in causing the differential plateau potentials between the D1R and D2R MSN's. Morphologies of the D1 and D2 medium spiny neurons were collected from neuromorpho.org and validated to determine the cell type. Analysis of the morphologies using measures derived from the TREES toolbox and L-measure showed differences in morphologies. We performed computer simulations of neurons using physiologically plausible multi-compartment cell models to explore the generation of plateaus in SPN dendrites using the NEURON simulation software. We simulated both D1R and D2R neurons, using identical channel distributions. Our simulations showed that NMDA-generated dendritic plateau potentials could occur in dendrites, and these were different among D1R and D2R neurons despite identical channel distributions. Thus morphology is a determinant of differential plateau potentials, which may lead to differences in the ability to perform spatiotemporal integration of convergent inputs.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR174.04/U4

Topic: F.03. Basal Ganglia

Support: NIH Grant EY022411
NIH Grant EY034640
NIH Grant EY029091

Title: Contributions of the subthalamic nucleus to reward-biased perceptual decision making in monkeys

Authors: K. BRANAM, J. I. GOLD, *L. DING;
Neurosci., Univ. of Pennsylvania, Philadelphia, PA

Abstract: The subthalamic nucleus (STN) is a part of the indirect and hyperdirect pathways in the basal ganglia (BG) and has been implicated in movement control, impulsivity, reward-based decision making, and noisy evidence-based perceptual decision making. We recently demonstrated that, for noisy evidence-based decisions, the STN includes at least three subpopulations of neurons with different decision-related activity patterns. Here we examined how this kind of response diversity in the STN relates to more complex decisions, including whether and how the different subpopulations process reward information, sensory evidence, and/or combinations of the two when both are used to form decisions. We measured the activity of individual STN neurons in two monkeys performing an asymmetric-reward visual motion discrimination saccade decision (“AR-dots”) task, for which we separately manipulated the noisy evidence and reward context. The monkeys were trained to make saccades at a self-chosen time to indicate their perception of the global motion direction of a random-dot kinematogram. For each trial, the motion strength and direction were chosen randomly from five values and two directions, respectively. In a block of trials, one choice was paired with a large reward and the other was paired with a small reward. The choice-reward association (i.e., reward context) was alternated between blocks. The monkeys were only rewarded for a correct choice. In a sample of 67 neurons, we found that the three STN subpopulations all included neurons with activity that was modulated jointly by motion strength and reward context/size during decision formation, albeit with a significantly higher prevalence in one particular subpopulation (~60% of cells in the subpopulation vs ~20% in the others; chi-square test, H_0 : no subpopulation difference, $p = 0.004$). To relate neural activity modulation to behavioral performance, for each neuron and reward context, we split the trials by firing rates and fitted a drift-diffusion model to the behavioral data. The three subpopulations showed different relationships between firing rates and changes in fitted parameters across reward contexts, consistent with playing different computational roles in the decision process. These results suggest that STN subpopulations make distinct contributions to the decision process that incorporates visual evidence and reward information.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

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Program #/Poster #: PSTR174.05/U5

Topic: F.03. Basal Ganglia

Title: Somatotopic arrangement of multisynaptic projections from the ventral striatum to the primary motor cortex in macaque monkeys

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Abstract: The basal ganglia constitute parallel loop circuits with the cerebral cortex via the thalamus and subserve various functions in behavioral control: the motor loop includes the putamen and the motor cortex, the cognitive loop includes the anterior striatum and the prefrontal cortex, and the limbic loop includes the ventral striatum (VSt) and the limbic cortex. It is well known that each nucleus of the motor loop (e.g., the putamen and subthalamus) has a somatotopic map. Previously, Miyachi et al. (2006) injected rabies virus, as a retrograde transsynaptic tracer, into the hindlimb, proximal forelimb, distal forelimb, or orofacial representation of the primary motor cortex (M1) of macaque monkeys, and examined the distribution of labeled (3rd-order) neurons via the thalamus and internal pallidum. The results clearly showed a somatotopic pattern of the multisynaptic projections from the putamen and subthalamus to the M1. Interestingly, in the same study, the authors also found that the VSt sends strong multisynaptic projections to the M1. In the present study, we analyzed the same specimen and found some somatotopic arrangement in the multisynaptic projections from the VSt to the M1. Labeled neurons were plotted on coronal sections through the striatum anterior to the anterior commissure. Numerous neurons were labeled in sectors of the VSt, including the nucleus accumbens (NAc), olfactory tubercle, and ventral putamen. In the case of rabies virus injection into the M1 hindlimb region, a large majority of labeled neurons were clustered in the anteromedial part of the NAc. In the orofacial injection case, labeled neurons were seen more frequently in the ventral putamen. The proximal and distal forelimb injection cases showed intermediate patterns of neuronal labeling. The present results support the notion that the VSt functions as a transitional hub between the motor and the limbic loop circuit, distributing limbic information to different body part representations of the M1. This work enhances our understanding of the role of the VSt in sensorimotor processing and lays the groundwork for future studies on its involvement in motor control.

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Poster

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Topic: F.03. Basal Ganglia

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Title: Elucidating the anatomical and functional characteristics of subthalamic nucleus projection pathways

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Abstract: The subthalamic nucleus (STN) is thought to play a key role in the control of various motor functions. However, it is still unclear how the connectivity of the STN enables these abilities. Here we used anterograde and retrograde viral tracing methods to establish the main projection targets of STN pathways, then used pathway-specific optogenetic techniques to establish the roles of these pathways in motor control. Anterograde projection tracing was performed by injecting the cre-dependent adeno-associated virus (AAV) AAVDJ-phSyn(s)-FLEX-tdTomato-T2A-sypEGFP-WPRE into the STN of a transgenic mouse line expressing cre recombinase in cells containing Pitx2, a marker for STN neurons. This method enabled detailed mapping of the axonal projections and synaptic targets of STN pathways, and revealed that the STN sends strong axonal projections to the substantia nigra pars reticulata (SNr) and the globus pallidus (GPe). Next, a retrograde viral tracing method was used to establish the degree to which the STN sends separate or collateral projections to the SNr and GPe. AAVretro-hsyn-DIO-EGFP and AAVretro-hsyn-DIO-mCherry were injected into the SNr and GPe, respectively of Pitx2-cre mice, and fluorescence microscopy revealed that a large proportion of STN neurons co-expressed mCherry and GFP, indicating that the majority of STN neurons send collateral projections to both SNr and GPe. Following identification of these two strong STN pathways, we next sought to establish their functional roles by using pathway-specific optogenetics. We infused an AAV expressing a cre-dependent channelrhodopsin 2 (ChR2) excitatory opsin and the fluorescent protein EYFP, or just EYFP (as a control), into the STN of Pitx2-cre mice, then implanted bilateral optic fibers connected to lasers in either the SNr or GPe. To investigate motor control, we conducted an open field test. We found that optogenetic stimulation of the STN-to-GPe pathway had no significant effect on the percentage of time the mouse spent mobile; however, stimulation of the STN-to-SNr pathway significantly reduced the percentage time spent mobile compared to EYFP control mice. Then, we performed optogenetic inhibition of these pathways to investigate whether STN neurons are able to bidirectionally control locomotion. We injected a cre-dependent virus Jaws (AAV5-CAG-FLEX-rcJaws-KGC-GFP-ER2) into the STN. We again conducted the open field test and found that inhibition of either pathway did not significantly affect locomotion. These studies provide novel insights into the connectivity and functional roles of STN projection pathways and have important implications for understanding motor control in the brain.

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Poster

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Title: Cortical noradrenergic denervation accompanies cognitive impairments in the MPTP-treated monkey model of Parkinson's disease

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Abstract: Clinical studies have reported that, cognitive abilities dependent on the prefrontal cortex decline in most patients with Parkinson's disease (PD), often before the onset of motor symptoms. Many of these cognitive impairments appear to be associated with attention, executive functioning, and working memory, significantly affecting the quality of life. However, the mechanisms underlying cognitive decline in PD remain largely unclear. In the present study, we assessed changes in catecholaminergic innervation of prefrontal cortical regions in four monkeys. All animals underwent cognitive testing with a battery of attentional set shifting (cognitive flexibility), self-ordered spatial search (SOSS, working memory), and visual paired-comparison (recognition memory and visual acuity) tasks before and after MPTP treatment. Three animals were chronically treated with low doses of the pro-parkinsonian neurotoxin MPTP (0.1-0.2 mg/kg) for a period of four weeks, the other animal served as control. The MPTP-treated animals were observed weekly for changes in motor behavior. To determine the striatal dopamine terminal loss, we carried out dopamine transporter specific (18)F-FECNT PET at baseline and after the MPTP treatment. Our preliminary results show that the animals remained motor-asymptomatic, but as compared to the control, showed a ~40% striatal dopamine denervation and significant impairments on tests of cognitive flexibility, spatial working memory, and recognition memory, while visual acuity was not altered. Postmortem analysis confirmed the striatal dopamine depletion and revealed a significant loss of noradrenergic axonal profiles in the dorsolateral prefrontal cortex in the cognitively impaired MPTP-monkeys as compared to the control, raising the possibility that degeneration or dysregulation of ascending noradrenergic afferents to the prefrontal cortex contributes to the development of early cognitive impairments in PD. These preliminary data suggest that the chronic MPTP-treated monkey model can be used to study the pathophysiology for early cognitive impairments in PD.

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Poster

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Title: Striatal Dynamics Drive Moment-to-Moment Movement Execution and Vigor

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Abstract: In well-learned operant tasks, dorsolateral striatal neurons exhibit phasic firing locked to specific task components. However, it remains unclear whether these dynamic patterns encode procedural memory, reflect sensory feedback from movement, or actively drive sequential motor elements during behavior. To address this, we conducted chronic recordings, including with Neuropixels probes, in freely moving rats performing a simple reaction time (SRT) task, in which rats released a lever in response to an auditory cue to receive a reward. We observed that different striatal neurons displayed transient spiking activity that was sequentially aligned to critical behavioral events, such as lever approach, pressing, holding, releasing, and whole-body turning toward the reward port. Using closed-loop optogenetic perturbation, we inhibited the striatum with millisecond precision coupled to specific motor behaviors. Striatal inhibition delayed, but did not prevent, movement initiation, disrupted ongoing forelimb reaching and subsequent lever pressing, and slowed cue-conditioned lever-release responses. These results suggest that sequential neural dynamics in the striatum play a key role in driving movement. Notably, while whole-body turning movements were slowed, they were not halted by striatal inhibition, indicating a stronger influence on forelimb actions. Additionally, recordings from downstream substantia nigra pars reticulata (SNr) neurons revealed mixed, non-unidirectional effects of striatal inhibition on this output nucleus. Our findings demonstrate that the dorsolateral striatum actively modulates moment-to-moment movement execution and vigor in operant procedures, supporting a functional role for its sequential neural dynamics in motor control.

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Poster

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Topic: F.03. Basal Ganglia

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Title: Involvement of endocannabinoid signaling in midbrain dopaminergic neurons during interval timing

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Abstract: Interval timing—the conscious perception of time on the scale of seconds to minutes—is critical for daily functioning. Deficits in interval timing have been implicated in several neurological disorders, including Parkinson’s disease (PD), in which patients tend to overproduce single time intervals and exhibit a migration effect when estimating multiple intervals. Interval timing depends on corticostriatal circuits, with dopamine playing a key role. However, how dopaminergic signaling is modulated during interval timing remains unclear. We hypothesized that endocannabinoids (eCBs), particularly 2-Arachidonoylglycerol (2-AG) produced by midbrain dopaminergic neurons, play an important modulatory role in interval timing. To test this, we generated conditional knockout mice with a selective deletion of *Dagla* and *Daglb*, the primary enzymes responsible for synthesizing 2-AG in midbrain dopaminergic neurons (DANs). These mice were tested using nose-poke-based interval timing tasks. In a task with a single 30-second criterion interval, mice lacking both *Dagla* and *Daglb* in DANs significantly overproduced the interval, whereas mice lacking only *Dagla* or *Daglb* did not. In a dual-interval task (15s and 30s), mice lacking either *Dagla*, *Daglb*, or both in DANs exhibited a migration effect—overproduction of the shorter interval and underproduction of the longer one. Fiber photometry recordings in control mice showed a ramping increase in dopamine release in the dorsomedial striatum (DMS), but not in the dorsolateral striatum, leading up to the criterion interval. This ramping dopamine release in the DMS was absent in the transgenic mice deficient in 2-AG production in DANs. To further investigate the input pathways through which 2-AG may influence DANs, we selectively blocked GABAergic or glutamatergic transmission onto a subset of DANs during the task. Interestingly, only blocking glutamatergic transmission significantly impaired task performance. Together, our results reveal a novel modulatory role for eCBs produced by midbrain DANs in time perception and provide circuit-level insight into the timing deficits observed in Parkinson’s Disease.

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Title: Subsecond dopamine fluctuations do not specify the vigor of ongoing actions

Authors: *J. TANIGUCHI¹, H. LIU³, R. MELANI⁴, M. MALTESE⁴, A. SANKARAMANCHI⁵, J. MARTIN⁴, N. X. TRITSCH²;

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Abstract: Ever since the discovery that the degeneration of midbrain dopamine (DA) neurons projecting to the striatum underlies bradykinesia (i.e., slowness of movement) in Parkinson's disease (PD), DA has become synonymous with motor vigor. However, the mechanisms through which DA contributes to the speed and amplitude of individual voluntary movements are still debated. Initial investigations suggested a somewhat slow or permissive role for DA, but recent experiments in rodents proposed a stronger and faster role for DA in the dynamic control of the gain of motor commands. Using a combination of behavioral, lesion, pharmacological, photometry and optogenetic experiments in male and female mice, we show that sub-second (i.e. phasic) DA transients are neither necessary nor sufficient for the invigoration of skilled forelimb movements. Our findings call into question the widely-held view that phasic fluctuations in extracellular dopamine control the vigor of ongoing movements, constraining the kinds of mechanisms and timescales that dopamine likely acts on to modify behavior.

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Title: The indirect pathway in the tail of striatum regulates inhibitory control over sensory driven behavior

Authors: *S. M. FERRIGNO, N. ZHANG, E. ILIAKIS, S. PANDEY, J. GALANAUGH, M. V. FUCCILLO;
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Abstract: Inhibitory control, or the ability to suppress inappropriate actions according to situational context, is essential for daily functioning and is often disrupted in

neurodevelopmental and neuropsychiatric disorders. While often attributed to frontal executive circuits, the basal ganglia's established role in goal-directed behavior suggests they may serve as key subcortical mediators of this process. As the main input structure of the basal ganglia, the striatum receives projections spanning virtually the entire neocortex, making it well suited to integrate goal-directed strategies and sensory context with action selection. Moreover, synaptic regulation of these inputs onto striatal direct and indirect pathways is thought to mediate selection of task-relevant cortical representations through pathway-specific amplification and suppression. Recent work shows that 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 choice. Additionally, recent findings in rhesus monkeys suggest the indirect pathway is involved in rejecting low-value visual targets. Together, these data support the possibility that the opponent basal ganglia pathways in the tail may function in outcome-dependent auditory selection to shape behavior. Therefore, we hypothesize that iSPN recruitment is necessary to inhibit inappropriate responses to unrewarded auditory stimuli. To investigate this, we designed a lick-based go/no-go behavioral paradigm where lick responses to distinct sounds were either rewarded or punished with a timeout. To observe pathway-specific SPN recruitment as mice performed this task, we utilized fiber photometry methods to visualize dSPN and iSPN population activity and identified differential modulation for the respective sounds. While on Go trials we find similar absolute peak fluorescence for dSPNs and iSPNs, we observe greater iSPN activity on NoGo trials. Moreover, optogenetic inhibition of iSPNs but not dSPNs is sufficient to interfere with appropriate NoGo responses resulting in increased false alarms. Furthermore, we observe similarly increased errors in *Nrxn1α* mutant mice, which have known corticostriatal synaptic deficits to iSPNs. Together these data suggest that iSPN activity in the tail of striatum supports proactive inhibitory control or conservative strategic approaches for auditory driven action. These findings provide important insight into a subcortical circuit for inhibitory control that may inform future therapeutic strategies for neurobehavioral conditions.

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Poster

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Topic: F.03. Basal Ganglia

Title: The subthalamic nucleus in the regulation of motor variability

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Abstract: Motor skills underlie much of what we do, from tying shoes to serving a volleyball. A hallmark of skill learning is a gradual transition from variable, exploratory behavior to precise and stereotyped movement patterns. However, stereotyped skills can become flexible again when conditions change to allow for renewed exploration and adaptation. Motor variability must therefore be flexibly, but tightly regulated: while it impairs peak performance, it is necessary to explore the motor space to find rewarded solutions in de novo learning and adaptation. However, despite insights into variability regulation in songbirds, the underlying mechanisms in mammals remain largely unclear. Inspired by the songbird and the exploration/exploitation balance in decision-making, the basal ganglia have been implicated in variability regulation. A transition from dorsomedial striatum (DMS), mediating variable behavior, to dorsolateral striatum (DLS), driving stereotyped kinematics, correlates with the variability decrease during learning. However, how the DMS-DLS balance is regulated and whether it indeed underlies variability regulation remains unclear. Here, we suggest a novel mechanism which contributes to the DMS-DLS balance and thereby to motor variability regulation during skill learning and execution. The subthalamic nucleus (STN), an indirect basal ganglia pathway node, sends largely unexplored feedback connections to striatum: directly to DLS and indirectly to DMS via the anterior thalamic nuclei (ATN). STN also receives broad cortical and subcortical input, allowing an integration of striatal signals with internal and external state information. Based on this, STN may dynamically modulate the DMS-DLS balance and motor variability. Chronic silencing of the STN-DLS projection indeed impairs, while silencing of the STN-ATN or ATN-DMS projections promotes development of kinematic stereotypy and overall learning. Consistent with a shift from DMS to DLS, STN-ATN silencing in experts has no effect, while STN-DLS silencing disrupts stereotypy. Our results suggest novel roles for STN in regulating motor variability, likely by modulating the DMS-DLS interplay, as well as unappreciated complexity in the basal ganglia circuitry.

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Poster

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Title: Investigating the effects of restoring SAPAP3 in the Striatal Pathways of the Sapap3-KO Mice

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Abstract: The deletion of SAPAP3 protein expression results in a mouse model that exhibits excessive grooming, a hallmark compulsive behavior. Previous studies have shown that restoring SAPAP3 expression in the striatum reverses this phenotype; however, the effects of restoring this protein in the striatal pathways are unknown. The striatum is the main input nucleus of the basal ganglia and is composed of approximately 90% spiny projection neurons (SPNs), which are divided into two subpopulations based on their projection targets: the direct pathway and the indirect pathway. These pathways are proposed to have differential contributions to the animal's behavior. To investigate the effects of restoring SAPAP3 in each striatal pathway on compulsive behaviors, we developed a viral vector that enables Cre-dependent expression of SAPAP3 and injected it into double-transgenic mice: Sapap3-KO::A2A-Cre to restore SAPAP3 in the indirect pathway, or Sapap3-KO::D1-Cre to restore it in the direct pathway neurons at postnatal day 10 (P10), allowing protein expression for a period of two months. Our preliminary results show that restoring SAPAP3 in the direct pathway increases excessive grooming. In contrast, its restoration in the indirect pathway reduces anxiety-like behaviors. Furthermore, we conducted single-cell calcium imaging in these animals to determine how the neuronal activity is modified following the restoration of SAPAP3. These results highlight the specific role of the striatal pathways in the control of anxiety and compulsions.

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Title: Physiological Characterization of Motor Thalamic Subregions Following Striatal Dopamine Loss

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Abstract: Motor thalamic (Mthal) subregions are reciprocally connected with motor cortices and integrate subcortical input from the basal ganglia (BG) and cerebellum (CB). BG- and CB-recipient Mthal subregions (CB-Mthal and BG-Mthal, respectively) are largely segregated, but their specific functions in motor control remain unclear. Furthermore, Mthal is a key node in Parkinson Disease (PD) pathophysiology. The goal of this study is to determine the functional correlates of Mthal subregion activity, and how they change after dopamine depletion. We previously identified two functionally distinct subpopulations of Mthal neurons that predict either: 1) movement onset, or 2) movement speed and direction. We hypothesized that “initiation” movements reside in CB-Mthal, while “directional” units reside in BG-Mthal. To test this, we recorded single units and local field potentials in Mthal as intact (n=9) and 6-hydroxydopamine (n=6) lesioned rats performed a two-alternative forced choice task. As predicted, “directional” units localized largely to VM, a predominantly BG-recipient zone, while units localized largely to CB-Mthal are not directionally selective. Surprisingly, Mthal single unit task-specificity was largely lost after unilateral dopamine depletion (Fisher's $p < 0.01$), despite continued (albeit impaired) task performance. These results provide insight into mechanisms of impaired motor control in PD, as well as normal mechanisms of action selection and initiation.

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Title: Pavlovian Conditioned Approach Phenotype Predicts Motor Adaptability

Authors: *K. M. CODEN¹, R. ZAVERI², J. SEARCY², K. ULMER³, M. ELKOURI¹, R. LASH³, M. ASHKENAZI², F. CZESAK¹, A. HODGE³, J. D. MORROW^{4,5}, S. B. FLAGEL^{5,4}, C. R. BURGESS^{5,6}, D. K. LEVENTHAL^{3,5};

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Abstract: The neurobiological source of variation in motor performance (learning, execution, and adaptation) is poorly understood. Converging evidence implicates dopamine (DA), particularly in the dorsal striatum, as a potential source of variation in motor performance. In the ventral striatum (VS), DA is directly related to the propensity to attribute incentive value to reward-related cues. This can be captured using Pavlovian Conditioned Approach (PavCA).

PavCA is a well-established paradigm that distinguishes “sign-trackers,” who attribute both predictive and incentive value to reward-related cues, from “goal-trackers” who only attribute predictive value to reward-related cues. These behavioral phenotypes are directly related to differences in ventral striatal DA profiles. Given the functionally analogous nature of motor cortical-dorsal striatal circuitry and limbic cortical-ventral striatal, we hypothesized that PavCA phenotype also predicts motor phenotype. Specifically, we hypothesized that sign- and goal-trackers would learn a reach-to-grasp task at similar rates, but only “goal-trackers” would adapt to changing task requirements. To test this, we characterized the PavCA phenotype of rats (n = 40), and then trained a subset (n = 26) on the reach-to-grasp task. To test motor adaptation we shifted the reach target to a novel location after 10 sessions at the initial location. As hypothesized, PavCA phenotype is not predictive of initial motor learning, but is predictive of motor adaptability. Future studies will explore the relationship between dorsal striatum DA signaling and motor flexibility, further elucidating the neural mechanisms underlying natural variation in motor performance.

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Poster

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Topic: F.03. Basal Ganglia

Title: Cortical-subcortical phase synchrony of beta waves in parkinson's disease

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Abstract: INTRODUCTION: In Parkinson’s Disease (PD), beta waves are abnormally exaggerated and synchronized with other frequency waves. Coupling between beta-frequency electrical signals in the cortex and subthalamic nucleus (STN) is a potential biomarker for effective symptom control in PD. Closed loop feedback for STN deep brain stimulation (DBS) may be provided from electrocorticography (ECoG) to decrease pathological activity in a STN-synchronized region. Moreover, synchronized cortical regions may present a promising target for less invasive stimulation. For these reasons and to better clarify the electrophysiological circuitry in PD, we aim to assess the synchrony of beta activity between the cortex and STN. We will compare this to measurements of intracortical synchrony and power measurements. METHODS: A 56-year-old male with PD had a grid of 63 subdural electrodes (PMT Corporation, Chanassen, MN) placed over the right cortex and bilateral DBS electrodes (Boston Scientific, Boston, MA)

placed in the STN. Electrophysiology from the grid and one depth electrode was recorded simultaneously for 105 seconds using a Neural Signal Processor (Blackrock Neurotech, Salt Lake City, UT). Pre-implant MRI was used to guide neuroanatomical references and post-implant CT was used to verify electrode placement using the FieldTrip and FreeSurfer toolboxes in the MATLAB programming language (The Mathworks, Natick, MA). Synchrony between pairs of channels was assessed using the Phase Locking Value (PLV), a measure of temporal phase variability ranging from 0 (unrelated signals) to 1 (signals with constant phase difference). Each channel was filtered to the beta range (13-30Hz), and average power was computed. Phase was calculated using the Hilbert Transform. The average PLV between each channel and all others measured overall intracortical synchrony; the PLV between each channel and the STN measured cortical-to-subcortical synchrony. **RESULTS:** Beta power was highest over the primary motor cortex. While PLV reached up to 0.998 in some adjacent channels on the cortex, maximum PLV between the STN and any cortical channel was 0.193. Phase synchrony with the STN was strongest in the primary somatosensory and motor cortices, whereas overall intracortical synchrony was higher in the sensory than motor cortex. **CONCLUSION:** This method enables selection of a cortical region for feedback in closed-loop DBS whose activity is synchronized with the deep brain structures being targeted. Choosing the recording location based on cortical measurements alone, be they power or intracortical synchrony measurements, is not necessarily equivalent.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR174.17/V1

Topic: F.03. Basal Ganglia

Support: NIH

Title: Stn-m1 cross-frequency coupling reflects sensory and motor state in parkinsons disease.

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Abstract: Parkinson's disease (PD), the second most common neurodegenerative movement disorder, affects over 10 million people globally. PD motor symptoms are linked to abnormal neural oscillations, particularly exaggerated beta-band activity (13-30 Hz) in the subthalamic nucleus (STN), which is associated with movement suppression. In contrast, gamma-band activity (>30 Hz) in the primary motor cortex (M1) is associated with movement initiation and

execution. Our previous results show that STN beta activity is modulated by both sensory and motor behavior. This motivated our current goal: to investigate sensory processing links between STN and cortex using phase-amplitude coupling (PAC) between STN beta phase and M1 gamma amplitude, which may reflect critical communication mechanisms disrupted in PD. We recorded simultaneous local field potentials from the STN via deep brain stimulation (DBS) electrodes and from M1 via electrocorticography (ECoG) in PD patients undergoing surgery. Recordings were obtained during rest, passive sensory stimulation (vibration), and voluntary hand movements. We analyzed PAC across these conditions to determine how STN beta phase modulated M1 gamma amplitude. Clear PAC was observed at rest in a subset of patients, with variability in strength and frequency specificity. During sensory and motor conditions, PAC patterns shifted, suggesting dynamic reorganization of STN-cortex communication. In some patients, gamma amplitude was suppressed at specific beta phases, consistent with pathological gating; in others, gamma was facilitated, potentially supporting movement. These findings suggest that STN-M1 PAC is behaviorally modulated and may reflect both dysfunctional inhibition and adaptive motor control. Our results highlight PAC as a potential biomarker for disrupted motor network coordination in PD and support further development of closed-loop DBS strategies targeting beta-gamma interactions.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

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Topic: F.03. Basal Ganglia

Support: UNAM-DGAPA- PAPIIT Grant # IN207625
CONAHCyT 164300

Title: Perinatal exposure to glyphosate or a glyphosate-based herbicide alters behavior in adult albino rats

Authors: *V. RODRIGUEZ CORDOVA¹, I. HERNÁNDEZ², M. S. MENDOZA TREJO³, J. SANCHEZ⁴, J. SANTIAGO⁵, D. GASCA-MARTINEZ⁶;

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Abstract: Glyphosate (Glyph) is the active ingredient in several herbicides. Some studies have suggested that exposure to Glyph is associated with autism spectrum disorder (ASD) in humans, as well as autism-like phenotypes in young rodents. In the present study, we analyzed the effects

of Glyph exposure during gestation and lactation on motor behavior and memory in adult male and female rats. Additionally, we compared our findings with a classical model of autism in rats induced by valproate administration. Pregnant Sprague-Dawley rats were exposed to either 50 mg/L of Glyph in distilled water (DW) or to a glyphosate-based herbicide (Faena®) containing 50 mg/L of Glyph in DW throughout gestation and lactation. The valproate group received an intraperitoneal injection of 500 mg/kg body weight on gestational day (GD) 12.5. Control and valproate groups received only DW. Glyph treatments were discontinued after weaning. Two male and two female pups from each dam were selected at weaning. Locomotor activity was assessed monthly from 1 to 8 months of age. Learning and memory tests were conducted using the Morris water maze at 5 months and the radial maze at 9 months of age. No significant effects of Glyph, Faena®, or valproate were observed on locomotor activity in male rats. However, female rats treated with valproate or Faena® exhibited hypoactivity at 5 months of age, while those treated with Glyph or Faena® showed hypoactivity at 8 months. Learning and memory functions were unaffected in female rats. In contrast, male rats exposed to Glyph showed impairments in retrieval memory at 9 months of age. These findings suggest that exposure to Glyph or Faena® during gestation and lactation alters locomotor activity in adult female rats and impairs memory in aging male rats. We thank the Ing. Luis Prado, Dra. Alejandra Castilla, MVZ. Martín García-Servín, M. en C. Moises Mendoza, and Gabriela Vera-Rivera for their technical assistance.

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Poster

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Topic: F.03. Basal Ganglia

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Title: Functionally Distinct Contributions to Value-Based Choice Along the Anterior-Posterior Dorsomedial Striatal Axis

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Abstract: While the dorsoventral and mediolateral organization of striatum has resolved clear functional distinctions, far less is known about how the anterior-posterior striatal axis contributes to behavioral control. We explore this within the dorsomedial striatum (DMS), a key region for

value-based choice, by comparing population neuronal activity and function within anterior (A-DMS) and posterior (P-DMS) subregions while mice operantly seek reward. Neural recordings show that P-DMS encoded action values and strategy information before choice selection, while A-DMS activity represented recently selected choices and their anticipated values via a dynamic population reorganization immediately following action selection. Optogenetic perturbations were consistent with these temporally distinct coding properties as unilateral manipulation of the P-DMS prior to choice biased choice contralaterally in a value-dependent manner, and unilateral inhibition of the A-DMS following choice impaired future value-based action selection. Using anterograde tracing, we found that the A-DMS and P-DMS projected to a common region within the ventromedial substantia nigra pars reticulata (vmSNr), which contained value-related signals combining aspects of upstream DMS processing. Together, our results support a model for temporally distributed influence on value-based choice across the anterior-posterior axis of the DMS.

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Poster

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Topic: F.03. Basal Ganglia

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Title: Dense Microelectrode Recording & Stimulation of the Cortico-Basal Ganglia-Thalamic Motor Circuit in Awake and Freely Moving Pigs

Authors: *K. FORSETH¹, K. LEE⁴, J. GU⁷, W. JEON¹, J. LEE², G. MISHNE⁵, H. LE¹, E. HALGREN⁸, A. RASLAN⁹, A. C. PAULK¹⁰, S. S. CASH¹¹, S. BEN-HAIM³, S. DAYEH⁶; ²Electrical and Computer Engin., ³Neurosurg., ¹Univ. of California San Diego, San Diego, CA; ⁴Electrical Computer Engin., UC San Diego, San Diego, CA; ⁶Dept. of Electrical and Computer Engin., ⁵UC San Diego, La Jolla, CA; ⁷UCSD, La Jolla, CA; ⁸Ctr. for Human Brain Activity Mapping, Univ. of California at San Diego, San Diego, CA; ⁹Neurolog. Surgery, OHSU, Portland, OR; ¹⁰Massachusetts Gen. Hosp., Boston, MA; ¹¹Dept Neurol, Mass Genl Hosp, Boston, MA

Abstract: The motor circuit comprises corticostriatal, direct and indirect striatofugal, and thalamocortical projections with nodes at the cortex, putamen, globus pallidus, substantia nigra, subthalamic nucleus, and thalamus featuring complex interactions. This structural architecture of the motor network has been derived from a convergence of multidisciplinary studies including tract-tracing, immunohistochemistry, optogenetics, and electrophysiology in human and animal models. Resolving the functional network architecture of this network will require novel systems to capture global fine-scale electrophysiology. The Integrated Electronics and Biointerfaces Lab

at UCSD has developed high-fidelity, low-impedance, micrometer-scale penetrating electrodes with wireless data transmission. Here we present the first implantation of this full recording & stimulation system in a large animal survival model. Pigs were selected given their motor network homology to humans, large cerebral volume for a non-primate, and biologic tolerance of implanted hardware for semichronic experiments. The pig underwent a first stage anesthetic event for CT and MRI imaging to facilitate surgical planning before a second stage implantation of stereotactic leads with neuronavigation. Each of the 8 implanted leads comprised 128 microcontacts and 16 macrocontacts distributed over 5cm. Head-mounted acquisition and stimulation hardware enabled wireless recordings at 30kHz and current injection of up to 128 channels by chronometric or closed-loop triggers. The pig was neurologically intact after successful surgical implantation of 8 microelectrode leads (1152 total contacts) to primary nodes of the motor circuit: sensorimotor cortex, globus pallidus, putamen, caudate, VIM, SNr, and subthalamic nucleus. Normal ambulatory, feeding, and socializing behavior were observed. Wireless transmission of intracranial electrophysiology was successful and single-pulse stimulation induced evoked responses across distributed electrodes revealing the functional architecture of the complex subcortical motor network. Successful survival implantation of a large-scale micro-electrophysiology system for subcortical targets has now enabled global recording and stimulation of the cortico-basal ganglia-thalamic motor circuit.

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Poster

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Topic: F.03. Basal Ganglia

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Title: Dopamine depletion alters striatal cholinergic interneuron membrane voltage rhythmicity in awake mice

Authors: *S. ZHOU¹, J. FREIRE², X. HAN¹;

¹Biomed. Engin., ²Pharmacol. & Exptl. Therapeut., Boston Univ., Boston, MA

Abstract: Cholinergic interneurons (ChIs) are crucial regulators of striatal output and provide the striatum with the highest levels of acetylcholine in the brain. In Parkinson's Disease, loss of nigrostriatal dopaminergic neurons leads to aberrant striatal dynamics and debilitating cognitive

and motor deficits. It is theorized that loss of dopamine leads to an imbalance between acetylcholine and dopamine in the striatum, which contributes to Parkinsonian motor symptoms. However, it remains unknown how dopamine loss in the striatum alters ChI activity patterns and their relationship to network dynamics and behavior. We previously found that ChIs membrane voltage exhibits strong delta oscillations, which organize membrane voltage beta oscillations and are coupled to animals' stepping cycles (Shroff et al, *Nature Comm*, 2023). Here, we performed high-speed voltage imaging of individual dorsal striatal ChIs in awake mice expressing the genetically encoded voltage indicator, SomArchon, following dopamine depletion using 6-OHDA. Simultaneously, we recorded local field potential and gait to investigate their relationship to ChIs under dopamine depleted conditions. We found that dopamine depletion enhanced ChI membrane voltage delta rhythmicity, leading to exaggerated burst firing during both movement and rest. Further, delta-rhythmic ChIs were more strongly coupled with LFP beta oscillations, a pathological biomarker of Parkinson's Disease. These results provide direct evidence on the impact of dopamine loss on striatal ChI dynamics that are relevant for Parkinsonian pathology.

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Poster

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Topic: F.03. Basal Ganglia

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Title: Striatal cholinergic interneurons are excited by behaviorally relevant stimuli during reinforcement learning

Authors: *Y. ZHOU¹, S. ZHOU¹, C. RAVASIO¹, Y. WANG¹, H.-A. TSENG¹, C. D. FIORILLO², X. HAN¹;

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Abstract: To select an action, the mammalian brain integrates sensory evidence concerning the value of each potential action. The value of actions is continually shaped through reinforcement learning driven by prediction error signals. While dopamine (DA) is well known to signal reward prediction error, the role of acetylcholine and other neuromodulators is less well understood. The striatum is critical for sensorimotor learning and is densely innervated midbrain DA neurons by striatal cholinergic interneurons (ChIs). ChIs are suppressed by DA and are robustly modulated

during both reward and aversive learning tasks. ChI spiking is prominently suppressed by salient sensory stimuli, which is often preceded by a transient excitation. However, it is unclear how the distinct excitatory and inhibitory responses of ChIs evolve during learning. We performed cellular membrane voltage imaging of ChIs with high temporal resolution during both reward and aversive conditioning tasks. We found that ChIs are transiently excited by conditioned stimuli predicting both reward and punishment, exhibiting a prominent membrane depolarization followed by long-lasting suppression. Membrane depolarization is generally accompanied by high frequency spike bursting and differentiates the predicted outcomes. These results demonstrate that ChI dynamics are shaped by learning, and are consistent with a role of ChI in reinforcement learning.

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Poster

PSTR174: Basal Ganglia: Systems Behavior

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Topic: F.03. Basal Ganglia

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Title: A synaptic locus of song learning

Authors: *D. C. SCHREINER¹, S. N. BRUDNER¹, A. LI^{1,2}, J. M. PEARSON³, R. D. MOONEY⁴;

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Abstract: A juvenile male zebra finch imitates the multisyllabic song of an adult tutor, affording a powerful system in which to identify the neural and synaptic substrates of complex motor learning. Although juvenile song learning depends on a specialized cortico-basal ganglia circuit, the cellular and synaptic locus of learning remains unknown. By combining a computational framework to quantify song learning with synapse-specific chemogenetic and optogenetic suppression, we identify the specific premotor cortico-basal ganglia synapses necessary for the acquisition and ongoing expression of juvenile song learning and characterize the hours-long timescale over which these learned changes consolidate. We also uncover a double dissociation between a specific premotor nucleus's two outputs; while a cortico-cortical projection is necessary for the expression of learning, its cortico-basal ganglia projection is necessary for the acquisition of learning. This double dissociation pinpoints the basal ganglia as a key locus of

learning. Furthermore, transiently augmenting postsynaptic activity in the basal ganglia was sufficient to briefly accelerate learning rates and persistently alter song. These results reveal a synaptic locus, circuit logic, and behavioral timescale of juvenile birdsong learning.

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Poster

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Title: Beta-frequency sensory stimulation modulates striatal neuron membrane voltage dynamics related to gait

Authors: *M. NASIMOVA¹, Y. ZHOU¹, S. SRIDHAR¹, J. FREIRE², J. WARNER¹, H.-A. TSENG¹, X. HAN³;

²Pharmacol. & Exptl. Therapeut., ³Biomed. Engin., ¹Boston Univ., Boston, MA

Abstract: Gait is highly delta rhythmic (~1-4 Hz) in humans and mice. While the spinal central pattern generator is critical for regulating gait temporal dynamics, gait is heavily influenced by cortical and subcortical sensorimotor regions. Our previous cellular calcium imaging study revealed that audiovisual stimulation at 10Hz and 145Hz promoted locomotion and desynchronized striatal network (Sridhar et al, *Nat Commun* **15**, 8336, 2024). Interestingly, only 10 Hz, but not 145 Hz stimulation prominently entrained striatal local field potentials (LFPs), enhanced gait rhythmicity, and strengthened the coupling between stepping and striatal LFP delta and beta oscillations. However, calcium imaging is too slow to reveal temporally precise neural dynamics beyond ~1Hz, and cytosolic calcium changes provide an indirect measure of membrane voltage activities. Thus, it remains unclear how striatal neurons coordinate higher beta frequency sensory inputs with the lower delta frequency gait-related dynamics. To understand the cross-frequency coupling mechanism underlying higher frequency sensory stimulation-mediated improvement in gait rhythmicity, we performed cellular voltage imaging of striatal cholinergic interneurons in voluntarily locomoting mice exposed to audiovisual stimulation at 10-20Hz. We found that the membrane voltage of striatal cholinergic interneurons was sensitive to rhythmic audiovisual stimulation, with many showing enhanced delta rhythmicity. These results provide a cellular mechanism of cross-frequency coupling between higher frequency sensory stimulation and lower frequency locomotion, providing a mechanistic insight on sensory

modulation of gait, and further highlighting the translational potential of using noninvasive higher frequency sensory stimulation to influence gait in individuals with gait disorders.

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Poster

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Program #/Poster #: PSTR174.25/V8

Topic: F.03. Basal Ganglia

Title: Sensory modulation of gait rhythmicity in healthy individuals

Authors: *J. K. WARNER¹, E. SAN ANTONIO², M. NASIMOVA², H.-A. TSENG², L. SHIH³, X. HAN¹;

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Abstract: Gait deteriorates with aging. Gait is highly rhythmic and occurs at delta frequencies (~0.5-3Hz). Increasing gait variability, or decreasing gait rhythmicity, is associated with many negative health outcomes in aging, including falls, frailty, cognitive decline, dementia, and mortality. Gait is regulated by sensory inputs, and sensory cues are often used as a compensation strategy to improve gait. Our previous work in preclinical murine models demonstrated that beta frequency (10Hz) audiovisual stimulation improved gait rhythmicity through strengthened interactions between basal ganglia neural dynamics and stepping movement. Building upon this observation, we investigated the effect of higher frequency sensory stimulation on gait rhythmicity in healthy individuals. We delivered auditory or mechanical stimulation to individuals of 24-78 years of age with no known history of orthopedic or neurological conditions, and measured various gait characteristics, including full-step duration, swing duration, stance duration, ankle orientation, and stride acceleration. We found that sensory stimulation at 5Hz, 10Hz, and 20Hz differentially modulated gait features across subjects, with many subjects exhibiting a reduction in step duration variance, though the effect of different sensory frequencies varied across subjects. These results demonstrate that sensory stimulation robustly influences gait features in healthy adults, highlighting the therapeutic potentials of sensory stimulation in improving gait in aging adults and in patients with gait disorders.

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Poster

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Topic: F.03. Basal Ganglia

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Title: Functional divergence of inhibitory Pedunculopontine neurons during the selective mediation of goal-directed behaviors

Authors: *S. ZHANG¹, J. MENA-SEGOVIA²;

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Abstract: Goal-directed behavior is the selection and execution of actions that increase adaptive fitness. The basal ganglia (BG) have long been recognized as a nexus of action selection, with dopamine being its primary neuromodulator. The GABAergic pedunculopontine nucleus (PPN_{GABA}) sends its most prominent projections to the dopaminergic neurons of the substantia nigra pars compacta (SNc), which receive dense PPN innervations that are qualitatively similar to the afferent projections from the globus pallidus or the dorsal striatum. However, compared to these well-characterized basal ganglia pathways, the understanding of the role of the inhibitory PPN input in basal ganglia function remains limited.

To elucidate the role of the GABAergic PPN in BG-mediated goal-directed behaviors, we conducted a series of behavioral and anatomical experiments. A progressive fixed-ratio lever pressing task was used in conjunction with single/dual-region fiber photometry (FPh) calcium imaging to identify the behavioral correlates of PPN_{GABA} neuronal activity, while intersectional viral tracing strategies characterized the projection targets of PPN_{GABA} neurons to aid the functional interpretation of the behavioral observations.

We identified distinct event-related population activities between the SNc-projecting PPN_{GABA} neurons and the whole PPN_{GABA} population, suggesting the existence of functionally distinct PPN_{GABA} subpopulations that track different behavioral parameters. Complementary anatomical tracing of the SNc-projecting and non SNc-projecting PPN_{GABA} neurons revealed distinct connectivity profiles and identified a prominent projection from the non SNc-projecting PPN_{GABA} neurons to the superior colliculus (SC). Additional FPh recordings of the retrogradely identified SC-projecting PPN_{GABA} neurons showed similar activity patterns to that of the whole PPN_{GABA} population, and prompted us to propose an overarching framework, in which the SNc-projecting and SC-projecting PPN_{GABA} neurons synergistically mediate goal-directed behaviors by encoding behavioral switching and task engagement, respectively. The present studies provide in-depth characterization of the GABAergic PPN by revealing the functional and anatomical heterogeneity of projection-based subpopulations, and contribute to the understanding of BG-mediated goal-directed behaviors by detailing the role of prominent inhibitory PPN afferents.

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Poster

PSTR175: Oral Motor and Speech

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Program #/Poster #: PSTR175.01/V10

Topic: F.04. Voluntary Movements

Support: HFSP Grant RGP0019

Title: Neural adaptations for vocal plasticity and vocal learning in seals and sea lions

Authors: *P. COOK;
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Abstract: The evolutionary neurobiology of mammalian vocal learning is poorly understood. Pinnipeds are among the most promising model clades for addressing this knowledge gap. The whole clade has been adaptively endowed with exquisite volitional breathing control to which the monachinae seals add developmental call plasticity and the phocinae add the capability for formant and frequency modulation and potentially mimicry. Until now, there were no comparative neurobiological data on vocal behavior in this clade. Here, using histology and ex vivo dMRI tractography, we provide strong first evidence for a phylogenetic spectrum of accumulative neural adaptations supporting aspects of volitional vocal control across pinniped species. Otariids and phocid seals, but not coyotes, showed robust direct cortical vocal motor connectivity to the brainstem nucleus ambiguus. This pathway may have evolved to facilitate volitional breathing, submerged prey consumption, and underwater call production for an amphibious lifestyle in a basal pinniped prior to exaptation for vocal production learning in select clades. Phocid seals, but not otariids, showed a robust arcuate-like auditory-premotor cortical pathway potentially related to developmental call learning. Harbor seals (branch phocinae) showed hypertrophic connectivity in the pathway between anterior ventrolateral thalamus and vocal premotor cortex, one part of the striatal-thalamocortical anterior forebrain circuit related to vocal motor reward learning in birds. Thalamic-premotor connectivity is specifically implicated in human language production and vocal mimicry in parrots.

Disclosures: P. Cook: None.

Poster

PSTR175: Oral Motor and Speech

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Topic: F.04. Voluntary Movements

Support: NIH/NIDCD R01DC020707

Title: Can speech sensorimotor adaptation be enhanced by manipulating auditory feedback frequency range or by specifying sensory rather than motor goals?

Authors: J. J. LI¹, *L. MAX²;

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Abstract: Sensorimotor adaptation tasks are commonly used to investigate movement planning and plasticity in human motor control. When using speech production as the model system, participants typically produce words while hearing real-time auditory feedback in which an acoustic parameter is experimentally manipulated. In many studies, the perturbation is applied to the formant frequencies—i.e., vowel-specific vocal tract resonances that depend on the specific articulatory movements and positions. Typical participants show auditory-motor adaptation in the form of an adjustment in speech movement planning across trials such that the produced formant frequencies change in the opposite direction of the perturbation. One unresolved question is why speech auditory-motor adaptation is substantially more limited (~20-40% of the perturbation) than reach visuomotor adaptation (~85-90%). Identifying factors that enhance speech adaptation may increase our understanding of the mechanisms underlying typical and disordered speech production and inform novel clinical treatment approaches. Here, we investigated whether the extent of speech adaptation varies with (1) manipulations of the auditory feedback frequency range or (2) task instructions that are specified in terms of motor vs sensory goals. In Experiment 1, 18 native speakers of English completed an auditory-motor adaptation task with three types of insert earphones that differ in their frequency response characteristics. Participants read monosyllabic words, while hearing auditory feedback through the earphones, across baseline (unperturbed), ramp (formants gradually shifted up to 250 cents), hold (250 cents), and wash-out (unperturbed) phases. The participants' produced formant frequencies were measured to assess extent of adaptation, quantified as the change from baseline to end of the hold phase. Although, descriptively, there was more adaptation for the earphones with the most restricted frequency range (still encompassing the first two formants), this effect was not statistically significant. In Experiment 2, one group of 16 participants completed an auditory-motor adaptation task with standard instructions to “produce the presented words” (motor domain instruction) whereas another group of 16 participants completed the task after being instructed to produce each word in such a way “that it sounds right” (sensory domain instruction). The extent of adaptation was not statistically significantly different between the two groups. Overall, these findings indicate that the two experimental variables investigated here did not significantly influence speech auditory-motor adaptation.

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Poster

PSTR175: Oral Motor and Speech

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Topic: F.04. Voluntary Movements

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R21DC021557

Title: Enhanced Pitch Centering in Individuals with Laryngeal Dystonia

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Abstract: Speakers subconsciously correct early pitch deviations during an utterance, converging towards a median pitch target, demonstrating the central nervous system's ability for precise, online motor corrections. This process is referred to as *pitch centering*. While this mechanism has been shown to be impaired in Alzheimer's disease, its role in patients with voice-specific motor disruptions, such as laryngeal dystonia (LD), remains unexamined. In a novel study, we examined pitch centering in 24 individuals with LD vs 29 healthy controls. Pitch centering was defined as the difference in the absolute values of initial (0-50 ms) and mid-trial (150-200 ms) pitch. Positive values (centering > 0) indicated a shift toward the median pitch defined as *centering* trials, whereas negative values (centering < 0) reflected a movement away from it defined as *anticentering* trials. Primary outcome measures were: 1) Centering and 2) *Pitch Movement*, calculated as the difference between mid-trial and initial pitch. Additionally, a subset of trials were classified as *overshoot* trials, defined as instances in which the normalized pitch movement exceeded the absolute value of the initial pitch at voice onset, termed as initial pitch deviation. Individuals with LD exhibited more pronounced centering responses compared to controls, with greater centering magnitude observed by a significant group-by-tercile interaction ($p=0.023$). Additionally, initial pitch deviation ($p<.0001$) and pitch movement magnitude ($p<.0001$) was significantly greater in individuals with LD compared to controls across all trials. While individuals with LD and controls showed similar distributions of centering and anticentering trial types, LD patients exhibited significantly greater centering magnitude compared to controls across each trial type. Across all centering trials, LD patients exhibited greater centering magnitude than controls ($p<.001$), with significant effects of tercile as well ($p<.001$). This pattern persisted within the subset of centering with overshoot trials, showing significant group ($p=0.049$) and tercile ($p=0.008$) effects. In anticentering trials, individuals with LD showed significantly greater centering magnitude than controls, with significant main effects of group ($p=0.0003$), and a group and tercile interaction ($p=0.016$). Within the overshoot subset of anticentering trials, a significant group and tercile interaction was observed ($p=0.029$). These findings offer valuable insights into speech motor and predictive

control processes in LD, with potential implications for clinical assessment and treatment strategies aimed at improving patient quality of life.

Disclosures: **R. Rangwala:** A. Employment/Salary (full or part-time): University of California San Francisco. **A. Subrahmanya:** A. Employment/Salary (full or part-time): University of California Santa Barbara. **K. Brent:** A. Employment/Salary (full or part-time): University of California San Francisco. **S. Gupta:** A. Employment/Salary (full or part-time): University of California San Francisco. **K. Ranasinghe:** A. Employment/Salary (full or part-time): University of California San Francisco. **C.L. Dale:** A. Employment/Salary (full or part-time): University of California San Francisco. **J. Gaines:** A. Employment/Salary (full or part-time): University of California San Francisco. **A. Pongos:** A. Employment/Salary (full or part-time): University of California San Francisco. **J.F. Houde:** A. Employment/Salary (full or part-time): University of California San Francisco. **S.S. Nagarajan:** A. Employment/Salary (full or part-time): University of California San Francisco.

Poster

PSTR175: Oral Motor and Speech

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR175.04/W2

Topic: F.04. Voluntary Movements

Support: R01DC017696
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P50DC019900
R21DC021557

Title: Atypical Compensatory and Following Responses to Pitch Perturbations in Laryngeal Dystonia

Authors: ***K. M. BRENT**^{1,4}, J. GAINES², R. RANGWALA², A. PONGOS², S. GUPTA², V. RAMANARAYANAN⁵, B. PARRELL⁶, J. M. BARKMEIER-KRAEMER⁷, K. SIMONYAN⁸, J. F. HOUDE³, S. S. NAGARAJAN²;

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Abstract: Auditory feedback perturbation paradigms offer a powerful method for evaluating the real-time integrity of the speech motor control system, particularly its ability to detect and correct sensory prediction errors. Laryngeal Dystonia (LD), a neurological voice-specific motor disorder characterized by involuntary laryngeal muscle contractions, may involve disrupted

feedback control. Yet, prior studies of pitch feedback perturbation responses in LD have produced conflicting findings (Kothare et al. 2022, Thomas et al. 2020). This exploratory study aimed to clarify how individuals with LD respond to pitch feedback perturbations during sustained vocalization by examining individual trial response types. Here, we analyzed 16 participants with LD and 16 matched healthy controls. During sustained vowel production, participants received either upward or downward pitch-shifted auditory feedback. Following the classification framework proposed by Franken et al. (2018), individual trial responses were categorized as compensatory, following, or unclassified based on the direction and timing of pitch change relative to the perturbation. Specifically, compensatory responses reflect pitch changes in the opposite direction of the perturbation, following responses in the same direction, and unclassified responses show no discernible pitch change post-perturbation. Our findings revealed a statistically significant reduction in the proportion of compensatory responses in LD patients compared to controls ($p = 0.021$) accompanied by a discernible increase in following responses compared to controls ($p = 0.065$). Further analysis of response magnitude and time course shows that on average LD participants exhibit following responses with greater amplitude and compensatory responses with earlier onset compared to controls. Together, these findings suggest atypical feedback-based pitch regulation in LD, characterized by a shift toward following behaviors and altered response dynamics. These differences may reflect greater intrinsic motor variability in LD, which could reduce the effective signal-to-noise ratio for sensory error detection and correction.

Disclosures: **K.M. Brent:** None. **J. Gaines:** None. **R. Rangwala:** None. **A. Pongos:** None. **S. Gupta:** None. **V. Ramanarayanan:** A. Employment/Salary (full or part-time): Salaried by Modality.AI, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Receives equity from Modality.AI, Inc.. **B. Parrell:** None. **J.M. Barkmeier-Kraemer:** None. **K. Simonyan:** None. **J.F. Houde:** None. **S.S. Nagarajan:** None.

Poster

PSTR175: Oral Motor and Speech

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Topic: F.04. Voluntary Movements

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Title: A single computational mechanism can account for both compensatory and following responses to auditory feedback perturbations of vocal pitch

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Abstract: A classic task to investigate the neural mechanisms of speech motor control is pitch perturbation, in which speakers hear a near real-time version of their voice with an artificial error: a brief shift in vocal pitch to sound higher or lower than their true acoustic behavior [1]. Speakers tend to respond to this perceived error by changing their produced pitch in the opposite direction of the shift (opposing or compensating for the error); however, some utterances instead appear to change in the same direction as the shift (following the error). The mechanism of this following behavior remains an open question highly relevant to dozens of studies involving altered auditory feedback during speech. On the one hand, it has been suggested that opposing and following responses represent separate mechanisms or modes of operation of the speech motor control system [2]. On the other hand, it is possible that opposing and following represent a unitary process or mechanism [3].

In this study, a computational model of speech motor control was used to simulate three possible mechanisms of following behavior in vocal pitch perturbation. The first (Model A) implemented a mechanism in which speakers begin to target the pitch they are hearing, as if singing in a choir [4]. The second (Model B) implemented a theory that controller gain, a motor cortex parameter that determines the magnitude of the change in behavior, varies in a random distribution that includes some negative values [5]. Finally, we implemented a new hypothesis (Model C) in which a single controller with high noise stochastically produces both opposing and following behavior.

A dataset of opposing and following behavior was generated from the pitch perturbation responses of a group of typical speakers by classifying individual trials as opposing or following or neither. Simulation-based inference (SBI), a technique that infers the model parameters most likely to produce a given model output, was used to fit a state feedback control model of speech to the group average pitch timecourse of opposing, following, and neither categories. The empirical pitch time course of following trials could not be replicated by Models A or B but could be successfully replicated by Model C, suggesting that opposing and following behavior may arise from a single mechanism.

[1] Burnett, T.A. et al. (1998). J. Acoust. Soc. Am. 103, 3153-3161. [2] Behroozmand, R. et al. (2012). J. Acoust. Soc. Am. 132, 2468-2477. [3] Miller, H.E. et al. (2023). J. Speech Lang. Hear. Res. 66, 4315-4331. [4] Patel S. et al. (2014). J. Acoust. Soc. Am. 135, 3036-3044. [5] Kearney, E. et al. (2022). Front. Hum. Neurosci. 16, 929687

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Modality.AI, Inc.. **K.S. Kim:** None. **J.M. Barkmeier-Kraemer:** None. **K. Simonyan:** None. **J.F. Houde:** None. **S. Nagarajan:** None.

Poster

PSTR175: Oral Motor and Speech

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR175.06/W4

Topic: F.04. Voluntary Movements

Support: NSF Grant 2242080

Title: Evidence of distinct speech control pathways for prosody and syllabic articulations using speech repetition under fMRI

Authors: ***M. KIM**¹, C. NABER², C. A. NIZIOLEK³, J. VENEZIA⁴, B. R. BUCHSBAUM⁵, G. S. HICKOK^{6,7};

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Abstract: Recent models suggest two partially independent speech-motor subsystems: a phonetic/syllabic subsystem located in the ventral precentral speech area (vPCSA) and a pitch/prosodic subsystem located in the dorsal precentral speech area (dPCSA). We tested this model using a speech-repetition task that independently varied prosody and phonetic content. Fifty healthy adults repeated four-syllable consonant-vowel (CV) sequences during fMRI scanning. Each sequence combined one of three prosodic contours (flat, stressed, interrogative—e.g., *babababa*, *babábaba*, *babababa?*) with one of three segmental patterns (one, two, or four distinct syllables—e.g., *babababa*, *badibadi*, *badigule*), resulting in nine distinct conditions. If pitch and phonetic coordination rely on separate neural circuits, prosodic variation should primarily activate the dPCSA, while segmental variation should engage the vPCSA. Whole-brain representational similarity analysis (RSA) supported this prediction: prosodic variation correlated with activation in the left dPCSA (putative area 55b in the Glasser atlas) and posterior superior temporal gyrus, with weaker correlation in the vPCSA. In contrast, variation in syllabic content activated the left vPCSA (classical Broca's area) and anterior superior temporal gyrus, with minimal dPCSA involvement. An interaction analysis revealed a double dissociation between the dorsal and ventral premotor regions, supporting the existence of specialized circuits for pitch and phonetic processing. These findings replicate and extend previous work by showing that simple repetition can differentiate these subsystems. Our results support the model of dual speech-motor pathways in the precentral gyrus. This work may inform neuromodulation or rehabilitation strategies for disorders affecting prosody or articulation.

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Poster

PSTR175: Oral Motor and Speech

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Program #/Poster #: PSTR175.07/W5

Topic: F.04. Voluntary Movements

Support: R01DC017718

Title: Single Neuron Activity in the Subthalamic Nucleus During Speech Production and Finger Tapping

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Abstract: Deep Brain Stimulation (DBS) of the subthalamic nucleus (STN) is a well-established treatment for the motor symptoms of Parkinson's disease (PD). However, speech symptoms often do not improve with DBS, and in some individuals speech worsens with STN stimulation. Recent work has demonstrated STN modulation during a variety of speech tasks, but the role of the STN in speech production remains unclear. This study aimed to characterize STN single neuron activity during speech and non-speech motor tasks to better understand its role in speech tasks of varying complexity. Eighty individuals with PD undergoing STN-DBS implantation performed a diadochokinetic task, sentence repetition, and a repetitive finger movement task. Single neurons were simultaneously recorded from STN microelectrodes and isolated offline with a spike sorting algorithm. Neural responses were time-locked to task onset and task-related firing rates were compared to baseline firing rates with permutation tests ($\alpha \leq 0.05$). Z-scores were used to further quantify the magnitude and direction of modulation. Across patients, we isolated more than 300 STN neurons. We found that a greater proportion of STN neurons were modulated by speech tasks compared to finger movement tasks. Furthermore, a proportion of speech-modulated neurons exhibited task-specific modulation based on the complexity of the speech task. No significant laterality effects were observed. These findings demonstrate the heterogeneous nature of STN neurons and their task-specific role in speech production. Studies are ongoing to characterize the relationship between STN activity and speech outcomes following DBS surgery, with an aim to optimize treatment strategies.

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Poster

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Program #/Poster #: PSTR175.08/W6

Topic: F.04. Voluntary Movements

Support: NSF Grant 2242080

Title: Coordination of pitch versus phonetic features in speech motor control rely on distinct sensorimotor circuits

Authors: ***G. HICKOK**¹, M. KIM³, C. NABER⁴, C. A. NIZIOLEK⁵, K. SABERI², J. VENEZIA⁶;

¹Dept. of Language Sci., ²Dept Cog Sci., Univ. California, Irvine, CA; ³Dept. of Cognitive Sci., Univ. of California Irvine, Irvine, CA; ⁴Univ. of Wisconsin, Madison, WI; ⁵Communication Sci. and Disorders, Univ. of Wisconsin–Madison, Madison, WI; ⁶Loma Linda VA, Loma Linda, CA

Abstract: Recent evidence suggests that speech motor coordination is supported by two separate systems, a phonetic/syllabic system involving the ventral premotor cortex (the ventral precentral speech area, vPCSA) and a pitch/prosodic system involving the dorsal premotor cortex (the dorsal precentral speech area, dPCSA). Here we tested this hypothesis using altered auditory feedback (AAF). AAF involves recording the participant's speech production, digitally altering it, and then feeding it back to them via headphones in real time, which typically leads to compensation responses to correct the perceived error. Two types of the AAF are commonly employed: pitch perturbation involves shifting the fundamental frequency (F0), which leads to a pitch change, while formant perturbation involves shifting the first formant (F1) of a spoken vowel, which leads to a phonetic change in the vowel category. If pitch versus phonetic coordination during speech production involve different neural networks, these two types of AAF should lead to spatially distinct activation patterns. Fifty participants were scanned while speaking CVC words (e.g., bed). On some trials, F0 shifts were imposed, on other trials, F1 shifts were imposed, and on yet other trials, no shift was imposed. We predicted that F0-shift trials compared to no-shift trials would drive activation in the dPCSA, while F1-shift trials compared to no-shift trials would drive activation in the vPCSA. We also predicted spatially distinct activations in the posterior superior temporal gyrus. Our predictions were confirmed. This finding provides direct support for separate systems controlling pitch versus phonetic features during speech production.

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Poster

PSTR175: Oral Motor and Speech

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR175.09/W7

Topic: F.04. Voluntary Movements

Support: NIH Grant R03DE028395

Title: Kinematic feature characterization of craniofacial movement coordinations using a TMD rat model

Authors: I. GARG¹, *K. TAKAHASHI²;

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Abstract: Temporomandibular disorders (TMDs) are a group of disorders that negatively affect the craniofacial muscles, temporomandibular joint, and surrounding structures. Recent research efforts have unveiled how tissue changes take place and how such changes can be correlated to TMD related pain. However, it remains unknown as to how behavior changes take place in TMD patients and at what time scale such changes occur. In this study, we seek to explore how behavior adaptations can be characterized during feeding sequences using a rodent TMD model. In order to quantify the craniofacial behaviors, we implanted radiopaque markers into cranium, both sides of hemimandibles, and tongue and used XROMM technology to capture unconstrained 3D feeding behaviors at 250 frames per second. We first capture the control data prior to the temporomandibular joint disectomy to the right side of the animal which has been shown to cause TMD-like symptoms. We then captured one and six days after the procedure to characterize the behavioral adaptations through the individual motion of different markers (in the cranium, left and right mandibles, and the tongue) during their process of mastication. Trajectories of radiopaque markers were tracked using XMALab with a maximum reprojection error of 0.6. Each marker trajectory was filtered using a 3rd order Butterworth filter whose cutoff frequency was at 15 Hz. Power spectral densities (PSDs) of the distances between certain markers were then computed. In addition, we computed an Akaike Information Criterion (AIC) to find the best order of the Gaussian Mixture model for each marker pair to quantify the significant peak frequencies.

We found that dominant mastication frequency measured at the peak frequency of the distance between the cranium and hemimandibles changed from 2.93 Hz, 3.66 Hz, to 4.15 Hz (Control, Day1, and Day6) without showing any significant differences to the hemimandible sides. The secondary peak for the same distance occurred at 6.10 Hz, 7.57 Hz, to 6.83 Hz exhibiting no hemimandible side preferences. However, the secondary and third peaks between cranium and tongue or hemimandible and tongue are significantly different between them within Day 1 and Day 6 or across Day 1 and Day 6.

These preliminary observations indicate that the behavioral adaptations are very dynamic across this short window of a week. They will give us more insight on how TMD symptoms progress and how behaviors change adaptively or maladaptively.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.01/W8

Topic: F.09. Motor Neurons and Muscle

Support: U.S. Department of Education Hispanic-Serving Institution Grant

Title: Feature-level sensor fusion between surface electromyography and force myography for hand gesture classification

Authors: A. M. GUTIERREZ, T. M. PHAM, *M. A. BATDRAW;
California State University, Chico, Chico, CA

Abstract: Advanced prosthetic upper-limb control employs surface electromyography (EMG), a sensing modality that measures electrical muscle activity from the skin surface to decode motor intent. Force myography (FMG), which measures volumetric muscle changes, is a well-studied alternative modality that complements EMG but has yet to achieve widespread commercialization. The fusion of EMG and FMG has the potential to enhance the classification accuracy of intended hand gestures by leveraging the complementary strengths of each modality, thereby enabling more robust prosthetic control methods. However, the optimal features for effectively fusing EMG and FMG sensing modalities remain underexplored. In this study, we utilized our previously collected EMG and FMG data from N = 27 able-bodied participants who performed four hand movements across eight positions, each subjected to five load conditions. We systematically investigated feature combinations by employing a sequential forward selection algorithm, to evaluate univariate and multivariate single-modality features, as well as novel multivariate cross-modality features. We hypothesized that integrating multivariate cross-modality features, derived from interactions between EMG and FMG signals, would significantly improve hand gesture classification accuracy. Unlike generalized feature sets typically tuned within individual sensing modalities and subsequently fused, optimal feature sets for maximum classification accuracy rely on tuning across modalities simultaneously. This research establishes a structured framework for evaluating and optimizing feature-level sensor fusion, aiming to develop more intuitive and robust prosthetic control systems.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.02/W9

Topic: F.09. Motor Neurons and Muscle

Title: Neuromuscular activation during gait in women with large breasts: role of garment support and biological factors

Authors: *S. YAZDEKHASTI¹, S. L. GORNIAC², E. LAVOY¹;

²Dept. of Hlth. & Human Performance, ¹Univ. of Houston, Houston, TX

Abstract: Neuromuscular Activation During Gait in Women With Large Breasts: Role of Garment Support and Biological Factors S. Yazdekhashti¹, E.C. LaVoy¹, & S. L. Gorniak¹

¹Department of Health and Human Performance, University of Houston, Houston, TX, 77204

Women with large breasts frequently report upper body musculoskeletal pain, postural issues, and neurological symptoms, which often worsen during high-impact physical activities (Aref et al., 2024; Pernia et al., 2000). However, little is known about how breast support design and physiological factors influence neuromuscular responses (Gibson et al., 2019). This study investigated the effects of breast support on upper body muscle activation during gait-based activities, as well as the role of physiological variables in modulating these responses. Twenty adult women (age 33 ± 12 years; bra cup sizes D-H) completed treadmill trials (walking, jogging, running) while wearing a conventional bra and two sports bras in a randomized crossover design. Surface electromyography (EMG) recorded from the anterior deltoid, upper trapezius, and lumbar erector spinae was processed using wavelet-based denoising to extract root mean square (RMS) and integrated EMG (iEMG) features. Muscle activation increased with speed, showing up to a 55% rise in RMS and 26% in iEMG at higher speeds. Sports Bra II consistently showed slightly higher muscle activity than Sports Bra I, but the differences were small and not statistically significant across muscles or gait speeds. A significant side by muscle interaction was identified using MANOVA, and follow-up tests revealed asymmetry in lumbar activation, with higher RMS values on the left side ($p = .008$), suggesting uneven postural loading. Additional modeling indicated that testosterone levels, bra band size, high-density lipoprotein (HDL) cholesterol, and gynoid fat were the strongest predictors of RMS, while total cholesterol:HDL ratio and gynoid fat influenced iEMG. These findings suggest that both biomechanical and biological factors contribute to variability in muscle activation which in turn may impact motor patterns generated during gait-based activities in women. These data highlight the importance of integrating both garment structure and individual physiological profiles when designing supportive interventions to reduce neuromuscular strain in active women.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.03/W10

Topic: F.09. Motor Neurons and Muscle

Support: The Sasakawa Scientific Research Grant 2025-6017

Title: Evaluation of tracking accuracy and activity characteristics of motor units in static and dynamic tasks using High-density EMG

Authors: *K. NOGI¹, T. KOKUBUN^{2,1};

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Abstract: Recently, many studies have aimed to elucidate muscle control mechanisms by measuring motor units (MUs) activities—the final pathways of voluntary movement—using high-density surface EMG (HDEMG). This study aimed to track MU detection during isometric contraction (IM) in a static task and a dynamic task involving joint movements (isokinetic contraction, IK) to verify tracking accuracy and to determine MU activity characteristics across tasks. HDEMG was recorded from the tibialis anterior of five adult males using BIODEX and HDEMG. Target torques were set at 10% and 25% MVC. The ROM was 20° plantarflexion to 10° dorsiflexion. IM was measured every 5°, and IK was measured at joint angular velocities of 5°/s and 10°/s. MUs were identified using blind source separation (BSS) based analysis, and only MUs with PNR ≥ 28 were included. MU tracking between tasks was conducted using MU Filter. Correlation coefficients were calculated for discharge rate (DR), PNR, and maximum MU action potential (MUAP) between tasks. MUAPs from all 64 electrodes were used to generate MUAP maps, and 2D correlation coefficients (2D-Corr) were calculated for identical MUs. Mean DR was compared between contraction types and angular/velocity conditions using tracked MUs. In total, 3055 MUs were detected in IM and 3275 in IK; 3019 MUs were tracked across both tasks. Correlation coefficients between DR and PNR and between tasks were -0.50 and 0.90 for DR and MUAP, respectively. For 10% MVC, mean 2D-Corr values between IK and IM at 20°/5° PF/10° DF were 0.58/0.58/0.45 at 5°/s, and 0.57/0.61/0.55 at 10°/s. Mean DR at 10% MVC was significantly higher in dorsiflexion than in plantarflexion in IM. In IK, DR differed significantly between concentric and eccentric contractions at both torque levels, but little difference was observed across angular velocities. Many accurate MUs were detectable in IK, and most were successfully tracked between IM and IK. A strong correlation in maximum MUAP across tasks suggests IK preserves MU waveform features. However, negative correlations between DR and PNR, and lower 2D-Corr at low torque, imply that low-threshold MUs with high discharge rates may have synchronized activity, introduce EMG noise, and reduce PNR. DR patterns across contraction types for tracked MUs aligned with previous findings. The minimal effect of angular velocity on DR may reflect a small number of discharges and a narrow velocity range, limiting feature extraction.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

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Program #/Poster #: PSTR176.04/W11

Topic: F.09. Motor Neurons and Muscle

Support: Leave a Nest Grant Fuso Chemical Award

Title: Malic acid facilitates swallowing activity through the epithelial sodium channel (ENaC) in rats

Authors: *K. NAGOYA¹, T. TSUJIMURA², Y. IHARA¹, M. INOUE²;

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Abstract: Objective: The malic acid is one of the organic acids contained in various fruits and vegetables, called fruit acids. Many previous studies reported that acids have positive effects on the swallowing activity. However, precise mechanisms of acid-induced swallows have not fully been evaluated. In this study, we examined how topical application of fruit acid to the larynx affects swallowing activity. Methods: Electromyographic (EMG) activities in the digastric (Dig) and thyrohyoid (TH) muscles were recorded in urethane-anesthetized SD rats (1.3 g/kg, ip). Swallowing was evoked by topical administration (3 μ l) of malic acid and gluconic acid to the vocal folds. The number of swallows and the mean of swallowing EMG burst duration for 30 s after drug administration was analyzed. To elucidate which nerves are involved in the fruit acid-induced swallows, bilateral transection of the superior laryngeal nerve (SLNx) and recurrent laryngeal nerve (RLNx) was conducted. Possible receptors involved in acid-induced swallows were explored using acid receptor antagonists. Results: The number of swallows induced by malic acid administration was significantly increased in a dose-dependent manner but not by gluconic acid. Only with malic acid, the EMG duration of Dig and TH muscles was increased in a dose-dependent manner. These results indicate that the malic acid facilitates the swallowing activity. The number of the malic acid-induced swallows was significantly decreased by SLNx. RLNx did not significantly decrease the number of malic acid-induced swallows. This supposed that SLN is dominantly involved in the malic acid-induced swallows. Amiloride and benzamil, antagonists of epithelial sodium channel (ENaC), decreased the number of swallows in a dose-dependent manner but not diminazene, antagonist of acid sensing ion channel (ASIC). The results suggest that ENaC plays a key role in inducing the swallowing with the malic acid. SB366791, HC-067047 and SKF-96365, antagonists of TRPV1, TRPV4 and TRPC respectively, also decreased the number of swallows evoked by the malic acid. It is said that those channels are related to the osmotic pressure. However, because the osmotic pressure of the malic acid is very low, we suggest that the receptors which are related to the osmotic pressure are minor to induce the swallowing by the malic acid. Summary: The malic acid increases the number of swallows and burst duration of swallowing muscles through the ENaC and the receptors which are related to the osmotic pressure. In particular, ENaC may be responsible for peripheral activation.

Disclosures: K. Nagoya: None. T. Tsujimura: None. Y. Ihara: None. M. Inoue: None.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.05/W12

Topic: F.09. Motor Neurons and Muscle

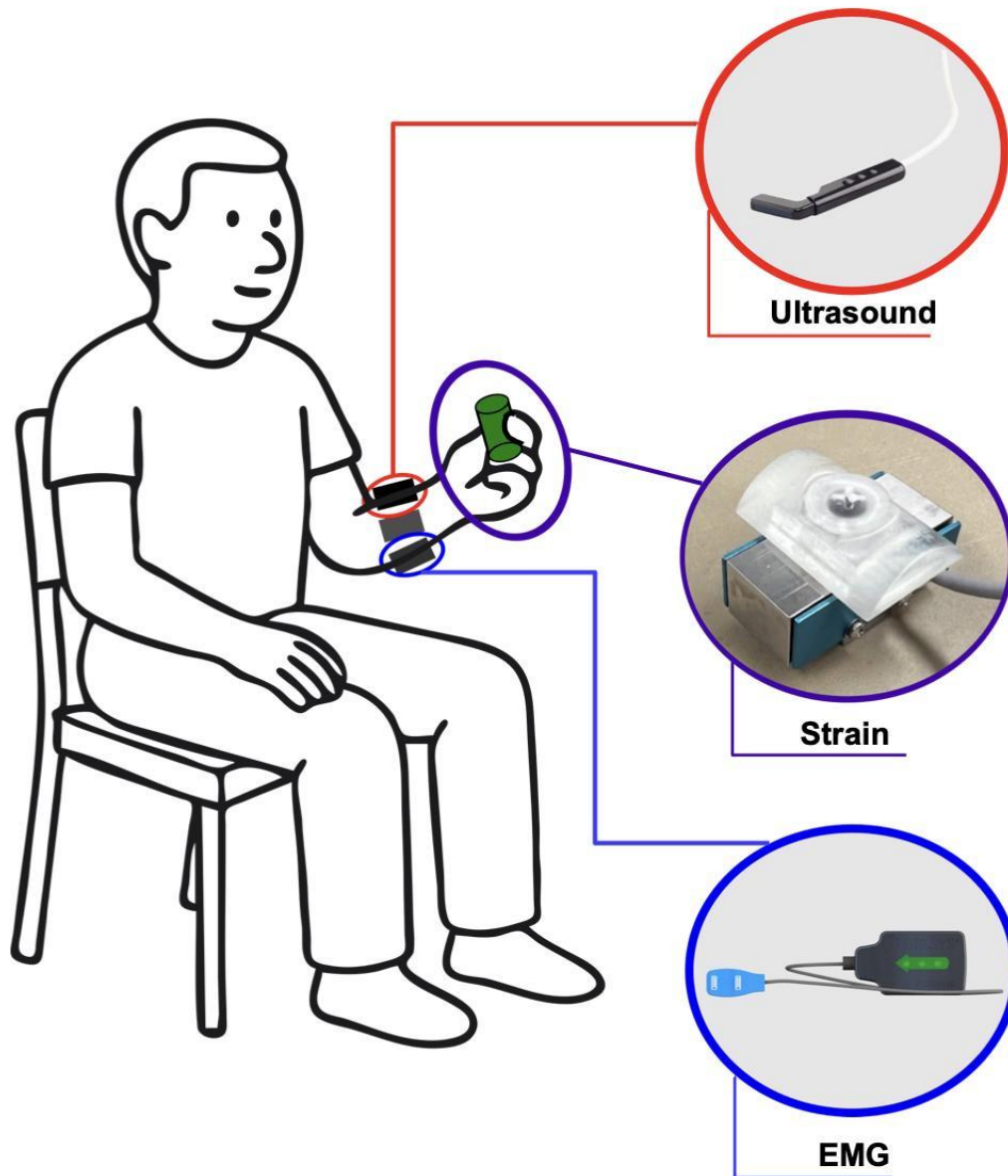
Support: Noyce Initiative Award

Title: Electromyography and Ultrasound Fusion for Improved Proportional Control

Authors: *G. SAGASTUME¹, E. WINSLOW², J. SCHOFIELD³;

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Abstract: Electromyography (EMG) is a well-established measurement modality used for non-invasive monitoring of muscle activity at the skin's surface. It has been deployed in research and clinical settings, excelling at determining contraction and relaxation states. While EMG has been shown to provide consistent performance in control models the look to isometric contraction to derive control signals, many advanced use cases benefit from identifying signals proportional to muscles' concentric states (e.g., as a body part or hand transitions through a movement). Devices such as bionic prostheses and exoskeletons function more fluidly and humanistically when they allow for proportional control of the position or force output. The use of ultrasound imaging to derive concentric muscle activity may be able to provide further information about intermediate muscle states. Ultrasound allows us to view changes in the size and shape of muscles in response to even subtle movements or contractions. As EMG and ultrasound excel at measuring separate muscular phenomenon, they may serve as complementary modalities to achieve more information-rich control signals. This work aims to investigate proportional position and force control through an experimental protocol utilizing ultrasound and EMG together. A pilot study involved participants (N=5) wearing an armband with an ultrasound transducer and 6 EMG sensors on each arm. Participants completed two tasks where they varied either their hand position or level of force in time with an on-screen prompt, while position and force information were captured by a motion capture system and load cell respectively. They did these tasks using 4 common hand grasps, and at two different speeds (fast and slow). Resultant data from these tasks was used to demonstrate each modality's accuracy in-predicting proportional control outputs and we quantified the effects of combining modalities in terms of prediction accuracy and robustness.



Disclosures: G. Sagastume: None. E. Winslow: None. J. Schofield: None.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

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Program #/Poster #: PSTR176.06/W13

Topic: F.09. Motor Neurons and Muscle

Support:

SPARC Grant SPARC/2024-2025/HCARE/P3672

Title: Characterizing the spatial activation profile of TMS-evoked responses in the forearm muscle using high-density surface EMG

Authors: A. SARKAR¹, M. TALESHI², S. PARVIN³, I. RISSANEN³, V. H. SOUZA³, P. LIOUMIS³, I. VUJAKLIJA², R. J. ILMONIEMI³, *N. THIRUGNANASAMBANDAM¹;

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Abstract: Transcranial Magnetic Stimulation (TMS) targeting the primary motor cortex (M1) evokes motor responses in the corresponding muscles, typically recorded as motor evoked potentials (MEPs) using surface electromyography (sEMG). MEPs reflect corticospinal excitability via synchronous motor unit recruitment. However, conventional sEMG recordings using a single bipolar electrode pair provide limited insight into motor unit recruitment patterns or the spatial distribution of muscle activation - factors that may contribute to the intertrial variability observed in TMS-evoked responses. High-density surface EMG (HDsEMG) offers a non-invasive way to capture spatial activation patterns under different stimulation parameters and muscle states, enabling detailed investigation of variability in corticospinal output. In this study, we used 128-channel HDsEMG with neuronavigated multi-locus TMS (mTMS) targeting the extensor carpi radialis (ECR) in 16 healthy participants (10 females; mean age: 30.12 ± 4.72 years). The 16×8 HDsEMG grid (10 mm spacing) covered the forearm in proximal-distal and ulnar-radial directions enabling high-resolution spatial mapping. mTMS was used to modulate pulse width, intensity, and current direction. An active state tonic forearm extension task was also included. Three pulse widths (60, 90, 120 μ s) were tested at 110%, 120%, and 130% of resting motor threshold (RMT). In the active state, 90 μ s pulses were applied at 110%, 120%, and 130% of the active motor threshold. Further, 90 μ s pulses were also tested in posterior-anterior (PA) and anterior-posterior (AP) directions. We computed the root-mean-square amplitude for the MEP time window to quantify muscle activity which were z-score normalized relative to each subject's 90 μ s, 110% RMT, PA condition (Ref). The Euclidean distance was calculated between the Centre Of Gravity (COG) of the Ref and that of other conditions. Preliminary results (n = 9) show significant shifts in COG from Ref for different pulse-widths: 90 μ s vs 60 μ s ($p < 0.001$), 90 μ s vs 120 μ s ($p < 0.001$); intensities: 110% vs 120% ($p < 0.001$), 110% vs 130% ($p = 0.0012$); directions: PA vs AP ($p < 0.001$); and between rest vs active states ($p < 0.001$). TMS-evoked muscle activation pattern also differs significantly from tonic contraction alone ($p < 0.001$). Our findings suggest that TMS evokes spatial activation patterns that differ from those at tonic contraction, reflecting different motor unit recruitment strategies. These patterns also vary with stimulation parameters and muscle state. Ongoing work will involve full-cohort analysis and a more comprehensive characterization of these spatial activation patterns.

Disclosures: A. Sarkar: None. M. Taleshi: None. S. Parvin: None. I. Rissanen: None. V.H. Souza: None. P. Lioumis: None. I. Vujaklija: None. R.J. Ilmoniemi: None. N. Thirugnanasambandam: None.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.07/W14

Topic: F.09. Motor Neurons and Muscle

Title: Acute Neuromuscular Electrical Stimulation Enhances EMG Median Frequency and Delays Fatigue in Individuals with Rotator Cuff Disease

Authors: *X. LI, L. GRIFFIN;
the Univ. of Texas at Austin, Austin, TX

Abstract: Introduction: Rotator cuff disease (RCD) is associated with impaired muscle endurance and early fatigue during sustained shoulder activity. While neuromuscular electrical stimulation (NMES) has been shown to alter the recruitment pattern of motor units and modulate motor and sensory neural pathways, its acute effects on muscle fatigue resistance and EMG spectral properties remain underexplored in this population. This study investigated whether a single session of NMES alters EMG median frequency (MF) shifts and improves fatigue resistance during sustained isometric shoulder abduction. **Methods:** Twenty-one individuals (56 ± 19 yrs) with positive RCD symptoms were recruited in this within-subject, crossover study. Each participant completed two testing sessions: one following sham stimulation (0 mA) and one following active NMES (40 Hz, 0.46 ms pulse width, maximal tolerance intensity) applied to the supraspinatus and infraspinatus delivered in a 4 s on/6 s off cycle for 20 minutes. Each day, participants performed a sustained isometric shoulder contraction at 30° in the scapula plane at 25% MVC until task failure. Intramuscular EMG was recorded from the supraspinatus; surface EMG was recorded from the infraspinatus and middle deltoid. Median frequency was calculated in 1-second epochs of the EMG signal from three muscles across the fatigue task using a custom-written Spike2 script based on the fast Fourier transform of the power spectrum. Pre-fatigue and post-fatigue phases were defined as the first and the last 30 seconds of endurance time (time to task failure). Paired-sample t tests were used to compare endurance time between the two sessions. A two-way RM ANOVA (Treatment $\times$ Muscle) with Bonferroni's post hoc analysis was used to compare the median frequency slope across muscles and between groups. **Results:** Compared to sham, NMES significantly increased endurance time (NMES: 234.4 ± 19.7 sec vs. Sham: 183.8 ± 7.3 sec, $p < 0.01$). MF was better preserved in the NMES condition, with smaller Δ MF in SS (-14.7 ± 4.2 Hz vs. -19.9 ± 5.1 Hz, $p < 0.01$) and IS (-12.1 ± 3.9 Hz vs. -15.7 ± 4.8 Hz, $p < 0.05$). The rate of MF decline was significantly slower with NMES in two muscles. Participants reported lower perceived exertion after NMES. **Conclusion:** A single session of NMES improves fatigue resistance and modulates EMG spectral properties in individuals with RCD. These findings suggest that NMES can acutely enhance neuromuscular performance by preserving motor unit recruitment efficiency during fatiguing tasks. This supports the inclusion of NMES in rehabilitation protocols aimed at improving endurance and delaying fatigue in shoulder dysfunction.

Disclosures: X. Li: None. L. Griffin: None.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.08/W15

Topic: F.09. Motor Neurons and Muscle

Support: Coulter-Drexel Translational Program
PA CURE/PA Dept of Health

Title: Human Testing Results with Intramuscular BMEPs (Braided Multi-Electrode Probes) for Advanced Clinical Electrodagnosis

Authors: ***T. KIM**¹, A. P. BORISYUK¹, B. BINDER-MARKEY³, S. F. GISZTER²;
¹Neurobio. and Anat., ²Dept Neurobiol & Anat, Drexel Univ. Col. of Med., Philadelphia, PA;
³Physical Therapy and Rehabil. Sci., Drexel Univ., Philadelphia, PA

Abstract: We have developed an intramuscular Braided Multi-Electrode Probe (BMEP) for advanced clinical electrodagnosis with support from Coulter-Drexel translational research awards. The clinical electrodagnosis for neuromuscular disorders diagnosis is to examine abnormality of muscle activity with EMG (Electromyography) signals recorded in muscles, and a needle EMG electrode is used for this purpose. Commercially available clinical EMG needle electrodes have only one single EMG recording site and thus a clinician requires multiple muscle penetrations to search for 12~15 MUPs (Motor Unit Potentials) at different locations in a target muscle, as per standard of care. This repetition cumulatively increases discomfort and pain levels. To significantly reduce the number of penetrations and increase reliability and objectivity of test results, our strategy is to provide multisite recording capability with ultrafine microwires braided over the established current clinical EMG needle form. Custom multiple recording sites that are properly distributed along with the needle length are created by laser ablation on microwire bodies. The intramuscular 13Ch BMEP (12Ch braid + 1Ch needle) allows us to simultaneously record ~15 MUPs at different locations along the needle shaft in parallel. The in-parallel acquisitions also provide an opportunity to use various statistical measures among channels. After extensive animal tests (frogs and rats), we are working on first-in human tests with the BMEPs under a Drexel IRB in collaboration with the Tower Health PM&R department. Preliminary data collected in humans at Drexel support the possibility of single penetration diagnosis with our designs. At SfN 2025, we will show MUPs recorded with BMEPs and Natus monopolar needles in upper extremity and lower extremity of healthy human subjects, MUP comparisons between multichannel on braid and the clinical needle tip and the average number of MUPs recorded from BMEPs within a single penetration. We will also discuss needle robustness and insertion discomfort level comparisons in human tests, and PM&R doctors' feedback. Future directions in translation and research will be discussed.

Disclosures: **T. Kim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patents. **A.P. Borisyuk:** None. **B. Binder-Markey:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patents. **S.F.**

Giszter: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patents.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.09/X1

Topic: F.09. Motor Neurons and Muscle

Title: Correlation between TMS-EEG-EMG and task related hemodynamic responses

Authors: *K. MAHMAT, E. KALLIONIEMI;
Dept. of Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ

Abstract: Transcranial magnetic stimulation (TMS) is a noninvasive brain stimulation that activates neural responses. TMS-induced neural responses reflect cortical excitability and are measured by electroencephalography (EEG) and electromyography (EMG). TMS can be used to treat a variety of disorders, including anxiety and depression. However, TMS-evoked responses, i.e., how an individual responds to TMS, are highly variable across subjects, preventing the development of customized TMS protocols for specific brain disorders and reducing the efficiency of TMS treatments. To understand this variability and increase the effectiveness of TMS, the impact of brain blood oxygenation on brain responses should be well understood. Functional near-infrared spectroscopy (fNIRS) uses infrared lights to measure brain hemodynamic responses, such as oxygenated hemoglobin (HbO). fNIRS literature shows that breath-holding (BH) and finger-tapping (FT) tasks can increase brain hemodynamics. Retroactively, some studies have observed the relationship between cortical excitability and hemodynamics. However, none of them have established this link while considering the same stimulation and measurement area at the baseline level, which could be done using multimodal TMS-EEG-EMG-fNIRS. Therefore, the primary objective of this study is to investigate the correlation between cortical excitability and hemodynamic responses. To observe this relationship, 14 healthy adults (26.57 ± 4.43 years old, one female, and 13 males) were recruited for this study. The experiment included a TMS-EEG-EMG session and fNIRS. First, individual motor thresholds (rMTs) were identified, which represent the minimum intensity levels required to elicit muscle contractions. Then, 120% rMT was used to estimate the saturation of the recruitment curve (excitatory TMS-EMG activity) with 20 trials, the silent period, or SP (inhibitory TMS-EMG response) with 10 trials, and 90% rMT with 100 trials for TMS-EEG experiments. Secondly, the brain responses were recorded using fNIRS when the subjects performed FT and BH tasks. Our TMS-EMG results indicate that TMS-induced SP duration, rMTs, and saturation of the recruitment curve correlate negatively with finger tapping and breath-holding task-related HbO responses. TMS-EEG results for mu band activity show that inter-trial coherence and HbO of FT, as well as event-related spectral perturbations and HbO of BH, are positively correlated. These results help our understanding of how much differences in hemodynamics can explain the observed between-subject variability in TMS-evoked responses.

Disclosures: **K. Mahmat:** None. **E. Kallioniemi:** F. Consulting Fees (e.g., advisory boards); Nexstim Inc..

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.10/X2

Topic: F.09. Motor Neurons and Muscle

Title: From Mind to Muscle: Correlation between Electroencephalogram (EEG) and Surface Electromyography (sEMG) in Deadlift Performance

Authors: ***G. LOPEZ-ARMAS**¹, **R. MAGAÑA-DIMAS**², **C. A. LOPEZ RAMIREZ**¹, **H. I. AGUILAR-LEYTON, Sr.**³, **D. ESPINOZA ROMERO**⁴, **Y. I. DELGADILLO-FLORES, Sr.**⁵; ¹Ctr. De Enseñanza Técnica Industrial, Guadalajara, Mexico; ²Ctr. de Enseñanza Técnica Industrial, Guadalajara, Mexico; ³CENTRO DE ENSEÑANZA TÉCNICA INDUSTRIAL, Guadalajara, Mexico; ⁴CENTRO DE ENSEÑANZA TECNICA INDUSTRIAL, Guadalajara, Mexico; ⁵Ctr. de Enseñanza Técnica Industrial, Guadalajara, Mexico

Abstract: Introduction: Our study explored the relationship between brain activity (EEG) and muscle activation (sEMG) during strength training to determine which brain waves are involved during a strength training cycle. **METHODOLOGY:** For this study, we enrolled subjects aged between 20 and 40 (ten men and three women) with consistent training and, after signing a consent form, were given a deadlift routine with progressive loads, from the barbell without weight to their maximum effort (60-160 kg). All participants were asked to wear headphones for greater concentration. Biopac MP36 hardware was used for EEG and sEMG acquisition with Ag/AgCl electrodes; for EEG, the electrodes were placed in motor areas (C3, C4, Cz), parietal areas (P3, Pz), and occipital areas (O1, O2, Oz) according to the international 10-20 system; for sEMG, they were placed on the lumbar spinal erectors, respectively. For statistical analysis, wavelet transforms were performed for sEMG and the rest with Python, applying spectral coherence in the beta band (15-30 Hz) and gamma band (30-80 Hz). **RESULTS:** We obtained greater corticomuscular coherence in the beta band during the phases of most extraordinary effort, especially in subjects with powerlifting experience. We also observed that the amplitude of the EEG signals at C3 and C4 increased significantly during maximum load lifting, correlating with greater muscle recruitment recorded in the sEMG. In addition, activity in the parietal cortex (P3, P4) suggested a role in sensorimotor integration during exercise. **Conclusions:** The activity reflected in the motor cortex EEG is associated with greater muscle activation measured by sEMG during deadlifts. Future research may explore strategies to optimize training methods.

Disclosures: **G. Lopez-Armas:** None. **R. Magaña-Dimas:** None. **C.A. Lopez Ramirez:** None. **H.I. Aguilar-Leyton:** None. **D. Espinoza Romero:** None. **Y.I. Delgadillo-Flores:** None.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.11/X3

Topic: F.09. Motor Neurons and Muscle

Support: Tateishi foundation

Title: Muscle-specific interventions may prevent neurophysiological abnormalities in subacute stroke

Authors: *M. ITO¹, T. KOKUBUN²;

¹Grad. school of Saitama Prefectural Univ., Saitama, Japan; ²Physical Therapy, Saitama Prefectural Univ., Koshigaya-Shi, Japan

Abstract: The spastic muscle in stroke has abnormal neuromuscular physiological features, which is referred to as compression of motor unit recruitment. In muscles that exhibit compression of recruitment, the order of motor unit recruitment is disrupted, leading to inefficient force generation. In our previous work, we have reported that compression of recruitment occurs as early as the subacute phase of stroke onset, which worsens over time. We hypothesized that intervention on the affected muscle during the subacute phase could prevent future worsening of motor unit activity. The aim of this study was to investigate the effects of specific interventions on the affected muscles in subacute stroke. The participants were 10 subacute stroke patients, randomized 5 to the intervention group and 5 to the control group. We used high-density surface EMG to record biceps brachii muscle activity at 35% MVC in each participant. Recorded muscle activity was decomposed to motor unit action potentials, and discharge rate and recruitment thresholds were calculated. Additionally, we assessed the Modified Ashworth Scale (MAS) to evaluate the muscle spasticity. The intervention consisted of physical stimulation with extracorporeal shock waves applied to the biceps brachii on the affected side at 2000 shots, 8Hz, 2.0-2.5 bar per session. EMG measurements and MAS assessment were taken before and after one shock wave session for the intervention group and before and after a 15-minute rest for the control group (pre and post). The next measurement and assessment were taken one week later (week-1), during the interval, only the intervention group received the shock wave session twice a week. In the intervention group, the motor unit discharge rate increased significantly between Pre and week-1 ($p = 0.03$). The recruitment thresholds increased significantly between Post and week-1 ($p = 0.04$). In the control group, none of the differences were significant in the motor unit parameters. MAS in the intervention group decreased chronologically, while the control group showed no change chronologically. The motor unit discharge rate and recruitment thresholds increased after intervention for the affected muscle of the stroke. In contrast, no change was observed in the control group. However, voluntary motor function assessment (FMA) tended to improve in both groups, while spasticity assessment (MAS) improved only in the intervention group. Therefore, it is suggested that muscle-specific intervention for the affected sides from the early subacute phase may prevent the worsening of motor unit abnormalities, such as compression of recruitment, and improve spasticity.

Disclosures: M. Ito: None. T. Kokubun: None.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.12/X4

Topic: F.09. Motor Neurons and Muscle

Title: Scaling Up: Confirming the Size Principle in Dynamic, Real-World Muscle Activation

Authors: *B. ZHAO¹, S. KEALEY², K. CHAROONSRI SAWAD², S. CHAKRABARTY²;
¹Fac. of Biol. Sciences, Sch. of Biomed. Sciences, Univ. of Leeds, Leeds, United Kingdom; ²Fac. of Biol. Sciences, Sch. of Biomed. Sci., Univ. of Leeds, Leeds, United Kingdom

Abstract: Motor unit (MU) recruitment follows Size principle (Henneman, 1957). Surface EMG amplitude (root mean square, RMS) reflects overall MU activation, while median frequency (MDF) indicates the predominant muscle fibre type (Type I vs. Type II). MU recruitment strategies can be elucidated using RMS and MDF. The lowering of MDF indicates increased recruitment of slow, fatigue-resistant fibres, which offers an insight into MU behaviour. However, most MU studies use isometric and evoked responses, which miss the complexity of voluntary, dynamic movements typical of daily activities (ADL). We previously suggested that the ratio of change in RMS to MDF (FATi) may proportionally reflect muscle fatigability and MU recruitment dynamics in ADL conditions. We hypothesised difference in fibre composition would result in distinct recruitment strategies. We examined MU recruitment during unconstrained biceps curls while sEMG was recorded from 7 muscles. Participants were grouped as athletes (n=10; 5 F; 23.3 ± 1.2) and controls (n=15; 8 F; 22.2 ± 1.1). Each participant performed curls (x10) with progressively increasing loads (0.5, 1, 2, 4, and 6 kg). Maximal voluntary contraction was assessed before and after each load. Time-frequency analysis of sEMG using FAST (Desai et al., 2015) confirmed progressive MU recruitment with increasing load, consistent with the size principle. Intergroup comparisons revealed different strategies; at submaximal loads, controls exhibited higher FATi than athletes, reflecting greater reliance on fast-twitch fibres. In contrast, athletes showed marked increase in FATi only at higher loads (4-6 kg), indicating an efficient recruitment behaviour. All participants showed a proportional increase in power across sEMG frequency bands with increasing load, suggesting enhanced engagement of the central nervous system leading to increased MU recruitment. Notably, with identical loads, sEMG band power was lower in athletes than the controls. An individual's FATi profile with band power during a task, provides a measure of mechanical output of neuromuscular activation, revealing recruitment strategy. These findings confirm that the size principle is adhered to during dynamic tasks, with progressive activation as load increases. However, the variability observed across individuals and groups, particularly in FATi patterns, suggests recruitment strategies are modulated by task demands and training. Also highlights the value of sEMG and FAST as non-invasive tools for capturing neuromuscular adaptations during functionally relevant movements, such as those encountered in ADL.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.13/X5

Topic: F.09. Motor Neurons and Muscle

Title: Distinct Learning-Related Motor Unit Adaptations Revealed During Motor Sequence Learning

Authors: *Y. ESCALANTE¹, Y. LEI²;

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Abstract: A pivotal aspect of motor learning involves the process of sequencing actions to achieve a motor goal. Previous studies on motor sequence learning have focused on behavioral changes, such as reductions in reaction times and movement error, and neurophysiological changes in brain regions involved in motor control across different learning phases. However, little is known about how motor sequence learning influences the most distal aspect of the motor pathway; the motor unit. Traditionally, studying motor unit activity required invasive fine-wire electromyography, which directly limited experiments to prolonged isometric contractions. However, the emergence of high-density surface electromyography (HDsEMG) combined with advanced motor unit decomposition techniques has now enabled more detailed, non-invasive analysis of motor unit behavior. Our experiment investigated the impact of acquiring a novel force dependent sequence on motor unit activity. Participants were asked to make a series of force productions via isometric contractions of their biceps brachii in a sequential order. Simultaneously, advanced online HDsEMG decomposition was used to identify and record distinct single motor unit changes throughout the learning process. Unlike traditional offline decomposition, online motor unit decomposition allows for distinct learning related motor unit adaptations to be monitored across the sequence acquisition process, overcoming previous methodological limitations. Our preliminary results indicate both behavioral and motor unit level changes throughout the learning process - including improvements in task performance. Additionally, we observed adaptations in motor unit activity, indicating a shift in the neural strategy employed by the motor system as learning progressed from early to late stages. Data collection is ongoing, and a full overview of the results will be provided at the meeting. To our knowledge we are one of the first to investigate how motor unit activity changes through the sequence acquisition process using online decomposition methods. An examination of motor unit activity of this detail can help elevate the current field by understanding how motor neurons change as a result of skill acquisition.

Disclosures: Y. Escalante: None. Y. Lei: None.

Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.14/X6

Topic: F.09. Motor Neurons and Muscle

Support: SECIHTI (INFRASTRUCTURE 2022, ID 322333 TO FC)
SECIHTI CVU 1004334

Title: Rapid estrogenic regulation of pelvic floor muscle activity during micturition

Authors: *S. SANCHEZ MENESES¹, D. L. CORONA QUINTANILLA², O. SANCHEZ GARCIA³, E. CUEVAS⁴, M. MARTINEZ-GOMEZ⁵, F. CASTELÁN⁶;

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Abstract: Pelvic floor disorders, such as urinary incontinence, are frequently associated with decreased estrogen levels. The urogenital tract is highly sensitive to this hormone, making estrogen-based hormone replacement therapy (HRT) a common treatment. In micturition, estrogen modulates viscerosomatic reflexes involving the bladder and pelvic floor muscles. This study aimed to determine the influence of rapid estrogen actions on pelvic muscle reflex activity during the micturition reflex in rabbits. The results demonstrated that rapid estrogen actions contribute to pelvic floor muscle activity. EMG analysis supports asymmetrical responses. Bladder function was also disrupted. Estrogen actions play an essential role in the micturition reflex.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.15/X7

Topic: F.09. Motor Neurons and Muscle

Support: SECIHTI CF 1311312
SECIHTI AFH 1157306

Title: Analysis of the pattern of urethral external sphincter in response to selective stimulation of urethral regions in the female rabbit

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Abstract: The storage and voiding periodic of urine depends on the coordinated activity of two functional structures of the lower urinary tract: (1) a reservoir, the urinary bladder, and (2) an outflow duct with striated musculature, which reinforces the duct; this is formed by the bladder neck, the urethra, the external urethral sphincter (EUS) and the pelvic floor. The innervation of the urethra and the EUS comes from somatic and autonomic pathways. The EUS receives information from nerve roots S2-S4, through the pudendal nerve. For proper function, the EUS, along with other structures, regulate urethral closure. Currently, the main structures that support urethral closure are the anterior vaginal wall, the pubourethral ligaments, the tendinous arch of the pelvic fascia, the endopelvic fascia, and the pelvic diaphragm. During increased intra-abdominal pressure, these supporting structures together maintain the bladder and urethral base in an intrapelvic position. Therefore, the increased intravesical pressure is also transmitted to the bladder neck and urethra. However, it has been shown that continuity of the bladder and urethra is not essential for urethral closure and triggering EEU activity. Nevertheless, the anatomofunctional description of the afferent innervation of the urethra remains to be understood and its study represents a primary area. Accordingly, a first approach is the analysis of the pattern of EEU activity triggered by selective stimulation of urethral regions in the rabbit. For this purpose, EEU recordings were performed in anesthetized rabbits in response to selective mechanical stimulation of the proximal, medial and distal urethra. Selective mechanical distension of the urethral regions differentially triggered urethral pressure and EEU patterns.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.16/X8

Topic: F.09. Motor Neurons and Muscle

Title: Intermuscular differences in motor unit firing parameters between humans with and without chronic spinal cord injury.

Authors: *A. BENEDETTO^{1,5}, M. FARLEY², S. T. JENZ¹, E. CURUK⁶, B. HEIT³, J. A. BEAUCHAMP⁷, S. SANGARI⁶, C. HECKMAN⁴, M. A. PEREZ⁸, G. E. PEARCEY⁹;
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Abstract: There is substantial functional heterogeneity within the spinal cord-injured (SCI) population, yet we know little about the underlying mechanisms. Motor unit (MU) firing behavior after SCI may reveal physiological insights into this heterogeneity. We assessed MU firing patterns in individuals with SCI during triangular isometric contractions to a peak of 30% of maximum across six muscles: biceps brachii (BIC; n = 20), triceps brachii (TRI; n = 20), vastus lateralis (VL; n = 9), vastus medialis (VM; n = 9), tibialis anterior (TA; n = 14), and soleus (SOL; n = 14). These were compared to age-matched, non-injured (NI) participants (BIC: n = 18, TRI: n = 18, VL: n = 9, VM: n = 9, TA: n = 8, SOL: n = 8). High-density surface electromyograms (HDsEMG) were recorded during voluntary elbow flexion, elbow extension, knee extension, dorsiflexion, or plantarflexion, with each participant performing two trials per contraction. Blind source separation was used to identify MU spike times, and a total of 5,127 MUs were analyzed (SCI: n = 3,105; NI: n = 2,022). As is typical with HDsEMG MU decomposition, yield was variable across muscles and participants (SCI average yield per trial: BIC = 8.8 ± 4.6 , TRI = 9.3 ± 5.6 , VL = 7.6 ± 4.0 , VM = 5.6 ± 2.4 , TA = 40.3 ± 14.0 , SOL = 39.4 ± 13.9 ; NI average yield per trial: BIC = 9.2 ± 4.9 , TRI = 9.5 ± 6.4 , VL = 10.0 ± 11.1 , VM = 7.3 ± 2.6 , TA = 31.1 ± 23.6 , SOL = 45.2 ± 30.2). Firing rate hysteresis was quantified using the paired-MU analysis technique (ΔF) and normalized to account for differences in firing rate modulation between groups. In all muscles, peak discharge rates (pulses per second) were significantly lower in the SCI group compared to the NI group ($p < 0.001$). This difference was greater in flexor muscles (BIC: SCI = 14.0 ± 0.3 vs. NI = 17.7 ± 0.4 ; TA: SCI = 13.6 ± 0.4 vs. NI = 17.1 ± 0.5) compared to extensors (TRI: SCI = 13.9 ± 0.4 vs. NI = 14.6 ± 0.4 ; SOL: SCI = 9.6 ± 0.4 vs. NI = 10.9 ± 0.5 ; VL: SCI = 9.1 ± 0.6 vs. NI = 10.2 ± 0.6 ; VM: SCI = 9.5 ± 0.6 vs. NI = 10.0 ± 0.6). Similar results were found for the range of firing rates throughout contractions. There were no significant group differences in ΔF across muscles, but when normalized to firing rate modulation, ΔF values were significantly higher in the SCI group ($p < 0.001$). This difference was most prominent in TRI (SCI = 0.61 ± 0.03 vs. NI = 0.46 ± 0.03), TA (SCI = 0.72 ± 0.02 vs. NI = 0.61 ± 0.03), and VL (SCI = 0.54 ± 0.04 vs. NI = 0.38 ± 0.04), with modest differences in BIC (SCI = 0.58 ± 0.03 vs. NI = 0.50 ± 0.03), SOL (SCI = 0.69 ± 0.02 vs. NI = 0.64 ± 0.03), and VM (SCI = 0.54 ± 0.05 vs. NI = 0.46 ± 0.05). These results indicate substantial intermuscular heterogeneity in MU firing behavior after SCI, which may contribute to the observed heterogeneity in functional recovery.

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Poster

PSTR176: Motor Unit Recordings, Kinematics, and EMG

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR176.17/X9

Topic: F.09. Motor Neurons and Muscle

Support: The ALS Association Seed Grant

Title: Hd-emg detects muscle-specific fatigue patterns despite diagnostic overlap in als

Authors: ***E. H. BEDOY**¹, D. J. WEBER², C. L. KOLARCIK³;

²Mechanical Engin. and Neurosci. Inst., ¹Carnegie Mellon Univ., Pittsburgh, PA; ³Pathology, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that disrupts motor unit function, leading to muscle weakness and fatigue. Prior work in animal models suggests differential vulnerability of muscle fiber types during disease progression, with fast-twitch fibers typically degenerating earlier than slow-twitch fibers. This study leverages high-density surface EMG (HD-EMG) to evaluate muscle-specific fatigue patterns and fiber-type engagement during sustained submaximal contractions in individuals with ALS and matched healthy controls. We obtained HD-EMG recordings from the biceps brachii, triceps brachii, tibialis anterior, and soleus muscles of eight people with ALS and eleven control participants during sustained contractions at 20-50% of each individual's maximum voluntary contraction (MVC). We extracted force output and EMG features including root mean square (RMS), low-frequency power, and high-frequency power from multiple time blocks to assess fatigue-related changes. Across both groups, there was a trend for RMS and frequency power to decline at higher force levels, consistent with fatigue-related reductions in EMG amplitude and spectral content. Analyses revealed that while 100% MVC force measurements clearly differentiated groups, EMG features showed substantial overlap due to heterogeneous muscle involvement and variable disease progression in ALS. Notably, some muscles in people with ALS retained patterns similar to controls, underscoring the need for muscle-specific analyses in neuromuscular diseases. To improve sensitivity to early neuromuscular impairment, we plan to incorporate motor unit decomposition in future analyses. Metrics such as mean firing rate, inter-spike interval variability, and recruitment thresholds may provide greater resolution of fiber-type function and reveal subtle alterations not captured by aggregate EMG measures. Longitudinal tracking will enable within-subject comparisons over time to better characterize disease progression. These findings support the value of HD-EMG as a tool for probing muscle-specific pathology and suggest that combining surface EMG features with decomposed motor unit data may offer a more comprehensive understanding of fatigue and fiber-type decline in ALS.

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Poster

PSTR177: Social Behaviors

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.01/X11

Topic: G.02. Neuroendocrine Processes and Behavior

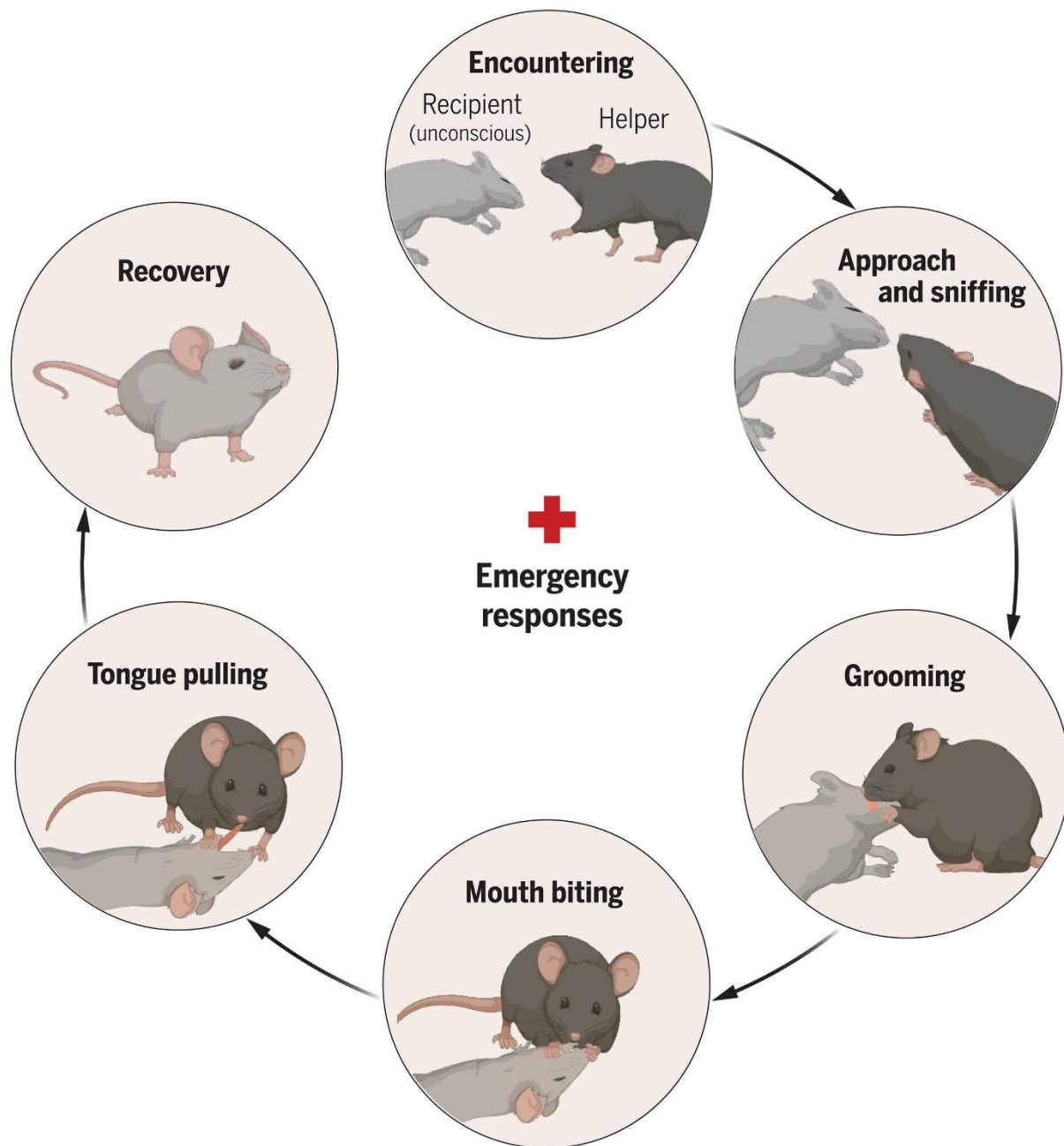
Support: NIH Grant NS132912
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NIH Grant EY019049
NIH Grant AG089756

Title: Reviving-like prosocial behavior in response to unconscious or dead conspecifics in rodents

Authors: W. SUN¹, ***G.-W. ZHANG**^{2,6}, J. J. HUANG³, C. TAO⁴, M. B. SEO⁵, H. W. TAO⁷, L. I. ZHANG²;

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Abstract: Whereas humans exhibit emergency responses to assist unconscious individuals, how nonhuman animals react to unresponsive conspecifics is less well understood. We report that mice exhibit stereotypic behaviors toward unconscious or dead social partners, which escalate from sniffing and grooming to more forceful actions such as mouth or tongue biting and tongue pulling. The latter intense actions, more prominent in familiar pairs, begin after prolonged immobility and unresponsiveness and cease when the partner regains activity. Their consequences, including improved airway opening and clearance and accelerated recovery from unconsciousness, suggest rescue-like efforts. Oxytocin neurons in the hypothalamic paraventricular nucleus respond differentially to the presence of unconscious versus active partners, and their activation, along with oxytocin signaling, is required for the reviving-like actions. This tendency to assist unresponsive members may enhance group cohesion and survival of social species.



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Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.02/X12

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant R01AG087537

Title: Consolatory Caring Behaviors in Mice: Dependence in Age, Sex, Familiarity and Distress Signals.

Authors: ***R. IBRAHIM-ABDULKAREEM**^{1,2}, A. KOBEISSI², A. BARAL³, M. BILAL⁴, H. DAI², W.-D. YAO⁵;

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Abstract: Fostering of cohesive and healthy relationship in social species arises from understanding the emotional and physical states of others. Empathy, the ability to share feelings of others, is an evolutionarily conserved trait that is impaired in many brain disorders. The underlying mechanisms are poorly understood. Consolatory caring behavior is a form of empathy, and a comforting act directed to a distressed conspecific. There are different variables (sex, age, familiarity, observation-visual cues) that is believed to play vital role in understanding others state and providing necessary help to alleviate distress, which is seen in human, but our understanding about how these variables influence empathic concern and behavior is vague. Here, using our recently developed distress-induced affiliative (DIA) behavior paradigm in mice, we characterize the roles the different variables play in empathic behavior. Our results show contributions of different variables to consolatory caring behaviors with more studies to be done to identify the underlying synaptic, circuit, and neuromodulatory mechanisms.

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Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.03/X13

Topic: G.02. Neuroendocrine Processes and Behavior

Title: Behavior monitoring of whole naked mole-rat colonies

Authors: ***W. FOSTER**¹, Y. HABA², W.-Y. TSAI², P. SHENG², I. ABDUS-SABOOR³;

¹Columbia Univ., New York, NY; ²Columbia Univ., New York, NY ; ³Biol., Columbia Univ., New York, NY

Abstract: Social relationships are critical for the health and well-being of social animals, particularly group-living animals like humans. In humans, impaired social relationships are a hallmark of many neuropsychiatric disorders, including schizophrenia, autism, anxiety, and depression. Despite the significance of social relationships, little is known about the basic

mechanisms supporting their formation and maintenance. Common laboratory animals do not naturally form and maintain affiliative social relationships in large groups, presenting a major barrier to understanding. In contrast, the naked mole-rat (*Heterocephalus glaber*) is an extremely social mammal that lives in cooperative colonies and maintains complex social relationships with up to hundreds of colony-mates over many years. Thus, naked mole-rats are an ideal animal model for social relationships. However, the basic mechanisms underlying the formation and maintenance of social relationships in naked mole-rat colonies are unknown. Historically, the difficulty of measuring behavior in large animal groups, like naked mole-rat colonies, has limited experimental study. Here, I established a system to continuously track behavior and quantify social relationships in whole colonies over extended time periods. My preliminary data demonstrate that social preferences are variable across colony members, that colony sociality is flexible, and highlight potential mechanisms for the maintenance of a stable colony. Ultimately, this work establishes the naked mole-rat as a laboratory model for understanding sociality.

Disclosures: W. Foster: None. Y. Haba: None. W. Tsai: None. P. Sheng: None. I. Abdus-Saboor: None.

Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.04/X14

Topic: G.02. Neuroendocrine Processes and Behavior

Title: A Scalable Platform for Social Neural Imaging: Integrating Multi-animal 3D Pose Tracking and Calcium Imaging in Freely Interacting Animals

Authors: *L. QI, R.-Z. ZHAN, T. LI, A. SABATH, J. WU, T. W. DUNN;
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Abstract: Locomotion and novel visual stimuli heighten layer-2/3 activity in primary visual cortex (V1) [Dadarlat & Stryker 2017]; whether social proximity similarly modulates V1 or primary motor cortex (M1) is unknown. Adult male C57BL/6J mice (V1 n = 6; M1 n = 7; 10-18 wk) received 250 nl AAV1-hSyn-Soma-jGCaMP8s in layer 2/3 of V1 (AP -3.5 mm, ML 2.5 mm, DV 0.32 mm) or M1. After 3-4 wk a 1 mm cranial window was implanted; ≥ 4 wk post-virus, Ca^{2+} transients were captured with a MiniScope V4 via a customized auto cable management system. Six synchronized 30 Hz cameras filmed behaviour in a 1 m arena, and s-DANNCE reconstructed 3-D pose [Klibaite et al. 2025; Dunn et al. 2021]. Unsupervised clustering of kinematics defined behavioural motifs, and head-centric field-of-view maps flagged frames when a partner entered each mouse's visual sector. Fluorescence traces were extracted with MininAn and CNMF [Dong et al. 2022; Pnevmatikakis et al. 2016]. For every ROI we calculated the 95th-percentile $\Delta F/F$ during single epochs and during "social-far" (> 250 mm) or "social-close" (≤ 250 mm) proximity. M1 - 55 ROIs from 2 social mice (single: 294 ROIs, 6 mice): social-close peaks (3.72 ± 2.15) exceeded single (2.94 ± 1.62);

Mann-Whitney $U = 6316$, $p = 0.010$), whereas social-far (3.13 ± 2.45) did not differ ($p = 0.223$). V1 - 211 ROIs from 4 social mice (single: 292 ROIs, 5 mice): neither social-close (3.50 ± 2.26) nor social-far (3.57 ± 2.18) differed from single (3.18 ± 1.72 ; $p > 0.05$). Population modes of M1 activity covaried with spontaneously discovered movement motifs and rose whenever a conspecific was nearby, whereas V1 showed only transient increases upon partner field-of-view entry. Given the limited social-M1 sample size, these statistics remain exploratory. This modular platform—combining head-centric visual mapping, 3-D pose clustering, and MiniScope imaging—sets the stage for data-driven dissection of naturalistic social circuits and readily accommodates optogenetic perturbation, multi-fiber photometry, and synchronized audio capture.

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Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.05/X15

Topic: G.02. Neuroendocrine Processes and Behavior

Support: Clemson University Biological Sciences Interdisciplinary Fellowship
Clemson University Biological Sciences Startup Fund
Clemson University College of Science Grant In Aid of Research

Title: A Single-Nucleus Multiomic Investigation of Adaptive Development Programming in Heat Call Exposed Embryonic Zebra Finches

Authors: *P. SUBBA¹, K. WILLIAMS², T. MCDONALD¹, V. SHANKAR², P. FREYMUTH², N. SHAY¹, T. F. C. MACKAY², J. M. GEORGE¹;

¹Biol. Sci., Clemson Univ., Clemson, SC; ²Ctr. for Human Genet., Clemson Univ., Greenwood, SC

Abstract: Organisms face the challenge of adapting to rapidly changing environments. In zebra finches (*Taeniopygia guttata*), adults exposed to extreme heat emit a unique “heat call” that triggers adaptive developmental responses in the morphology, physiology and fitness levels of the offspring, yet the underlying mechanisms remain unclear. We investigated how heat call exposure alters gene regulatory programs in the embryonic hypothalamus, hypothesizing that heat calls induce transcriptomic and genomic adaptations promoting thermoregulatory resilience. Due to the absence of a comprehensive embryonic brain cell atlas for this species, we performed single nucleus (sn) multiome RNA and ATAC sequencing to profile gene expression and chromatin accessibility across hypothalamic cell populations in heat call-exposed embryos. Additionally, we utilized fluorescent in situ hybridization (FISH) to localize somatostatin, a growth hormone regulator previously linked to heat call responses. Our snRNA-seq analyses

revealed downregulation of neuroendocrine genes such as transthyretin (involved in thyroid transport) and sexual dimorphic expression in glutamatergic cell clusters. Cholecystokinin, a neuroendocrine gene involved in appetite regulation and stress response, was upregulated in glutamatergic clusters. Our sn-ATAC results demonstrated motif enrichment for Nuclear Factor I-C (NFIC) isoform 2, a transcription factor implicated in stress response, in both neuronal and glial cell clusters. FISH confirmed specific somatostatin localization in distinct hypothalamic cells of exposed embryos. Together, our results indicate that heat call exposure drives coordinated genomic and transcriptional reprogramming that primes offspring for warmer environments. These findings provide novel insights into how vocal communication and neuroendocrine signaling intersect to mediate adaptive developmental programming in response to environmental stress, highlighting the hypothalamus as a critical hub for integrating sensory and endocrine signals to promote survival in changing climates. These results have broad implications for understanding the neurobiological basis of resilience and adaptation in vertebrates facing global climate change.

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Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.06/X16

Topic: G.02. Neuroendocrine Processes and Behavior

Support: Stengl-Wyer
AAUW
IB Research Endowments
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Title: Know thy neighbor: the neural basis of reciprocity in a highly social cichlid

Authors: *E. LESSIG¹, H. BAIER³, H. A. HOFMANN²;
²Integrative Biol., ¹The Univ. of Texas at Austin, Austin, TX; ³Genes - Circuits - Behavior, Max Planck Inst. of Neurobio., Planegg, Germany

Abstract: Cooperation is a hallmark of human behavior and is also found across a wide variety of species, yet the neural underpinnings of cooperative behavior are poorly understood. A special case of cooperation is reciprocity, where individuals reciprocate the previous behaviors of their partner. To do this successfully, individuals must consider information about their social partner and the likelihood they will receive help, which may require sophisticated cognitive mechanisms for assessing, evaluating, and responding to a variety of social cues. However, few studies have empirically tested reciprocity, and the neural mechanisms underlying reciprocity are virtually unknown. Here, we used the highly social African cichlid fish, *Astatotilapia burtoni*, to quantify

behavior and circulating hormones in a novel reciprocity paradigm, where socially dominant males form resource defense coalitions and jointly attack a territorial intruder. We found that territorial *A. burtoni* males show direct reciprocity within two hours of receiving assistance or defection from a neighbor. We then adapted whole mount *in situ* hybridization chain reaction for this species and examined neural activity patterns using the immediate early genes *c-fos* and *egr-1* as well as the role of dopaminergic signaling in both cooperating and non-cooperating neighbors while exhibiting reciprocity behavior. Our results show that the activity of dopaminergic neurons in both fore- and midbrain varies by behavioral role and experimental treatment. Taken together, our work increases our understanding of social decision-making and deepens our understanding of cooperation across species.

Disclosures: E. Lessig: None. H. Baier: None. H.A. Hofmann: None.

Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.07/Y1

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant R01AG058762
HFSP Long-Term Fellowship

Title: Electing Queens: The Establishment of Social Hierarchy in the Indian Jumping Ant

Authors: *C.-H. LEE¹, S. LIU¹, M. BEN KIRAN¹, C. DESPLAN²;

¹Biol., New York Univ., New York, NY; ²Biol., New York Univ., New York, NY

Abstract: Social insects can undergo dramatic changes in their physiology and behavior to support the collective needs of the colony. In the ant *Harpegnathos saltator*, when a colony loses its queen, a few workers can transition into reproductive pseudo-queens (gamergates) to re-establish the hierarchy in the colony. The workers engage in a prolonged antennal dueling tournament, exchanging ritualized strikes for several weeks to establish social dominance. Most workers withdraw from dueling within two weeks and retain their worker status. In contrast, a few persist in dueling for several weeks and eventually transition into gamergates, sharing reproductive dominance within the colony. Previous studies have primarily relied on manual video analysis to identify dueling behavior; however, dueling activity does not always correlate with gamergate fate. This suggests that social hierarchy is not established by high levels of dueling alone, and that other social behaviors contribute to caste transition. To investigate this, we applied NAPS (Neural Annotation of Pose with SLEAP and ArUco) to generate pose estimation data while preserving individual ant identities throughout the transition period. Using a spatiotemporal graph convolutional network (ST-GCN), we automatically detected and quantified stereotyped charging events during dueling tournaments. The model also identified the target of each charge, enabling the reconstruction of detailed social interaction networks. We

found that most individuals who became gamergates exhibited sustained high dueling activity, but one gamergate stood out by engaging in dueling much less than others. To explore this further, we quantified how often each individual was targeted during dueling interactions. Surprisingly, frequent targeting showed a strong positive correlation with gamergate fate. Furthermore, individuals that received strikes from others early in the tournament were more likely to sustain dueling behavior throughout the competition. We propose a novel mechanism of caste transition in which receiving strikes acts as a mechanosensory stimulus, triggering a positive feedback loop that reinforces dueling behavior and promotes ovary activation. Our high-throughput behavioral tracking approach provides new insight into how eusocial insects establish social hierarchies and offers a foundation for uncovering the underlying molecular mechanisms.

Disclosures: C. Lee: None. S. Liu: None. M. Ben Kiran: None. C. Desplan: None.

Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.08/Y2

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant R01AG058762

Title: Using Neural Network Models To Track Social Behaviors in Indian Jumping Ants

Authors: *S. LIU, C.-H. LEE, M. BEN KIRAN, C. DESPLAN;
Biol., New York Univ., New York, NY

Abstract: Understanding how social behaviors give rise to group-level organization is a central goal in behavioral neuroscience and ethology. In eusocial insect species such as *Harpegnathos saltator* (Indian jumping ants), antennal dueling plays a pivotal role in establishing reproductive hierarchies during caste transition. This behavior is often characterized by the reciprocal exchange of rapid antennal strikes between nestmates, often accompanied by coordinated charging and retreating movements toward the opponent. Although dueling follows a stereotypical motor motif, it displays considerable variability across social contexts and individuals, such as the presence of charging motion or the duration of rapid antenna movement. Previous studies have primarily relied on manual video annotation to identify the presence of dueling behavior. While this approach has provided valuable qualitative insights, it is time-consuming, subjective, and poorly suited for high-throughput, long-duration analysis in densely populated colonies. To fill this gap, we conducted NAPS (NAPS is Aruco Plus Slep) to generate 11-node skeletonized pose estimation data that preserves individual ant identity across time. We further decomposed dueling into discrete antennal strikes—defined as rapid swings of the antennae toward a target lasting approximately one second, often accompanied by forward charging motions. From the identity-preserved trajectories, we constructed ego-target feature windows for each focal ant and its nearest neighbor. Each window encoded 6 channels of

information per node: 2D position, velocity, antenna joint angles, distance to the target tag, and a behaviorally relevant angular feature. These ego-target windows were used to train a spatiotemporal graph convolutional network (ST-GCN). To account for behavioral variation of dueling, we trained two separate models: one for dueling events occurring within the first 24 hours after feeding—when ants often aggregate but rarely perform sustained dueling—and another for the subsequent 24+ hour period, when dueling behaviors become more prominent. The current model achieves over 85% precision and recall on both the training and testing sets. The similar logic was also used to design the model for the detection of biting, which is a dominant behavior we observed during caste transition. By combining the high-resolution ethogram and the reproductive outcome of caste transition, we aim to build behaviorally annotated social networks. This framework provides new insight into how social behaviors contribute to dominance hierarchy formation and collective decision-making in eusocial insects.

Disclosures: S. Liu: None. C. Lee: None. M. Ben Kiran: None. C. Desplan: None.

Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

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Program #/Poster #: PSTR177.09/Y3

Topic: G.02. Neuroendocrine Processes and Behavior

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Title: Neural mechanism of sexually dimorphic winner effect in mice

Authors: *D. ZHENG, Q. XIN, S. JIN, A. ZHOU, X. JIA, Y. TAN, H. HU;
Zhejiang Univ. Sch. of Med., Hangzhou, China

Abstract: The “winner effect”, where prior victories increase the likelihood of future wins, profoundly shapes social hierarchy dynamics and competitive motivation. While human literature suggests a less pronounced winner effect in females, the neural mechanisms underlying these sex differences remain unclear. Here we show that compared with male mice, female mice take longer to form social hierarchy and exhibit a weaker winner effect. The dorsomedial prefrontal cortex (dmPFC), crucial for social dominance in males, plays a similar role in female

mice. However, female mice exhibit reduced long-term potentiation (LTP) at the mediodorsal thalamic (MDT)-to-dmPFC synapses. In vitro recordings revealed that female mice have heightened excitability of dmPFC parvalbumin interneurons (PV-INs). Bidirectional modulation of dmPFC PV-IN activity regulates LTP and the winner effect in a sexually dimorphic manner. This work identifies the dmPFC PV-INs as a target for enhancing the winner effect, establishing a circuit-level framework for sex differences in competitive behaviors.

Disclosures: **D. Zheng:** None. **Q. Xin:** None. **S. Jin:** None. **A. Zhou:** None. **X. Jia:** None. **Y. tan:** None. **H. Hu:** None.

Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.10/Y4

Topic: G.02. Neuroendocrine Processes and Behavior

Support: 1R01MH135553-01A1

Title: Social Investigation-Dependent Activity within Vasopressin 1a-Expressing Cells of the Lateral Septum

Authors: ***N. A. SCHAPPAUGH**¹, G. J. DE VRIES³, A. PETRULIS²;

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Abstract: The lateral septum (LS) is a critical area for processing of social information and regulation of social behavior. These processes are often regulated by neuropeptide action in the LS, most prominently by vasopressin (AVP). The major source of AVP to the LS originates from the sexually-differentiated AVP cells from the bed nucleus of the stria terminalis and has been shown to act on LS vasopressin 1a receptors (V1aR) to preferentially drive social investigation in males. To determine how LS V1aR-expressing cells encode social interactions, we imaged their bulk calcium responses via in vivo fiber photometry in male and female V1aR-cre⁺ mice during social investigation of male and female conspecifics. We observed increased calcium activity during onset of social investigation, a decrease during social investigation, followed by a rebound in activity upon investigation termination. This was observed in both males and females irrespective of sex or reproductive state of stimulus animals, repeated investigations of the same animal, or estrus state of female subjects. These results lay the groundwork for understanding the network mechanisms underpinning the behavioral actions of sexually-differentiated AVP within the LS.

Disclosures: **N.A. Schappagh:** None. **G.J. De Vries:** None. **A. Petrulis:** None.

Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.11/Y5

Topic: G.02. Neuroendocrine Processes and Behavior

Support: Charitable Trust Created by R. W. Morrison
NIH Training Grant R25NS115552

Title: Dietary fat effects on social and cognitive traits of serotonin transporter knock-out mice

Authors: *J. E. SCHULTZ^{1,2}, K. RIEDER^{3,1}, A. SHAKOCIUS^{1,3}, J. JOHNSON¹, L. STEWART¹, A. WINDSCHEFFEL¹, P. PEREZ¹, P. B. STEWART¹, A. JOHNSON⁴, S. M. GREENE⁵, G. G. GOULD¹;

¹Univ. of Texas Hlth. San Antonio, San Antonio, TX; ²Univ. of California, Davis, CA; ³Trinity Univ., San Antonio, TX; ⁴Northwestern Univ., Chicago, IL; ⁵Univ. of the Incarnate Word, San Antonio, TX

Abstract: Impaired social interaction is a core autism symptom that also occurs in depression. Various common and rare mutations impairing expression or function of the serotonin transporter (SERT) coincide with these disorders in about 20% of affected individuals. The neurotransmitter/hormone serotonin is taken up by SERT from extracellular fluid into cells expressing it in brain and peripheral tissues. Extracellular serotonin levels are therefore elevated in SERT knock-out mice exhibiting social interaction deficits paralleling autism and depression symptoms. Ketogenic diets with 60 kcal% fat are gaining popularity as a treatment for autism and mood disorders. We hypothesized that a ketogenic diet could enhance social behaviors in SERT knock-out mice to a greater extent than Western diet with 45 kcal% fat. To test this, 20 each (10/sex) SERT knock-out and wild-type mice (on C57BL/6J background) were treated for 8 weeks with ketogenic 60 kcal%, Western 45 kcal% or control 10 kcal% fat diets. Two-way analysis of variance revealed that social interaction preference did not differ with dietary fat in three chamber tests of wild type or SERT knock-out mice, however SERT knock-out mice had significantly lower preference for interaction ($p < 0.05$) than wild-type mice on control diets. Social dominance, as measured in six matches with stranger 129S1/SvImJ mice in tube tests, revealed female knock-out mice had greater social dominance ($p < 0.01$) irrespective of dietary fat. To measure effects on these diets of restrictive repetitive traits, marble burying and reversal learning in the water T-maze were measured. While marble burying did not differ across treatment groups, wild type males displayed greater cognitive flexibility in spatial learning than females or knock-out mice irrespective of dietary fat, as measured on the day the location of a hidden escape platform in the maze was changed. Elevated serotonin is a likely mediator of the behavioral parallels to autism and/or depression symptoms in SERT knock out mice. In light of our research findings, it does not appear that increasing dietary fat in the 10-60 kcal% range will ameliorate autism symptoms in patients with SERT impairing mutations or deficiency.

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Poster

PSTR177: Social Behaviors

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Program #/Poster #: PSTR177.12/Y6

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant R21 MH135324A1

Title: Genetic control by *Foxp2* of neural circuits in the amygdala that mediate innate social behaviors

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Abstract: Innate social behaviors such as aggression, mating, and parental care emerge without prior learning and are essential for reproductive success and species survival. These behaviors are triggered by environmental cues which activate specific neural circuits that comprise the social brain. These circuits are hardwired by genetic programs during development and are later refined by hormones and experience. The medial amygdala (MeA), a key sensory integration hub receiving direct input from the accessory olfactory system, plays a central role in directing behavioral outcomes in response to pheromonal input across mammals. Our prior studies identified a large population of inhibitory projection neurons in the MeA expressing the transcription factor *Foxp2*, present from embryogenesis (E11.5) through adulthood. While *Foxp2*+ MeA neurons have been implicated in intermale aggression, the developmental versus adult-specific contributions of *Foxp2* gene function to MeA circuit function remain unclear. Using a range of *Foxp2* mutant mice, we examined how *Foxp2* gene function influences innate behavioral outputs and the associated MeA circuit function across different time points. Our initial studies revealed that global heterozygous mutants for *Foxp2* exhibit sex-specific behavioral differences in aggression, social interaction, and olfactory investigation of social stimuli, along with deficits in maternal care. These are accompanied by subtle morphological changes in MeA *Foxp2*+ neurons, despite no change in overall neuron number. We have found that targeted conditional deletion of *Foxp2* in the MeA during late adolescence or early adulthood does not disrupt these behaviors, indicating that adult *Foxp2* expression in the MeA is not required for the execution of innate social behaviors. Together, our findings demonstrate an essential role for *Foxp2* in the developmental programming of innate social behavior and

neuronal morphology in the MeA. Currently, we are identifying critical periods during which *Foxp2* is required for proper MeA circuit function and behavioral outcomes.

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Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR177.13/Y7

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIDA Grant 5R01DA039062-08

Title: Sex specific effects of developmental $\Delta 9$ -tetrahydrocannabinol (THC) exposure on neonatal amygdala circuitry and adolescent social play behavior in a rodent model

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Abstract: Cannabis use during pregnancy is increasing in the United States due to expanding legalization and decriminalization. Its federal status as an illicit drug of abuse and status as a DEA Schedule 1 substance greatly restricts researchers' access for cannabis use research. Studies of prenatal cannabis exposure in humans have focused on child behavior, but little is known how mechanistically cannabis impacts the developing fetal brain. We use an early postnatal injection model in rodents to mimic 3rd trimester exposure in humans and investigate long-term behavioral deficits from developmental exposure of $\Delta 9$ -tetrahydrocannabinol (THC), the primary psychoactive component of cannabis. Endocannabinoid (ECB) signaling in the developing amygdala sculpts sex specific circuitry that mediates adolescent social play (PMID:35390290). Adolescent social play is essential to establish proper socio-sexual adult behaviors (PMID:36755666). Previous lab findings discovered ECB levels regulate microglial phagocytosis in the developing amygdala, with higher ECB levels in males producing more phagocytosis and fewer newborn cells than in females. Mimicking male-like ECB levels by treating females with ECB receptor agonists masculinizes phagocytosis and later social play. THC exerts its effects, at least in part, by binding to these same ECB receptors. Females developmentally exposed to THC exhibit increased microglial phagocytosis and subsequent increases in social play, matching levels observed in males. These findings are limited by use of peripheral THC injection, precluding the ability to connect the behavioral effects to changes in the amygdala. We seek to directly target the amygdala through intra-amygdala infusion of THC. We hypothesize that during the critical period for sexual differentiation intra-amygdala THC is sufficient to masculinize cellular and behavioral readouts in females (increased phagocytosis, decreased newborn cell number, increased social play) with no change in males. We also explore

necessity of the amygdala for THC's masculinizing effects on play by administering peripheral THC and blocking cannabinoid receptors in the amygdala. Preliminary immunofluorescence data shows intra-amygdala THC infusion on postnatal days 0-3 increases microglial phagocytosis in the amygdala of females to match levels seen in control males (n=2). This novel region-specific targeting of THC will elucidate both the neurological mechanism and long-term behavioral impact of developmental THC exposure and address the critical issue of cannabis use during pregnancy.

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Poster

PSTR177: Social Behaviors

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Program #/Poster #: PSTR177.14/Y8

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIDA Grant 5R01DA039062-08

Title: Evidence that Δ^9 -Tetrahydrocannabinol binds to the androgen receptor and acts as an inverse agonist in the medial amygdala

Authors: *N. MOIN AFSHAR¹, D. STRICKLAND², M. M. MCCARTHY³;
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Abstract: The developing brain is characterized by its sensitivity to gonadal steroid hormones, particularly androgens produced by the fetal testis during the perinatal period. The surge of androgens from the fetal testis establishes the critical period of masculinization, during which androgen-sensitive brain regions undergo morphological and functional changes to prepare males for appropriate behaviors later in life. The ability of androgens to organize neural substrates depends on the direct or indirect activity of the androgen receptor (AR). The AR is a nuclear steroid receptor that binds to the promoter regions of specific genes. Alongside these direct effects, we have shown that AR activity indirectly organizes the masculine phenotype of the medial amygdala by increasing endocannabinoid signaling, which promotes microglial phagocytosis of astrocytic progenitors (PMID: 30827729). Importantly, exposure of female rat pups during this sensitive period to exogenous cannabinoids such as Δ^9 -tetrahydrocannabinol (THC) induces a masculinized phenotype in their microglia. With recent changes in legalization of cannabis, cannabis consumption during pregnancy has increased, which has been associated with a heightened risk of neuropsychiatric disease in offspring, an aspect of which may lie in disrupting the androgen-mediated recruitment of the endocannabinoid system necessary for proper brain development. However, our recent work highlights an additional and direct role of THC in disrupting androgen-mediated brain development. We demonstrate *in silico* through Site

Identification by Ligand Competitive Saturation that THC can bind to the AR with an affinity like testosterone, thereby creating the potential to directly affect brain development through actions at the AR. Similar computational modeling showed that the endogenous cannabinoids, 2-AG and Anandamide, were unable to bind to the AR. We next used surface plasmon resonance (SPR) to evaluate in vitro binding affinity of THC at the AR. Our results demonstrate similar binding affinity for testosterone at the AR to values reported in the literature. The results of SPR indicate a binding affinity of THC like those of AR, supporting the in silico computational data. Finally, we examined the expression of androgen-responsive autism risk genes in the medial amygdala following THC exposure through qPCR. We show that THC had sex-specific effects on the expression of these genes, highlighting a potential inverse agonist role for THC at the AR. These findings highlight a potential direct role of THC at the AR, offering insights into how gestational cannabis exposure may affect androgen-mediated neurodevelopment.

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Poster

PSTR177: Social Behaviors

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Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIMH Grant R01MH052716
NIDA Grant R01DA039062

Title: Active feminization of astrocyte density in the developing medial amygdala by TNF- α drives sex differences in social play behavior

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Abstract: Sex differences established during neurodevelopment have been well characterized in the context of either the presence or absence of masculinizing androgen production by the fetal testis. The prevailing assumption is that the lack of neonatal androgen exposure results in neurodevelopment of the female sex by default. However, despite this prevailing theory, the mechanisms underlying the development of regions in the female brain have remained largely unknown. We have recently discovered evidence that microglia derived NF- κ B signaling supports the survival of astrocytes in the medial amygdala (MeA) of females, actively feminizing astrocytic cell density [BioRxiv; DOI: 10.1101/2024.08.19.608675]. Male juvenile rats have lower astrocytic cell counts in the MeA than females, and this astrocyte cell density is causally linked to sex differences in a complex social behavior, juvenile play. At baseline, males display

more robust social play behavior than females. Pharmacological depletion of microglia in females on postnatal (P) day 0, P2, and P4 masculinizes play behavior and results in a significant decrease in astrocyte density in the MeA in adolescence. Therefore, microglia are essential to the survival of newborn astrocytes in the MeA of females. This decrease in astrocyte survival is due to the loss of microglial derived tumor necrosis factor α (TNF- α) signaling. Pharmacological inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) pathway, which is downstream of TNF- α , significantly decreases astrocyte cell survival in the MeA of female rats to that of males and masculinizes play behavior. Here, we seek to interrogate the chemokine TNF- α as the microglia derived initiating factor upstream of NF- κ B activation that supports the survival of astrocytes in the female MeA and ultimately, lower social play behavior. Preliminary data indicate that in vivo intra-amygdalar injections of a TNF- α blocking monoclonal antibody on P0-3 decreases survival of newborn astrocytes in the MeA of neonatal female rat pups by P4. These findings are consistent with a novel role for TNF- α in actively feminizing the MeA, and is to our knowledge, the first mechanistic example of active feminization of a brain region and social behavior.

Disclosures: G.E. Voithofer: None. A. Marquardt: None. M.M. McCarthy: None. J.W. Vanryzin: None.

Poster

PSTR177: Social Behaviors

Location: SDCC Halls B-H

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Program #/Poster #: PSTR177.16/Y10

Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIH Grant DA039062

Title: Deep phenotyping of juvenile rat social play

Authors: *L. A. SIRRS¹, A. P. PHAM¹, G. E. VOITHOFER², M. M. MCCARTHY³;

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Abstract: Social play is a dynamic and rewarding behavior expressed by most mammals in the juvenile period. In rats, social play is essential for the development of appropriate sociosexual behavior (PMID: 36755666). There is a robust, experience-dependent sex difference in playfulness (a stable character trait) such that males play more than females. However, following a brief period of social isolation, females increase their play to male-like levels, eliminating the sex difference. To date, quantification of play has been limited to counting predetermined play elements: pounces, pins, boxing, and chasing. Here, we leverage recent advances in machine learning to expand our understanding of play. We use the pose tracking algorithm SLEAP in combination with the behavioral analysis platform Keypoint-MoSeq to deeply sample the behavior space of play and probe its sex- and experience-specificity. We paired juvenile Sprague

Dawley rats with sex- and age-matched non-littermate partners for 10 minutes across four days. The first three days served as a measure of baseline playfulness (referred to as “play dates”). On the fourth day, the same animals were paired following a 24-hour period of social isolation as a measure of motivated play (referred to as “play pulse”). We fit a Keypoint-MoSeq model to our SLEAP pose tracking data, which segmented behavior into 22 different 400-millisecond syllables. Both males and females exhibited all syllables and syllable frequency was not significantly different between males and females. 8 “play-associated” syllables accounted for 90 percent of all scored play events. Of these 8 play-associated syllables, 4 occurred with greater frequency during play pulse sessions and 3 occurred with greater frequency during play date sessions ($p < 0.05$, Wilcoxon signed-rank test, FDR correction for multiple comparisons). Furthermore, the transition probabilities between specific high velocity syllables were upregulated and the transition probabilities between specific low velocity syllables were downregulated during play pulse sessions relative to play date sessions. These initial findings suggest that the motivation to play changes not only the frequency of certain behaviors, but the qualitative structure and pattern of play behavior. Future research will continue to refine and characterize the syllables generated by Keypoint-MoSeq and probe the temporal structure of these syllables within individual rats and between interacting pairs of rats.

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Poster

PSTR177: Social Behaviors

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Topic: G.02. Neuroendocrine Processes and Behavior

Support: NIDA Grant 5R01DA039062-08
Brasil (CAPES) - Finance Code 001

Title: Timing Matters: modeling effects of gestational cannabis exposure on social behavior and microglia in Sprague Dawley rats

Authors: *A. PHAM^{1,2}, L. A. SIRRS², G. E. VOITHOFER², A. E. MARQUARDT³, M. M. MCCARTHY^{2,3}, J. W. VANRYZIN^{4,2};

¹Univ. of Maryland, Baltimore, Baltimore, MD; ²Univ. of Maryland Sch. of Med., Baltimore, MD; ³Univ. of Maryland Med. - Inst. for Neurosci. Discovery, Baltimore, MD; ⁴Dept. of Pharmacol., Univ. of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Cannabis is the most frequently used illicit drug during pregnancy, with use increasing following legalization in the United States and Canada. The primary psychoactive component of cannabis, delta-9-tetrahydrocannabinol (THC), is a partial agonist of the endocannabinoid (eCB) system, which is active during early neural development and is integral to the formation of

proper circuitry and subsequent behavior. Differential eCB tone in the developing medial amygdala (MeA) induces sex differences, mediated by microglial phagocytosis, in social play (PMID:30827729). As microglia express eCB receptors, we sought to determine if THC exposure would disrupt the effects of the differential eCB tone and alter sexual differentiation of the MeA and behavior. To model cannabis use during either early or late pregnancy, we exposed Sprague Dawley rats to THC (5mg/kg) either in utero via subcutaneous injection to the dam from gestational days 15-21, or to pups via intraperitoneal injection from postnatal days 0-7 respectively, and then investigated expression of social play during the juvenile period. Prenatal THC exposure resulted in males playing less and females trending towards an increase in play (2-Way ANOVA; sex x treatment, $p=0.005$). Postnatal THC exposure resulted in increased play in both sexes, with males playing more than females overall (2-Way ANOVA; effect of sex ($p=0.039$) and treatment ($p=0.032$)). In the MeA, microglial dynamics were differentially altered by THC exposure based on its timing. However, it appears that altered microglial phagocytosis following THC exposure does not fully explain the changes seen in social behavior. The mechanism by which THC exposure alters social behavior is not known and I seek to fill that gap. The current limitation of determining how THC exposure is altering social behavior is how we quantify play, which is currently measured by an observer scoring predetermined elements (pounces, pins, boxes), however it is likely more complex and cannot solely be evaluated as present/absent. I contend that machine learning will reveal latent features of play that differ at baseline between the sexes and are altered by developmental THC exposure. Social LEAP Estimates Animal Poses, a multi-animal pose tracking machine learning software (PMID: 35379947) paired with analysis using keypoint-MoSeq (PMID:38997595) will allow for an unbiased characterization of play. Results will yield insight into the spectrum of social behavior and the effect of THC exposure on its expression.

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Poster

PSTR178: Neuroimmunology and Neurovirology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR178.01/Y12

Topic: G.04. Neuroimmunology and Neurovirology

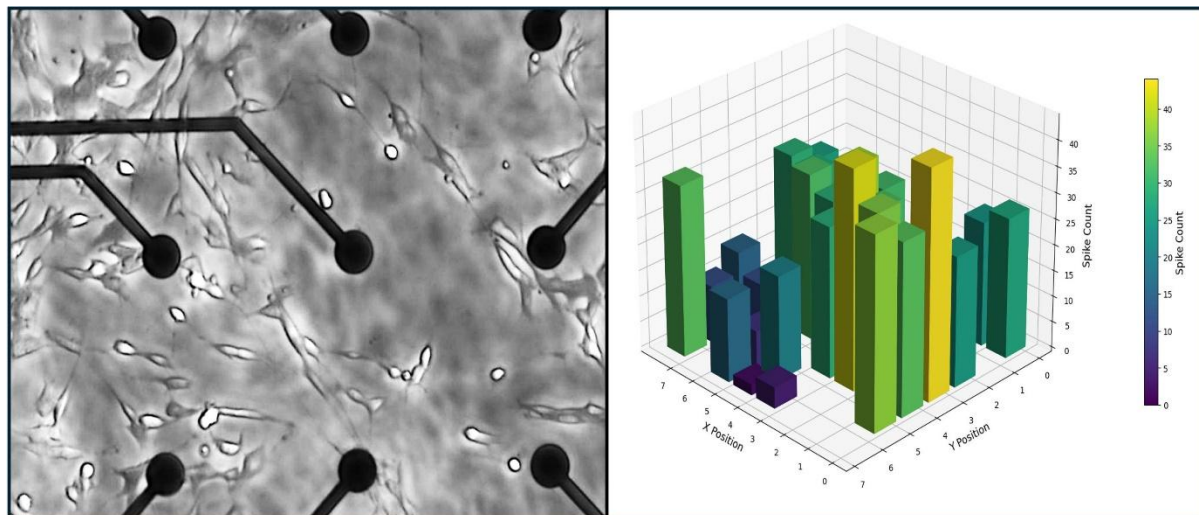
Support: NSF BII Award No. 2119968

Title: Neuronal Signaling in differentiated human neural stems cells infected with Roseolovirus.

Authors: E. BAHRAMIAN¹, Y. X. YANG², A. BAJPAI², *R. M. CEBALLOS¹;

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Abstract: Within the roseoloviruses, human herpesvirus-6A and -6B (HHV-6A and HHV-6B) have been implicated in neurological disorders, including: multiple sclerosis, epilepsy, and chronic fatigue syndrome. However, for several of these disorders, the mechanisms by which viral infection impacts neuronal activity leading to neurological dysfunction remains poorly understood. Differentiated human neural stem cells (dHNSC) provide an option to study roseolovirus-host cell interactions in vitro. There are very few studies that have been performed using microelectrode array (MEA) systems to assess how herpesviruses alter neuronal activity. Moreover, there are no studies demonstrating electrophysiological perturbations of dHNSC activity upon infection with HHV-6A or HHV-6B using an MEA system at different time-points post-infection. To assess herpesvirus-induced changes in neuronal firing and neuronal network activity, we have cultured and differentiated HNSCs in monoculture (and in astrocyte co-cultures) and then infected mature cells with HHV-6A and HHV-6B in separate trials on MEA plates on 2-D surfaces and in 3-D hydrogel preparations. Cytopathic effects and electrophysiological parameters were recorded in roseolovirus-infected cultures versus uninfected cultures (i.e., controls). Parameters such as mean firing rate, burst frequency, and network inter-burst intervals were measured using the MEA high-density platform at different multiplicity of infection (MOI) values for each HHV-6 subtype. Prior work in our lab suggests that HHV-6A and HHV-6B may have selective cell tropism in terms of neuronal neurotransmitter chemotypes. Thus, we also explore activity of distinct neurotransmitter chemotypes in HHV-infected versus uninfected control cultures. Cumulatively, these data demonstrate the impacts of roseolovirus infection on signaling from and between dHNSC and provide insights into potential mechanisms by which HHV-6A or HHV-6B infection may induce neurological dysfunction.



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Poster

PSTR178: Neuroimmunology and Neurovirology

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Topic: G.04. Neuroimmunology and Neurovirology

Support: Whitehall Foundation
Klingenstein-Simons Foundation
NIH grant 4R00NS114107-03

Title: Social isolation exacerbates LPS-induced sickness and alters neural and immune responses

Authors: *D. L. GERMUNDSON-HERMANSON, J. A. OSTERHOUT;
Univ. of Utah, Salt Lake City, UT

Abstract: Infection elicits specific physiological and behavioral responses, including changes in temperature, food consumption, and social behaviors, that conserve energy and aid in pathogen elimination. While the immune system directly detects pathogens, it is the brain that drives these sickness symptoms. Despite the brain's critical role in fighting infection and promoting recovery, the underlying neural mechanisms that govern sickness behaviors are poorly understood. This may be partly due to individual variability in sickness severity. Although sickness symptoms may vary due to factors like genetics and pre-existing conditions, social support is a key environmental influence on both immune and brain function. Here, we investigated how social environments impact sickness severity and underlying immune and neural activity. We found that isolated male mice challenged peripherally with bacterial lipopolysaccharides (LPS) exhibited significantly worsened sickness symptoms, including a greater hypothermic response and prolonged anorexia, compared to their group-housed sick counterparts. We found that sickness severity was unaffected in group-housed mice undergoing a chronic mild stress paradigm, suggesting social isolation uniquely affects sickness severity. Activity pattern analysis revealed that group-housed sick mice exhibited time- and social-context dependent changes in neural activity in the insular cortex (IC), a region that integrates sensory, social, and immune signals. IC activity was also correlated with changes in circulating pro-inflammatory cytokines in group-housed and isolated sick mice. These findings suggest the critical role of social support in modulating immune and neural responses to infection, revealing potentially novel social state-dependent neural mechanisms that may regulate sickness severity and recovery.

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Poster

PSTR178: Neuroimmunology and Neurovirology

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Topic: G.04. Neuroimmunology and Neurovirology

Support: The John W. Jarve (1978) Seed Fund for Science Innovation
Picower Fellowship

Title: Social touch promotes accelerated recovery from virally driven sickness via a brain-immune axis

Authors: *Y. JEONG¹, X. LIN², A. CHO¹, M. WITKOWSKI¹, J. HUH², G. CHOI¹;
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Abstract: Enhanced recovery from viral infections is associated with greater social interaction, yet the underlying mechanisms remain largely unknown. Using a murine model of sickness behaviors induced by a viral mimicry, we demonstrate that socially housed mice recover significantly faster than those housed individually. We further reveal that somatosensory input from social touch, mediated by Mrgprb4+ neurons in the dorsal root ganglion (DRG), facilitates the recovery via the oxytocin system in the brain. Moreover, social housing and the activation of oxytocinergic neurons in the paraventricular hypothalamus prime for systemic IL-10 production in response to immune challenge, contributing to faster recovery. Finally, we identify that IL-10 Receptor subunit A (IL-10RA) signaling in the ventromedial nucleus accumbens shell (vmNAcSh) is essential for this IL-10-driven, socially mediated enhanced recovery. Together, these findings uncover an extensive brain-body axis through which social context shapes the immune system towards an anti-inflammatory state, promoting IL-10-dependent recovery from sickness by engaging IL-10RA in the vmNAcSh. Our study, thus, provides a mechanistic understanding of how social behaviors influence recovery from viral illnesses.

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Poster

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Topic: G.04. Neuroimmunology and Neurovirology

Support: DFG Grant project number 316803389 - SFB 1280 (TP A18 -19/1-2)

Title: Functional connections modulating extinction of learned taste-immune responses

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Abstract: The sustained administration of immunomodulatory agents is critical for the management of various clinical conditions, such as cancer, inflammatory autoimmune disorders and other diseases. Nevertheless, the substantial adverse effects associated with these pharmacological interventions highlight the necessity for alternate or adjunctive therapeutic approaches. In this context, behavioral conditioning of immune responses has been proposed as a sophisticated strategy to facilitate controlled pharmacological dose-reduction while preserving

therapeutic efficacy. Conditioned taste avoidance paradigms (CTA) in rats are well-established and typically involve the pairing of a novel gustatory stimulus (e.g., saccharin) as conditioned stimulus (CS) with the administration of immunosuppressive drugs as unconditioned stimulus (UCS). Subsequent re-exposure to the CS at later time points results in alterations in immune functions, including T-cell activity and cytokine production, which closely mimic the immunopharmacological effects initially induced by the UCS. However, considering that conditioned immune responses gradually diminish over time at repeated unreinforced CS re-exposure, it is crucial to investigate the mechanisms by which learned immune responses may be preserved from extinction. While the insular cortex (IC) is considered to be the primary mediator in extinction/persistence of taste-immune associative learning, evidence strongly indicates the involvement of other brain regions as well. We here show increased activity of the nucleus of the solitary tract (NTS) during retrieval of learned taste-immune responses assessed by cFos staining. A subsequent retrograde tracing approach moreover labeled reciprocal connections between the IC and NTS. Finally, joint activation of inhibitory Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in the IC and NTS differentially affected extinction of taste-immune associative learning at the behavioral (CTA) and physiological (immune system) level, corroborating the hypothesis of a “extinction network” for taste-immune memories. This work was funded by center grants of the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG) project number 316803389 - SFB 1280 (TP A18 - 19/1-2).

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Poster

PSTR178: Neuroimmunology and Neurovirology

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR178.05/Y16

Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH Grant MH133070

Title: Airway Inflammation and Fear: Elucidating the Role of IL-1 Signaling

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Abstract: Post-traumatic stress disorder (PTSD) affects over 300 million people worldwide and is a leading contributor to disability, yet its biological underpinnings remain poorly understood. Emerging evidence suggests a contributory role for chronic inflammation in PTSD susceptibility. Strong genetic and epidemiological evidence support an association between PTSD and asthma, a disease characterized by chronic airway inflammation (AI). The link between asthma-relevant AI and PTSD is not understood and contributory mechanisms are currently unknown. To gain

mechanistic insights our lab has developed a murine model simulating AI effects on -PTSD-relevant behavior in which mice with severe AI exhibit compromised fear extinction. We are exploring the role of the subfornical organ (SFO) a BBB-devoid circumventricular brain region with a unique interoceptive capability to detect and translate peripheral inflammatory signals to emotion-regulatory areas. Recently, we identified a novel circuit from the SFO to the infralimbic cortex (IL) in relaying AI-associated extinction deficits, however, immune mediators and signaling pathways are unclear. SFO transcriptomic pathway analysis revealed significant upregulation of interleukin-1 (IL-1) secretion in severe AI mice. Given the role of IL-1 signaling in AI and fear regulation we hypothesized an engagement of IL-1 signaling in severe AI-associated extinction deficits. Male BALB/c mice received allergen house dust mite + C5aR antibody to generate severe AI and received IL-1 receptor antagonist (IL-1RA) intraperitoneally prior to behavior. Consistent with our hypothesis, IL-1RA treatment significantly attenuated AI-induced fear extinction deficits. IL-1RA mice showed increased neuronal activation (Δ FosB) in the IL cortex-in agreement with improved fear extinction. Importantly, SFO-targeted IL-1RA treatment recapitulated the extinction normalizing effect observed with the systemic treatment, highlighting that SFO IL-1 signaling mediates AI effects on extinction. Our data provide a mechanistic link between airway inflammation and PTSD-relevant fear extinction via IL-1 signaling within the SFO for IL modulation. Ongoing and future studies aim to further elucidate cell-specific IL-1 mechanisms, and SFO neuroimmune signaling using single-cell transcriptomics and whole cell patch-clamp electrophysiology. Overall, our work provides novel mechanistic insights on lung-brain communication pathways of relevance to PTSD risk and therapeutics.

Disclosures: E.R. Mancz: None. E.N. Allgire: None. R. Sah: None.

Poster

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Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH Grant R15MH119500

Title: Il-4-mediated immune changes drive offspring social deficits in a mouse model of maternal allergic asthma

Authors: *J. J. SCHWARTZER, J. RUSSO, V. RHOTEN, F. ABDEL MAKSOUD, X. STRICKLAND;
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Abstract: Changes in the immune environment during pregnancy are commonly associated with neurodevelopmental disorders including Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD). More specifically, studies have demonstrated a strong

association between allergies, asthma, and autoimmune diseases in the mother and an increased risk of having a child with ASD or ADHD. In addition, allergies during pregnancy are predictive of more severe social behavior impairments in the offspring. We have developed a mouse model of maternal allergic asthma (MAA) by sensitizing C57BL/6J female mice to ovalbumin (OVA) prior to mating and exposing them to OVA aerosol challenges at defined gestational timepoints. Compared to control mice, offspring of MAA dams exhibit behavioral deficits characterized by decreased social interactions and increased repetitive behaviors. We hypothesize that these offspring behavioral deficits resulting from MAA are dependent on maternal interleukin-4 (IL-4) signaling. To test this, C57BL/6 female mice were injected with one of three doses of IL-4 (1ng, 10ng, 100ng) throughout pregnancy and their offspring were assessed for social behavior deficits compared with MAA (positive control) and PBS-exposed (negative control) offspring. A total of 170 offspring (83 female and 87 male) from 5-6 litters per treatment group were assessed during the juvenile period and adulthood. Maternal serum cytokine concentrations were measured using multiplex bead-based immunoassays. Our results suggest a decrease in juvenile reciprocal social interaction in offspring born from dams exposed to elevated levels of IL-4 throughout their pregnancy, with social deficits comparable to offspring of MAA-exposed dams. These findings support a dose-dependent role for maternal IL-4 in shaping offspring social behavior. More broadly, the data implicate maternal Th2-skewed immunity as a mechanistic link between allergic asthma and neurodevelopmental risk.

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Poster

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Program #/Poster #: PSTR178.07/Z2

Topic: G.04. Neuroimmunology and Neurovirology

Support: RS-2024-00438988

Title: Cytokine-mediated restoration of social deficits in shank2-deficient mice, an animal model of autism

Authors: *Y. LEE¹, E. LEE²;

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Abstract: Autistic Spectrum Disorder (ASD) is a neurodevelopmental disorder shaped by genetic and environmental influences. In recent years, among various pathological mechanisms, neuroimmune modulation has emerged as a promising therapeutic target in ASD. However, the precise mechanisms through which cytokines act within the central nervous system (CNS) are still poorly understood. In this study, we conducted peripheral and central immune profiling of

Shank2-deficient (Shank2 KO) mice, a validated genetic model of ASD, and observed distinct immune dysfunction phenotypes even under non-inflammatory conditions. Based on prior evidence linking immune abnormalities with ASD, we hypothesized that the social deficits in Shank2 KO mice could be ameliorated by restoring specific cytokines whose expression levels were found to diverge significantly from those in wild-type (WT) controls. Using viral vector-mediated cytokine upregulation, behavioral testing, immunohistochemistry and in situ hybridization across various transgenic mice lines, we demonstrated that certain CNS-resident cell types express specific cytokine that regulates sociability in a bidirectional manner. To distinguish central from peripheral immune influences, we also performed bone marrow transplantation from WT CD45 congenic donor mice into Shank2 recipient mice; notably, this peripheral intervention failed to affect social behavior, underscoring the dominant role of CNS immune modulation. This study demonstrates that cytokine signaling within the CNS plays a direct and critical role in regulating social behavior in a mouse model of ASD. Furthermore, our findings also suggest that CNS cytokine functions not merely as passive markers but as active regulators of behavior, offering a novel and precise therapeutic target for ASD.

Disclosures: Y. Lee: None.

Poster

PSTR178: Neuroimmunology and Neurovirology

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Program #/Poster #: PSTR178.08/Z3

Topic: G.04. Neuroimmunology and Neurovirology

Support: JSPS KAKENHI JP23K17422
JSPS KAKENHI JP19H03538

Title: Nestin promoter-driven conditional Itch deletion induces increased locomotor activity, decreased anxiety-like behavior, and impaired novelty recognition in mice

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Abstract: The ubiquitin pathway is essential for maintaining cellular function and plays a key role in both immune regulation and neural function. E3 ubiquitin ligases ubiquitinate multiple target proteins involved in cellular homeostasis and differentiation. Itch, a member of E3 ubiquitin ligase family, was first identified as an enforcer of immune tolerance. In mice, loss-of-function mutations in Itch cause severe inflammation and excessive scratching behavior. In humans, homozygous mutations in ITCH cause not only multisystem autoimmune disease but also delays in gross motor and cognitive development. These reports suggest that Itch also

functions in the central nervous system (CNS). Indeed, Itch is expressed in the CNS of both mice and humans during embryonic development and in adulthood, and several known Itch substrates, such as Notch, are crucial for neural development and function. These findings collectively imply that Itch plays a role in modulating brain function. However, to date, no mouse models have been developed to specifically investigate the function of Itch in the CNS, and its roles in neurodevelopment and brain function remain unclear. In this study, to investigate the function of Itch in the CNS, we generated Nestin^{Cre};Itch^{FL/FL} (Itch^{ΔNes}) mice, in which Itch is deleted in neural progenitor cells. We subjected these mice to a comprehensive behavioral test battery. Compared to Itch^{FL/FL} (control) mice, Itch^{ΔNes} mice showed increased locomotor activity in the open field test. Furthermore, Itch^{ΔNes} mice spent more time in the center area than controls, suggesting reduced anxiety-like behavior. Consistently, in the elevated plus maze, Itch^{ΔNes} mice spent more time on the open arms than controls, supporting the interpretation of decreased anxiety-like behavior. In the three-chambered social interaction test, Itch^{ΔNes} mice showed a reduced preference for social novelty compared to controls. In the pattern separation test, Itch^{ΔNes} mice exhibited impaired performance in distinguishing between two similar contexts. These results suggest that Itch deficiency in the CNS induces hyperactivity, reduced anxiety-like behavior, and impairments in novelty recognition. These findings highlight the importance of Itch in brain function, although further investigation is needed to understand the cellular mechanisms affected by Itch deficiency.

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Poster

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Topic: G.04. Neuroimmunology and Neurovirology

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CONACYT-FORDECYT-PRONACES [6390]
APIIT-UNAM IA203021

Title: Implications of Systemic Lupus Erythematosus on Sleep Quality and Affective Disorders: Anxiety and Depression

Authors: *G. SEVILLA PARRA¹, D. MARTÍNEZ², A. MEDINA-RIVERA³;
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Abstract: Sistemic Lupus Eritematosus (SLE) is a chronic, multisystemic, autoimmune disease of unknown etiology that mainly affects women of reproductive age. Being multisystemic this disease can affect the nervous system and some of the psychological and behavioral

manifestations that may be affected are mood and sleep. There has been a relationship between these two manifestations in both healthy people and people with SLE, but this relationship has not been studied in the Mexican population. In this study, the relationship between SLE, sleep and affective disorders was analyzed using the IDARE, IDERE, SCL-90, Pittsburgh Sleep Quality and SLEDAI inventories. Permutation tests were performed to compare the scores of the inventories among people with SLE and controls, and a linear regression model was used to analyze the influence of the results of the inventories with the Pittsburgh sleep quality score in people with SLE. People with lupus were found to have worse overall sleep quality compared to controls (with a difference of 3.39 points and a Z-value of 7.20 ; p-value < 0.001) and according to the linear model, increased disease activity is associated with poorer sleep quality. Additionally, somatization was identified as one of the most relevant factors associated with poor sleep quality in people with SLE.

Disclosures: G. Sevilla Parra: None. D. Martínez: None.

Poster

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Topic: G.04. Neuroimmunology and Neurovirology

Support: The Stanley Medical Research Institute

Title: Pediatric Mental Health and *Trichophyton rubrum* Associations with Psychiatric and Behavioral Conditions

Authors: *X. CHEN^{1,2}, L. PRICHETT³, A. YOUNG⁴, J. BADIO³, D. CARMICHAEL³, E. WU³, M. ZHENG³, Y. NA³, R. H. YOLKEN², T. KUMRA³, E. G. SEVERANCE²;

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Abstract: The COVID-19 pandemic emerged amid pre-existing insufficient access to youth mental healthcare and intensified concerns about how early life infections influence neurodevelopment. In 2020, we launched a longitudinal study to track post-pandemic stressors, infectious agents, and mental health trajectories in an urban pediatric clinic cohort. While well-studied in dermatology, chronic *Trichophyton rubrum*, the dermatophyte responsible for most superficial fungal infections (Tinea, ringworm) has received little attention for possible neuroimmune and behavioral effects. We hypothesize that elevated *T. rubrum* IgG titers reflect chronic immune responses associated with behavioral problems. In the absence of reliable serological measures of *T. rubrum* antibodies, we developed a custom immunoblotting procedure to gauge sample positivity as negative, moderate, and strong based on number and intensity of immunoreactive bands. In a community cohort aged 8-20 (N=102), new behavioral symptoms were assessed using the Child Behavior Checklist, Youth Self-Report & Patient Health

Questionnaire-9 (PHQ-9). ANOVAs revealed significant associations between *T. rubrum* positivity and rule-breaking behavior ($p=0.002$), conduct problems ($p=0.016$), and ADHD-related symptoms ($p=0.032$), with stronger effects observed in females than males. Multinomial logistic regression, adjusting for relevant sociodemographics, demonstrated associations between *T. rubrum* positivity and elevated PHQ-9 scores (RRR=1.20, $p=0.037$), conduct problems (RRR=1.09, $p=0.044$), and ADHD scores (RRR=1.11, $p=0.002$). When examining antibody responses to specific *T. rubrum* antigens, we found that positivity to one 10 kDa protein was significantly associated with rule-breaking behavior (RRR=1.13, $p=0.035$), aggressive behavior (RRR=1.08, $p=0.032$), conduct problems (RRR=1.09, $p=0.039$), stress problems (RRR=1.08, $p=0.021$), and oppositional defiant traits (RRR=1.08, $p=0.034$). These findings suggest that *T. rubrum* reactivity and antibody profiles may serve as risk factors associated with behavioral dysregulation in youth and as potential biomarkers of mental health problems. Further research is needed to investigate the causal mechanisms linking dermatophyte exposure to neurobehavioral outcomes, and the impact of timely treatment of these infections on preventing and reducing behavior disorders. If children with behavioral problems are at increased risk for infection, caregivers should receive counsel on how to protect children against these pathogens.

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Poster

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Program #/Poster #: PSTR178.11/Z6

Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH Grant M2800 HL0041

Title: Examining the effects of autoantibodies derived from Post-Treatment Lyme Disease Syndrome patients on neurological dysfunction in mice

Authors: *K. MYKYTEN¹, P. GWYNNE², L. HU², C. G. DULLA¹;

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Abstract: Post-Treatment Lyme Disease Syndrome (PTLDS) is a condition that causes neurological dysfunction in a subpopulation of patients after acute Lyme Disease (LD) infection. PTLDS is characterized by a distinct set of neurological symptoms such as peripheral neuropathies, extreme fatigue, and cognitive difficulties. The cause of PTLDS is unknown and there are no clinical tests to identify patients who are positive for PTLDS. One theory is that PTLDS results from autoantibodies generated during the acute phase of LD infection, which then persist post-infection and cause long-lasting neurological dysfunction and damage despite clearance of the bacterial load. This suggests a need for a closer look at PTLDS from a

neuroscientific perspective.

Here we present a murine behavioral investigation of a potential neuro-autoimmune mechanism underlying PTLDS symptomatology. To test whether neurological dysfunction in PTLDS arises from an autoimmune mechanism, female 8-10 week-old C57 mice were injected with human serum from relevant experimental and control patient populations and underwent a series of behavioral tests related to PTLDS associated symptoms. Mice were injected with either saline (controls) or immunoglobulin isolated from blood serum collected from multiple patients groups, including 1) control patients from regions where LD is not prevalent and have not been exposed to LD (n=10), 2) patients previously infected with LD but did not have symptoms of PTLDS (n=10), and 3) patients previously infected with LD which progressed to PTLDS (n=10). Behavioral experiments were performed blind to the serum condition. Beginning with a baseline measurement before IgG injection, mice underwent behavioral testing daily for three days post-injection. Behavioral tests included Spontaneous Y-Maze Alternation, a forelimb Grip Strength Test, the Cold Plantar Assay, and the Hot Water Tail Immersion Assay. Mice were weighed daily to track general body condition. These tests were chosen as proxies for PTLDS symptoms, such as cognitive dysfunction (“brain fog”), musculoskeletal pain, fatigue, and thermal/mechanical sensitivity or numbness. We expect mice injected with PTLDS patient serum will exhibit lower cognitive function, motor output, and grip strength, as well as increased thermosensitivity in these tests. Behavioral changes in mice injected with serum from PTLDS patients would indicate a potential autoimmune component of disease pathology. Further understanding of this syndrome will significantly improve the outcomes of the PTLDS patient population not only in generating diagnostic tools but also in presenting pathways for treatment.

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Poster

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Title: The Effect of NLRX1 on Behaviour in a Multiple Sclerosis Mouse Model

Authors: *C. TOMLINSON¹, D. GRIS²;

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Abstract: Multiple sclerosis (MS) is the most prevalent neurological disease in young adults. It's triggered by activation of the innate and adaptive immune system targeting the central nervous system (CNS). MS is characterized by recurrent inflammatory events and chronic inflammation that lead to demyelination, axonal damage, neuronal death, and gliosis. MS negatively impacts quality of life due to general sickness behavior and a wide variety of lifelong MS-specific symptoms, including fatigue, mobility limitations, sleep disturbances, and cognitive decline. An interplay between innate and adaptive immune cells within the CNS is accomplished, in part, by activation of pattern recognition receptors, such as Nod-like receptors (NLRs), that regulate major proinflammatory pathways. One NLR that is ubiquitously expressed in mammals, NLRX1, inhibits inflammation, differentiation of encephalitogenic T cells, and reduces gliosis. The most common and widely accepted model for MS is experimental autoimmune encephalomyelitis (EAE). EAE replicates most of the pathophysiological features of MS, including activation of the innate and adaptive immune system, neuroinflammation, and key aspects of sickness behavior in mice.

We hypothesize that NLRX1 protects against MS. Female *nrlx1*^{+/+} (n = 8) and *nrlx1*^{-/-} mice (n = 8) in a non-obese diabetic background were induced with EAE at 9 weeks. Daily EAE scores were collected by two independent observers. The behavioral profile was evaluated using CleverSys, a behavioral monitoring software, and Python. The brains and lumbar spinal cords were extracted for the assessment of gliosis using immunofluorescence targeting CD11b and GFAP to measure microglia and astrocytic activation, respectively.

NLRX1 has a significant effect on the survival probability, progression, and behavioral changes throughout EAE. *Nrlx1*^{-/-} died significantly earlier than *nrlx1*^{+/+} mice (p value = 0.04). EAE scores indicate that *nrlx1*^{-/-} mice have a more severe onset of symptoms, shorter recovery periods, and an earlier transition from episodic to progressive disease (Kruskal-Wallis: p value < 0.05). Furthermore, locomotor- and feeding-related activities decreased while sleep-related and habituation activities increased at a significantly faster rate in *nrlx1*^{-/-} compared to *nrlx1*^{+/+} mice. Immunofluorescence quantification of the spinal cords and brains suggests an increase in gliosis in *nrlx1*^{-/-} mice. These results suggest that NLRX1 plays a critical role in the development and progression of EAE.

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Poster

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Topic: G.04. Neuroimmunology and Neurovirology

Title: Antinociceptive Effect of Grounding Mat on Trimethyltin-Induced Neurotoxicity in Rats

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Abstract: Grounding is a therapeutic technique that involves activities that electrically reconnect the body to the Earth. It has been explored for its potential to alleviate pain, inflammation, and neurotoxicity. Trimethyltin (TMT) is a potent neurotoxic compound known to induce pain and severe central nervous system damage, particularly neuronal death and neuroinflammation in the hippocampus. TMT is frequently used as an animal model to study pain and neurodegenerative disorders due to these effects, especially its ability to induce oxidative stress, inflammatory responses, and neurodegeneration.

This study investigated the effects of a grounding mat on pain relief and neuroprotection in rats with TMT-induced neurotoxicity. Pain responses and cognitive memory function were assessed using the Y-maze test and tail immersion test. Blood levels of interleukin (IL)-1 β , IL-4, prostaglandin E2 (PGE2), and hippocampal acetylcholinesterase (AChE) were measured using enzyme-linked immunosorbent assay (ELISA).

TMT administration resulted in increased pain responses, impaired memory, and elevated levels of IL-1 β and PGE2, along with a reduction in IL-4 compared to the normal group. Exposure to the grounding mat reduced pain responses and improved memory performance. It also led to decreased levels of IL-1 β and PGE2, and increased levels of IL-4 and AChE in the brain. These findings suggest that grounding may exert antinociceptive effects and enhance cognitive function by reducing inflammation and promoting neuroprotection in a neurotoxicity model.

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Poster

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Title: A neuro-immune circuit mediates cancer cachexia-associated apathy

Authors: *X. ZHU¹, S. STAROSTA², J. HOU⁴, Q. CHEVY³, F. LUCANTONIO³, R. MUÑOZ CASTAÑEDA⁶, F. ZHANG², K. ZANG³, F. FIOCCHI³, M. BERGSTROM⁴, A. SIEBELS⁷, M.

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Abstract: Cachexia, a debilitating wasting syndrome, arises in advanced stages of many chronic diseases such as cancer, leading to multi-organ failure and death. Cachectic patients experience weight and muscle loss, severe fatigue, apathy and clinical depression. Current treatments focus on preserving weight and muscle, while the motivational symptoms such as apathy and clinical depression are inadequately addressed. By training mice to do motivationally relevant tasks, we show that cachectic mice have a very specific motivational phenotype-- increased effort sensitivity, without affecting despair, anhedonia and movement. The development of cancer cachexia is associated with chronic inflammation. The pro-inflammatory cytokine, interleukin-6 (IL-6), is upregulated in both patients and mouse models of cancer cachexia. How the brain senses IL-6 and downregulates motivation in cancer cachexia remains unclear. To identify regions that are significantly activated in cancer cachexia, we did a whole brain c-fos screen and focused on the following regions of interest: area postrema (ArP), parabrachial nucleus (PBN) and nucleus accumbens (NAc). Using a mouse model of cancer cachexia, we identified a brain stem to basal ganglia circuit (ArP-PBN- substantia nigra pars reticulata (SNpr)- ventral tegmental area (VTA)- NAc) that senses IL-6 and reduces mesolimbic dopamine, leading to motivational deficits. The circuit we identified (ArP-PBN-SNpr-VTA-NAc) is distinct from previously described PBN- central amygdala (CeA) circuit which regulates food intake. Targeting key nodes of the circuit such as preventing IL-6 sensing in the ArP or boosting mesolimbic dopamine with a dopamine agonist in NAc rescued cachexia-induced motivational deficits but did not prevent anorexia or weight loss. These findings suggest a central neural circuit for the brain to sense inflammation and orchestrate behavioral changes, providing a link between chronic inflammation and depressive symptoms.

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Poster

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Topic: G.04. Neuroimmunology and Neurovirology

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Title: Intravenous chemotherapy in mice induces fatigue and effort-related motivational deficits

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Abstract: Chemotherapy commonly induces fatigue and motivational deficits (“chemo brain”), significantly diminishing patient quality of life, but the underlying neural circuits remain poorly understood. To investigate the brain pathways mediating these symptoms, we developed a clinically relevant intravenous (IV) cisplatin model that induces systemic inflammation while avoiding the local peritoneal inflammation associated with intraperitoneal administration. We used a serial injection regimen (2.3 mg/kg/day for 3 consecutive days), which minimizes off-target toxicities such as acute kidney injury seen in more aggressive dosing paradigms, allowing us to isolate key behavioral impairments. In our home-cage monitoring system, IV-cisplatin mice showed lower voluntary, running-wheel activity and higher effort sensitivity in progressive ratio tasks, pointing to an effort-related motivation deficit. Using c-Fos immunohistochemistry and in situ hybridization, we identified chemotherapy-induced neural activation within the area postrema (ArP) and the nucleus of the solitary tract (NTS), including — but not limited to — neurons expressing GFRAL, the exclusive receptor for the cytokine GDF15 implicated in chemotherapy-induced side effects. We also observed pronounced neuronal activation within the external lateral subdivision of the parabrachial nucleus (PBle), another cytokine-sensitive relay area. These findings establish an IV chemotherapy model that recapitulates human-like fatigue and motivational impairments, providing a foundation for future studies aimed at elucidating the neural circuit mechanisms underlying chemotherapy-induced behavioral symptoms.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.01/Z11

Topic: H.04. Emotion

Title: Drawn to Delight_A Vicarious Reward Paradigm Unveils Neural Circuits of Positive Empathy

Authors: *J. BYUN¹, J.-H. KIM³, H.-S. SHIN²;

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Abstract: Empathy fosters social bonding by enabling individuals to share affective states. However, the neural basis of positive empathy, particularly the transmission of rewarding emotions, remains elusive, partly due to the lack of robust animal models. In this study, we developed a novel rodent behavioral assay in which observer mice were exposed to conspecific demonstrators undergoing wireless medial forebrain bundle (MFB) stimulation (WBS), serving as an incentive reward. Observer mice exhibited real-time social preferences toward demonstrators receiving WBS, indicating vicarious reward perception. This behavioral phenotype was dependent on auditory sensation. Furthermore, observer mice formed a lasting rewarding memory, as evidenced by social conditioned place preference (sCPP) tested 24 hours post-conditioning, suggesting that the conditioning experience served as a strong social reward. Using whole-brain Fos-TRAP mapping and chemogenetic interventions, we identified the paraventricular nucleus of the thalamus (PVT) as a key node mediating these behaviors. Further optogenetic analyses revealed a critical projection from the PVT to the zona incerta (ZI), whose selective modulation was both necessary and sufficient for expressing vicarious reward. Notably, inhibition of the PVT-to-ZI pathway during a sucrose preference test did not alter direct reward-seeking behavior, suggesting that this circuit is specifically tuned to socially derived, rather than primary, reward processing. Collectively, our findings establish a robust animal model for investigating the neural substrates of positive empathy and highlight the specialized role of the PVT-to-ZI pathway in mediating socially transmitted rewarding experiences.

Disclosures: J. Byun: None. J. Kim: None. H. Shin: None.

Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.02/Z12

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Plasticity of Anterior Cingulate Cortex neuronal dynamics and neuromodulator release during reward associative learning

Authors: *M. CONGIU, B. LEONARDON, T. NEVIAN;
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Abstract: The ability to predict rewards from environmental cues is crucial for survival. This fundamental aptitude relies on the innate capability of the brain to associate neutral sensory stimuli to rewarding events that are proximal in time and/or space. This process requires the interaction of multiple cortical and neuromodulatory brain systems that interact together, ultimately leading to anticipatory behaviours. The anterior cingulate cortex (ACC) is an important cortical centre for integration of external stimuli and motor commands that contribute to goal-directed actions. Yet, it remains unknown how neurons in the ACC are engaged during reward associative learning and how neuromodulatory systems such as acetylcholine (ACh) and noradrenaline (NE) might shape this process. To investigate this question, we employed a head-

restraint behavioural paradigm where mice learn to associate an auditory cue (CS) to a reward (sucrose) during multiple days of training. We combined this behaviour with simultaneous two-photon imaging of ACC pyramidal neurons using the calcium sensor GCaMP6f. We discovered that ACC contains several functional ensembles encoding cue and reward associations. Specifically, we identified three important clusters that show plasticity after learning with various dynamics. Moreover, we carried out fiber photometry recordings to inspect ACh and NE release dynamics in the ACC during the learning task. Using ACh and NE biosensors (GRAB-ACh3.0 and GRAB-NE2h), we could detect release of both neurotransmitters in the ACC to auditory cues and reward and, notably, we observed plasticity of the release during learning. In conclusion, our study shows that pyramidal neurons of the ACC dynamically encode cue and reward associations during reward learning. Additionally, we observed that the release of neuromodulators such as ACh and NE, also evolve as mice learn to associate cues with rewards, possibly contributing to ACC pyramidal neuron dynamics and animal's learning process.

Disclosures: **M. congiu:** None. **B. Leonardon:** None. **T. Nevian:** None.

Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.03/AA1

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R01NS125877

Title: Learning modulates ventral striatal D1 and D2 medium spiny neuron dynamics

Authors: ***T. B. DAW**, J. CAO, R. LI, S. C. MASMANIDIS;
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Abstract: Associative reward learning depends on ventral striatal medium spiny neurons (MSNs), which express dopamine receptor type 1 (D1) or 2 (D2). Although both MSN types contribute to reward learning, the effects of learning on their firing dynamics remain poorly understood. We investigated how learning modulates the cue discrimination properties of D1 and D2 MSN populations. We utilized a classical conditioning paradigm in which mice learned to associate distinct olfactory cues with either unrewarded or rewarded outcomes (using sweetened milk as the reinforcer). Throughout learning of the task, we recorded from optogenetically identified D1 and D2 MSNs using silicon probes. For both anticipatory licking behavior and cue-evoked neural activity, we analyzed the learning-induced changes in selectivity index, a metric quantifying discrimination between the unrewarded and rewarded cues. Mice learned the cue discrimination task within a single session, demonstrated by anticipatory lick probabilities near 0% for the unrewarded cue and 100% for the rewarded cue. This rapid acquisition of the task enabled us to track populations of individual D1 and D2 MSNs throughout learning. Both D1 and D2 MSNs exhibited changes in their firing properties during learning, but to markedly

different degrees. D1 MSNs underwent a robust increase in selectivity index, driven primarily by decreased modulation in response to the unrewarded cue. Furthermore, D1 MSN selectivity correlated with behavioral selectivity. D2 MSNs exhibited less pronounced changes in both selectivity and cue-modulation across learning, and D2 MSN selectivity correlated less strongly with behavioral selectivity. Altogether, these results suggest differential roles for D1 and D2 MSNs during associative reward learning, whereby D1 MSN activity primarily drives the learning of stimulus discrimination.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.04/AA2

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Nacho's effects on nicotine reward

Authors: *K. A. MARQUEZ¹, J. I. VIDES VENTURA¹, B. DELIA¹, A. GONZALEZ¹, P. V. TRAN², Y. SHERAFAT¹;

¹California State Univ. San Marcos, San Marcos, CA; ²Dept. of Pediatrics, Univ. of Minnesota, Minneapolis, MN

Abstract: Nicotine is the main psychoactive ingredients found in tobacco products such as cigarettes and e-cigarettes. Continuous use of tobacco products such as cigarettes have been shown to be the leading cause of preventable death. When nicotine binds to nicotinic receptors within the reward pathway it, the receptors activate leading feelings of reward and pleasure. NACHO, a chaperone protein is a positive allosteric modulator for nicotinic receptors. Specifically, NACHO has been shown to aid in the assembly, trafficking and expression of alpha4beta2 nicotinic receptors that are important for enhancing the reinforcing effects of nicotine. For this study we utilized NACHO KO mice and wildtype mice to assess how the presence of NACHO impacts behaviors related to nicotine reward. In order to assess nicotine reward, all subjects completed the conditioned place preference task. The results from this test showed that NACHO KO displayed a significantly lower preference ratio compared to the wildtype mice. This indicates that removing NACHO aids in decreasing the reinforcing effects of nicotine. Pharmaceutical companies that aim to treat nicotine addiction can aim to reduce NACHO as a way to reduce nicotine seeking behaviors.

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Poster

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Location: SDCC Halls B-H

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Topic: H.02. Reward and Appetitive Learning and Memory

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Stanford Wu Tsai Neurosciences Institute Grant (to R.C.M.)

Title: Opponent regulation of striatal output pathways by dopamine and serotonin

Authors: ***D. F. CARDOZO PINTO**^{1,2}, M. Y. GUO², W. MORISHITA², M. B. POMRENZE², N. ESHEL², R. C. MALENKA²;

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Abstract: Classic theories propose opponent functions for striatal dopamine (DA) and serotonin (5-hydroxytryptamine; 5HT), with DA promoting approach and 5HT promoting patience or avoidance. How these neuromodulators regulate downstream circuits to achieve such antagonistic effects remains mysterious. Here, we used single cell RNAseq data to identify a subset of serotonin receptors expressed on striatal medium spiny neurons (MSNs), including members of the G_i-, G_q-, and G_s- coupled 5HT receptor families. We then used *in situ* hybridization to build a molecular map of 5HT receptor expression across striatal subregions and cell-types. Across subregions, we found that D1-MSNs expressed a mix of G_i-, G_q-, and G_s-coupled receptors while D2-MSNs were preferentially enriched with G_q-coupled receptors. Cell-attached recordings from genetically identified D1- and D2- MSNs revealed that DA and 5HT differentially modulate these striatal output pathways, with DA exciting D1-MSNs and 5HT exciting D2-MSNs. Similarly, pharmacologically upregulating DA or 5HT signaling *in vivo* preferentially induced expression of the immediate early gene *cfos* in D1- and D2-MSNs, respectively. Altogether, our results reveal striatal 5HT receptor expression motifs supporting the opponent actions of DA and 5HT in the striatum.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.06/AA4

Topic: H.02. Reward and Appetitive Learning and Memory

Support: 5R37DA032750-14

Title: Spatiotemporal heterogeneity of ventral striatum dynamics across cue-reward learning

Authors: *L. TIAN, G. D. STUBER;
Anesthesiol. and Pain Med., Univ. of Washington, Seattle, WA

Abstract: Dopamine release from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) is critical for reward learning and motivational behavior. The NAc is composed of medium spiny neurons (MSNs) expressing either D1 or D2 dopamine receptors, which are thought to respond to dopamine with opposing effects on plasticity and excitability. However, recent in vivo findings suggest more nuanced dynamics, raising key questions about how spatial and temporal patterns of dopamine release across NAc subregions shape MSN activity during associative learning. To characterize the diversity of MSN responses, particularly in underexplored lateral NAc regions, we trained head-fixed mice on a Pavlovian trace odor conditioning task using cues that predict sucrose reward with varying probabilities. Anticipatory licking served as a measure of learning, with mice achieving stable cue discrimination within 7-9 sessions. Throughout learning, we performed deep brain two-photon calcium imaging through recently developed microp prism lenses that allow for stable, large field-of-view recordings spanning the NAc core and lateral shell. This approach enabled longitudinal tracking of thousands of individual neurons across weeks of learning. We found that NAc activity to the cue was heterogeneous, with stronger excitatory responses developing in cue-responsive cells over the course of learning. In contrast, reward delivery elicited a largely homogenous inhibitory response across the MSN population, which increased in magnitude across learning. Individual NAc cells showed significant trial-to-trial variability, pointing to population coding of cue and reward responses. Ongoing studies aim to compare activity patterns between D1 and D2 MSNs and to measure dopamine release dynamics in the same behavioral paradigm using the fluorescent dopamine sensor GRABDA to map the spatiotemporal dynamics of mesolimbic dopamine and its relationship to MSN population activity. These findings reveal substantial heterogeneity in MSN responses during learning and establish a foundation for investigating how dopamine release shapes functional encoding across NAc circuits.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

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Program #/Poster #: PSTR179.07/AA5

Topic: H.02. Reward and Appetitive Learning and Memory

Support: AA030585

Title: A neutral CB1R antagonist, AM6527, alters spontaneous behavior and suppresses consummatory and motivational responses

Authors: *A. ECEVITOGLU^{1,2}, Q. FLANAGAN-BURT³, A. MAKRIYANNIS⁴, J. SUH^{3,2};
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Abstract: The cannabinoid type-1 receptor (CB1R) is a key modulator of feeding and motivational processes, with widespread expression in presynaptic terminals throughout the mesolimbic system. While CB1R antagonists have shown efficacy in reducing food intake and drug-seeking behaviors, their mechanisms of action, particularly in relation to dopamine (DA) signaling, remain incompletely understood. Here, we tested the effects of AM6527, a potent and orally bioavailable neutral CB1 antagonist, on a range of spontaneous, consummatory, and motivated behaviors in male mice.

Using motion sequencing (MoSeq, machine-learning assisted 3D video analysis), we found that AM6527 altered spontaneous behavior, notably increasing self-directed behaviors (e.g., grooming, scratching) and suppressing locomotor-related syllables at higher doses. In a home-cage drinking paradigm, AM6527 reduced consumption of natural reward, milk, but only at the highest dose tested. In operant paradigms, AM6527 dose-dependently suppressed correct nose poke performance on fixed ratio-3 (FR3) and progressive ratio (PR) schedules for milk reinforcement, with suppression most pronounced in high-baseline performers under PR schedules.

Given that CB1R antagonism is known to modulate the mesolimbic DA system, we co-administered various dopaminergic compounds (targeting DA1R, DA2R, DA transporter) to determine whether they could rescue the suppressive effects of AM6527 on motivated behavior. We observed that co-administration of DA-based compounds only partially reversed the AM6527-induced suppression of motivated behavior. These results suggest that the effects of AM6527 may be jointly mediated by the DA system and other brain regions. Ongoing work is focused on mapping responsive brain regions by assessing c-Fos expression through immunohistochemistry to better understand whether AM6527 engages distinct or overlapping neural circuits during operant and home-cage behaviors. Overall, these results provide new insight into how CB1R signaling shapes motivational output, offering a framework for developing CB-based interventions that selectively modulate appetitive drive.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.08/AA6

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Genetic and in-vivo analysis of striatal cAMP during reward learning

Authors: *A. HOLDER¹, J. LEE², A. SHERIDAN³, P. RAJEBHOSALE⁴, D. A. TALMAGE⁵, D. M. LOVINGER⁶;

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Abstract: Cyclic adenosine monophosphate (cAMP) is a key second messenger that mediates intracellular signaling cascades following neurotransmitter binding, playing a critical role in synaptic plasticity and learning. The striatum is a central neural substrate for reward-based learning, a well-established learning paradigm, where cAMP levels in medium spiny neurons (MSNs) are predominantly regulated by dopaminergic activity in a learning-dependent manner. The striatum is divided into the dorsal striatum (DS) and nucleus accumbens (NAc), each exhibiting distinct dopamine (DA) dynamics and differentially contributing to reward learning. DA acts opposingly on two main classes of striatal neurons: Gs-coupled D1-MSNs and Gi-coupled D2-MSNs. While the fundamental signaling mechanisms of DA are extensively studied, how this activity translates into cell- and region-specific cAMP signaling in-vivo and via molecular and genetic mechanisms remains unclear. To address this, we first analyzed single-cell RNA-sequencing (scRNA-seq) data from the Allen Brain Cell Atlas to identify region-specific differences in genes related to cAMP regulation. We validated spatial expression of sixteen molecular targets using RNAscope and quantified expression via normalized fluorescence intensity between DS and NAc, identifying a subset that were distinct in expression pattern across the two regions. In parallel, to examine how cAMP may differ by region and cell-type in-vivo, we developed a FRET-based biosensor (AAV-DIO-EPAC) delivered into D1- and D2-MSNs in DS and NAc, and monitored real-time cAMP activity using fiber photometry during reward learning in mice. Regional differences were observed in D1-MSNs, with fast and sharp increases in cAMP in the DS following cue presentation, while NAc exhibited slower, more prolonged responses. D2-MSNs demonstrated contrasting results, where cue-locked responses produced rapid cAMP dips, while reward-locked responses in DS revealed more gradual decreases in cAMP. These results suggest that both gene expression and in-vivo cAMP signaling vary significantly across striatal regions and cell types. Ongoing experiments aim to further characterize region-specific D2-MSN cAMP dynamics with varied behavioral paradigms. Together, these findings suggest that learning-related intracellular signaling cascades differ across neuron populations and brain regions, potentially underlying how distinct cells and circuits specialize in different aspects of learning.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

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Program #/Poster #: PSTR179.09/AA7

Topic: H.02. Reward and Appetitive Learning and Memory

Support: National Institute on Drug Abuse (R01 DA045783) and the State of California

Title: Wide-field Imaging of Nucleus Accumbens Dopamine Release in Behaving Mice with High Spatial and Temporal Resolution

Authors: *S. KANG, D. A. BURKE, V. K. NAMBOODIRI, J. D. BERKE;
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Abstract: Dopamine (DA) in the nucleus accumbens (NAc) plays a central role in reward learning and motivation. While photometry, voltammetry, and microdialysis have all provided valuable insights into NAc DA dynamics, they typically sample one or a few locations at a time with limited spatial and/or temporal resolution. This has hampered our understanding of how heterogeneous NAc DA signals over multiple spatiotemporal scales contribute to behavioral functions. To help address this, we used two-photon microscopy to image the DA sensor dLight 3.8 in awake, head-fixed mice implanted with micropisms (1.5 x 1.5 mm) in NAc. We used an electrically tunable lens to rapidly alter focal depth, enabling imaging of a substantial fraction of the NAc volume. Neuropil expression of dLight was visible over a broad excitation spectrum (760-960 nm). At longer wavelengths in this range we detected robust DA fluctuations both spontaneously and in response to sucrose liquid rewards. Imaging at high temporal resolution (up to 400 frames/s) revealed fast wave-like propagation of reward responses (~10 ms peak offset). Varying the rate of rewards (every 15 s or 75 s) revealed expectation-related “tonic” DA baseline shifts in select zones within NAc. After adding an auditory cue that predicted reward delivery 2 s later, we found that NAc DA cue responses were more spatially constrained than reward responses, and cue-responsive zones were complementary to zones with baseline shifts. Finally, as proof of principle of combining our imaging method with optogenetic control, we expressed ChRmine selectively in DA axons of DAT-Cre mice; we found that focal stimulation of this excitatory opsin evoked corresponding focal DA release. By simultaneously imaging and manipulating NAc DA at high resolution, our approach provides a powerful new framework for dissecting DA signals that drive adaptive behavior and can be disrupted in brain disorders including depression and addiction.

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Poster

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: International Center for Responsible Gaming
McKnight Brain Institute

Title: Pharmacological GLP1 Receptor Modulation Impacts Risk-Taking Behaviors and Corresponding Nucleus Accumbens Dopamine Responses In Rats

Authors: *Z. KRUMM¹, W. PYON², B. SETLOW³, J. L. BIZON⁴;

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Abstract: Predictions of expected rewards vs. costs are instrumental in several types of behaviors. Risk-taking behaviors rely on accurate and dynamic predictions of these variables to guide choice behavior, while extreme weighting of risk or cost is a feature of neuropsychiatric conditions such as substance use disorders (risk seeking) and anorexia nervosa (risk avoidance). Dopamine signaling in nucleus accumbens (NAc) circuits plays a fundamental role in mediating both expected and experienced rewards and costs, making it a compelling target for therapeutic modulation in conditions characterized by dysregulated risk-taking behaviors. Fortunately, pre-clinical evidence has identified the glucagon-like peptide 1 (GLP1) receptor agonist family of medications as modulators of NAc dopamine signaling, and initial clinical studies indicate that they may impact behaviors ranging from gambling to alcohol consumption. To determine if GLP1 receptor agonism can directly influence risk-taking behaviors, we evaluated the effects of acute administration of the GLP1 receptor agonist Exendin-4 (Ex4) on performance of a risky decision-making (RDT) task in 12-month-old Sprague-Dawley rats (n=8 male, 7 female). In this task, rats make discrete choices between two response levers, one that yields a small reward (1 food pellet) with no risk of punishment and another that yields a large reward (2 food pellets) accompanied by a mild foot shock that ranges in probability from 0 to 100%. The Ex4 (0, 0.1, 0.3, 1.0, 3.0 µg/kg in 0.9% saline vehicle, subcutaneous injection) was administered 1 hour prior to test sessions in the task, using a randomized, within-subjects design. Ex4 reduces choice of the large, risky reward (reduces risk taking) in a dose-dependent manner (two-way ANOVA, dose x risk, main effect of dose, $F_{(16,375)}=3.123$, $p<.001$ for males, $F_{(16,325)}=2.418$, $p=0.002$ for females). Trial omissions were significantly increased only at the highest dose (3.0 µg/kg), which was selected based on ability to reduce appetite. The magnitude of effect was larger in females compared to males. Co-administration of the GLP1 receptor antagonist Exendin-9 (Ex9) reduced the effect of Ex4 in a dose dependent manner, supporting a GLP1-GLP1 receptor-driven mechanism. Assessments of dopamine release in NAc during task performance via fiber photometry (GRABDA2m) demonstrate that Ex4 administration reduces both peak and area under the curve dopamine responses to reward/cost delivery in a dose-dependent manner, mirroring behavioral outcomes. Collectively, these data begin to inform the mechanism(s) by which the incretin family of medications influence risk versus reward-directed behaviors.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: Funding CF-2023-G-518 to RG

Title: Reward and aversion, two sides of the same glutamatergic and GABAergic neurons in the lateral hypothalamus

Authors: *L. A. RODRÍGUEZ-BLANCO¹, B. ARROYO², R. GUTIERREZ³;
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Abstract: Reward and aversion, two sides of the same glutamatergic and GABAergic neurons in the lateral hypothalamus

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Disclosures Luis Alfredo Rodríguez Blanco: none. Benjamin Arroyo: none. Ranier Gutierrez: none.

The lateral hypothalamus (LH) is crucial for coordinating adaptive behaviors by integrating sensory, cognitive, and motivational signals to guide reward-seeking and threat avoidance. While LH glutamatergic and GABAergic neurons are known to mediate opposing valence signals, the influence of their specific activity dynamics on reward and aversion behaviors within the same individuals remains incompletely understood. This study aimed to investigate how manipulating the activity of these neuronal populations with different optogenetic stimulation patterns affects behavioral outcomes. We expressed the inhibitory opsin stGtACR2 in Vglut2-ires-Cre and Vgat-ires-Cre mice and employed optogenetic inhibition during a real-time place preference (RTPP) task. In Vglut2-Cre mice, continuous pulsed inhibition of LH glutamatergic neurons induced place preference, indicating a rewarding effect. Conversely, despite stGtACR2's inhibitory nature, pulsed photostimulation of these same neurons at 5, 10, 20, and 50 Hz elicited frequency-dependent aversion. For Vgat-Cre mice, pulsed inhibition of GABAergic neurons at 10 and 20 Hz induced a place preference, whereas stimulation at 5 Hz and 50 Hz had no significant effect, and continuous inhibition did not alter behavior. In vivo electrophysiological recordings during RTPP revealed distinct glutamatergic neuronal ensembles responding either phasically to pulsed stimulation or continuous pulses, suggesting that aversive and rewarding responses are encoded by different firing patterns. Furthermore, in a negative reinforcement task, 20 Hz stimulation of LH glutamatergic neurons in the periphery of an open field induced a robust aversive effect in Vglut2-Cre mice, prompting increased visits to a stimulation-free center zone. These findings demonstrate that LH glutamatergic and GABAergic neurons differentially modulate reward and aversion behaviors depending on optogenetic stimulation parameters, underscoring the critical importance of considering stimulation frequency in experimental design and the interpretation of results related to LH function.

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Poster

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Topic: H.02. Reward and Appetitive Learning and Memory

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Title: Ensembles in the ventral hippocampus exert long-term control over habit-based behavior

Authors: *V. VALENTIN¹, S. L. GOURLEY²;
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Abstract: Habits are routinized behavioral patterns that can be elicited by environmental cues and occur almost automatically. The ventral hippocampus (vHC) is involved in the formation and execution of habits, and it can form stable ensembles controlling behavior. Here, we sought to investigate whether the vHC modulates habitual behavior via neuronal ensembles that remain functional throughout time. Using young mice, which are innately prone to display habit-like behavior, we tagged neurons that were active in the vHC during the execution of habit-like behavior. Later chemogenetic stimulation of these neuronal ensembles induced habit-like behavior under conditions in which mice typically demonstrate more goal-directed, flexible actions. Interestingly, though, chemogenetic inhibition of these ensembles did not block later habit-like behavior. Thus, neural ensembles in the vHC remain functional for long periods of time and are sufficient, but not necessary, to induce habitual response tendencies. We sought to further characterize these vHC ensembles by quantifying the overlap between neurons active during the formation vs execution of habitual actions. We found minimal overlap between cells active during habit formation vs execution, suggesting that the vHC recruits ensembles for habits that might change and drift over time. Future research will focus on understanding the specificity of these ensembles and what information they encode to promote habitual behavior.

Disclosures: V. Valentin: None. S.L. Gourley: None.

Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.13/AA11

Topic: H.02. Reward and Appetitive Learning and Memory

Support: T32 MH112507
BWF CASI 1019469

Title: Lateral habenula activity modulates reward-seeking behavior following aversive conflict

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Abstract: Major depressive disorder (MDD) is characterized by disrupted reward processing, often manifesting as reduced approach behavior and heightened avoidance. To investigate the neural basis of reward-seeking under conflict, we presented mice with unexpected foot shocks during reward acquisition, inducing a behavioral trade-off between avoidance (freezing) and approach. The lateral habenula (LHb), a hub interfacing with dopaminergic and serotonergic systems, has been implicated in both aversive and reward-related signaling. We hypothesized that LHb activity dynamically shifts between behavioral states and can influence an animal's ability to resume reward-seeking after aversive stimuli. Behaviorally, mice transiently suppressed reward-seeking for ~5 minutes post-shock and exhibited brief freezing bouts inversely correlated with licking behavior. Notably, mice exposed to shock without reward cues froze significantly longer, indicating that reward context buffers aversive responses. Fiber photometry revealed LHb suppression after shocks when reward was present, suggesting a role in encoding behavioral conflict. Slower return to lick strongly correlated with area under the curve. To probe causality, we optogenetically inhibited LHb neurons using ArchT during the post-shock phase. Inhibition significantly reduced reward retrieval compared to controls (2-way ANOVA interaction $F_{2,52}=4.93$, $P=0.0110$; Sidak's test, $P=0.0011$; $N=14$ per group), implicating LHb activity in promoting the return to approach behavior. These findings highlight the LHb as a key modulator of adaptive behavioral switching following aversive events, offering insight into neural mechanisms underlying motivational impairments in MDD.

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Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.14/AA12

Topic: H.02. Reward and Appetitive Learning and Memory

Title: A new theoretical framework for associative learning experiments: dopamine, Bayesian cause-effect learning, and causal reinforcement learning

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Abstract: The canonical temporal difference learning account of associative learning experiments, which posits that phasic dopamine signals reward prediction errors, appears to be in tension with experimental results showing that contingency (e.g., whether a cue is required for reward) impacts the learned value of a reward-associated cue. Attempts to explain these results generally invoke cause-effect learning, but either lack a rigorous theoretical foundation or are difficult to generalize. In this work, we present a Bayesian causal structure learning theory of these results that is simple, rigorously formulated, and easy to generalize across associative learning paradigms. According to the theory, animals experience continuous-time event sequences (e.g., cue, reward, cue, reward, ...) and use them to adjudicate between different possible underlying causal models (e.g., 'cue causes reward', versus 'cue and reward occur independently'). Dopamine is assumed to encode cause-effect prediction errors analogous to state transition prediction errors that can be used to learn the so-called successor representation. We discuss how this theory generically (i.e., without parameter tuning) explains contingency degradation experiments, as well as a plethora of other puzzling results in associative learning, like the observation that associations can be learned in fewer trials if each trial is longer. Finally, we discuss how this theory connects to causal reinforcement learning, and in particular defines a natural continuous-time analogue to the structural causal models usually used to formulate cause-effect learning.

Disclosures: J. Vastola: None.

Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.15/AA13

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R01MH135538

Title: Serotonin release in the Central Amygdala in appetitive and aversive behaviors

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Abstract: Anxiety and substance use disorders often co-occur and share overlapping neural mechanisms that influence maladaptive fear and reward learning. The central nucleus of the amygdala (CeA), a key region for integrating emotional information, plays an essential role in these processes. Additionally, dysregulated serotonin (5HT) signaling has been linked to both anxiety and addiction, however its role in reward and fear learning remains poorly understood. To investigate whether 5HT activity in the CeA tracks reward and aversive learning, we employed a 5HT biosensor to monitor real-time serotonergic release during operant reward and fear

conditioning in adult male and female C57BL/6 mice (8-12 weeks old, n = 15). We observed increased 5HT release during food consumption and a sustained elevation of 5HT levels while mice anticipated food during a delay period after performing an operant response. This sustained release diminished when rewards were made less predictable in a probabilistic omission task or when rewards were devalued through pairing with a mild footshock in our novel “FoodShock” paradigm. Moreover, in a fear conditioning setup, 5HT release spiked in response to footshocks and was similarly elevated by cues previously associated with the shock. These findings demonstrate that serotonergic signaling in the CeA dynamically tracks salient stimuli such as rewards and shocks, along with their predictive cues. This suggests that 5HT plays a role in both reward-based and fear-based learning. Furthermore, our results show that the sustained 5HT release during reward anticipation is sensitive to both the reliability and value of the reward, offering new insights into how CeA 5HT contributes to the neural circuits shared by anxiety and addiction.

Disclosures: E. Sethi: None.

Poster

PSTR179: The Nature, Neurobiology, and Computational Architecture of Reward

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR179.16/AA14

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIDA R21 DA052594
T32 DA7281
F31 DA062446

Title: Glucocorticoid receptor knockdown in a cortico-striatal pathway alters cue-reward learning without affecting the stress response

Authors: *P. FELIX¹, S. E. CHANG¹, J. P. HERMAN³, S. B. FLAGEL²;

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Abstract: Environmental stimuli, or cues, can guide our behavior in adaptive ways, bringing us closer to valuable resources like food. However, reward-associated cues can also elicit maladaptive and potentially psychopathological behavior. For instance, in substance use disorder (SUD), cues previously associated with drug use (i.e., paraphernalia) can trigger craving and relapse, even after long periods of abstinence. Such cues come to control behavior when they are attributed with incentive salience and thus transformed into powerful incentive stimuli. However, only some individuals are prone to attributing incentive value to reward-associated cues, and these individuals tend to lack inhibitory control over their behavior. Such behavioral disinhibition has been associated with insufficient top-down cortical control but the underlying neuromolecular mechanism remains to be determined. Here, we investigated the role of

glucocorticoid receptors (GRs) within a cortico-striatal pathway in the propensity to attribute incentive salience to a reward cue. Glucocorticoid receptors are critical modulators of stress response and have been implicated in stress-related psychopathologies, including SUD and impulse control disorders. Using transgenic Sprague-Dawley rats carrying a conditional GR knockdown allele, we selectively reduced GR expression in neurons projecting from the prelimbic cortex to the striatum. We then assessed the propensity to attribute incentive salience to a food-associated cue using a Pavlovian conditioned approach (PavCA) paradigm. Relative to wildtype controls, rats with GR knockdown exhibited greater sign-tracking behavior, suggesting that they were more likely to attribute incentive salience to the reward cue. Moreover, the degree of GR knockdown within the cortico-striatal pathway positively correlated with the tendency to sign-track. To determine whether GR knockdown in the same cortico-striatal pathway affects stress responsivity, we assessed plasma corticosterone (CORT) at four timepoints: before restraint stress (T0), immediately after a 30-minute restraint (T30), and during recovery (T60, T90). Although we observed significant sex differences in circulating CORT across timepoints, with higher levels in females, there were no genotype differences in baseline or stress-induced CORT levels. These findings suggest that GR within a top-down cortico-striatal pathway plays a critical role in regulating the motivational properties of reward-associated cues without altering the systemic response to stress.

Disclosures: P. felix: None. S.E. Chang: None. J.P. Herman: None. S.B. Flagel: None.

Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR180.01/AA15

Topic: H.04. Emotion

Title: Frontal midline theta enhancement is associated with mood changes during movie-watching

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²Grad. Sch. of Sci. and Technol., ¹Keio Univ., Yokohama, Japan; ³Keio Univ., Kanagawa, Japan

Abstract: The increase in the number of individuals suffering from mental health problems is a serious societal issue in modern society. In patients with depression or anxiety disorders, deviations in resting-state brain functional connectivity and amplitude of electroencephalogram (EEG) have been reported compared to healthy controls. These neural characteristics are suggested to be potential biomarkers of symptoms. Transient modulation of these metrics can be induced by stimulus presentation and linked with transient emotions; however, results have been inconsistent due to variability in stimulus types and insufficient validation of their effectiveness in reliably inducing mood changes. The establishment of standardized indices and application to clinical populations remain challenging. This study aimed to examine whether brain rhythms change along with mood swings induced by movie-watching, to explore the potential of EEG as

a biomarker for mental health. EEG signals were recorded from 22 healthy adults (mean age = 21.0 ± 1.0 years; 15 females) using a portable EEG system (electrodes placed at C3, Cz, C4, and Fz according to the international 10-20 system) while they watched emotionally evocative movie stimuli. The stimuli consisted of short movies classified by the experimenter as positive, neutral, or negative. Electrocardiogram (ECG) was also recorded to evaluate physiological responses. Personality assessments, stimulus evaluations, and cognitive tasks were conducted. A mixed-effects ANOVA on frontal midline theta activity during video viewing revealed a significant main effect of stimulus type ($p = 0.028$). Post hoc comparisons showed that theta power in the negative condition was significantly higher than in the neutral and positive conditions ($p = 0.028$, $p = 0.012$, respectively). Additionally, heart rate analysis showed a significant main effect of stimulus type ($p < 0.01$), with lower heart rate observed in the negative condition compared to the neutral and positive conditions (both $p < 0.01$). These findings suggest that mood and attentional changes induced by movie-watching may enhance activity in the anterior cingulate cortex, reflected as increased frontal midline theta rhythms. The EEG changes may also be accompanied by physiological responses such as heart rate modulation. EEG-based theta dynamics may thus offer a sensitive neural marker of transient affective shifts, supporting their potential for future use in noninvasive mental health monitoring.

Disclosures: **E. Iwashita:** None. **S. Iwama:** None. **J. Ushiba:** A. Employment/Salary (full or part-time): A representative director of LIFESCAPES Inc., receiving a salary and holding shares in the company, in which this research did not receive any equipment, financial support, or human resources..

Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR180.02/AA16

Topic: H.04. Emotion

Title: Emotionally Evocative Movie Stimuli Elicit Dynamic Brain State Transitions Linking SN, DMN, and CEN

Authors: ***E. SKOULLOU**¹, H. KANAZAWA², S. YONEKURA², Y. KUNIYOSHI³;
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Abstract: Emotions in real-world contexts unfold dynamically, engaging large-scale brain systems in time-varying configurations [Kragel & LaBar, 2016; Barrett & Satpute, 2013]. However, most fMRI studies utilize static paradigms, limiting insights into the temporal evolution of emotional states and the flexible engagement of distributed networks [Pessoa, 2008]. Here, we employed dynamic functional connectivity (dFC) analysis with naturalistic movie stimuli to examine how emotional processing reorganizes interactions among core cortical networks over time. We analyzed publicly available fMRI data from the StudyForrest project

[Hanke et al., 2014], in which 20 healthy adults (age 21-38 years, mean 26.6, 12 male) viewed the movie *Forrest Gump* (TR = 2s, TE = 22 ms, voxel size = 1.4 mm³, 36 slices, 3599 volumes across 8 segments, 7T MRI). After standard preprocessing and ICA-based denoising, group-level ICA identified intrinsic networks. The networks of interest—salience network (SN), default mode network (DMN), and central executive network (CEN)—were selected based on prior literature demonstrating their significance in emotion regulation [Seeley et al., 2007; Ochsner et al., 2012; Menon, 2011]. ICA components were categorized using spatial overlap with the Yeo et al. [2011] 7-network brain atlas. A sliding-window approach (30s) combined with k-means clustering (k = 6) [Allen et al., 2014] identified brain dFC states—recurring patterns of time-varying functional connectivity [Hutchison et al., 2013]. We consistently observed transitions from State 3, characterized by low connectivity and a neutral profile, to State 5, marked by increased coupling between SN and DMN (insula-PCC), DMN and CEN (MFG-ACC), and stronger within-DMN connectivity centered on the PCC. This emotionally engaged state emerged during segments of heightened narrative tension and affective salience. These transitions likely reflect detection of emotionally salient cues via enhanced SN-DMN coupling [Seeley et al., 2007; Menon, 2011], integrated with self-referential and autobiographical processing to assign personal meaning (Andrews-Hanna et al., 2014; Buckner et al., 2008). Concurrent DMN-CEN coupling suggests cognitive control mechanisms for evaluating and regulating responses [Ochsner et al., 2012; Etkin et al., 2015]. Together, these dynamic and reproducible reconfigurations support emotion-cognition integration during naturalistic experiences [Barrett & Satpute, 2013; Kragel & LaBar, 2016]. Future work will align these brain states with time-resolved emotional annotations from related studies using the same stimulus [Raz et al., 2016].

Disclosures: E. Skoullou: None. H. Kanazawa: None. S. Yonekura: None. Y. Kuniyoshi: None.

Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR180.03/BB1

Topic: H.04. Emotion

Title: The effect of exploring facial emotion diagnostic regions on emotion recognition in young and older adults: Evidence from the Moving Window Technique

Authors: *S.-Y. KIM¹, D.-E. LEE²;

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Abstract: Recent studies in young adults (YAs) have shown that exploring emotion-specific diagnostic facial regions (i.e., the eyes and mouth) enhances emotion recognition efficiency. In contrast, older adults (OAs) often exhibit age-related declines in accuracy and slower response

times (RTs), potentially due to changes in visual attention strategies. In the present study, we hypothesized that, as in YAs, prioritizing diagnostic regions would facilitate recognition efficiency in OAs. Thirty OAs (aged 65+) and 35 YAs (aged 18-30) completed a facial emotion recognition task using the Moving Window Technique. Participants viewed blurred facial expressions of six basic emotions (happiness, anger, sadness, disgust, fear, and surprise) through a mouse-controlled window and selected the appropriate label once the emotion was recognized. Two facial regions of interest (ROIs)—the eyes and mouth—were analyzed using two exploration metrics: (1) Spent Time (duration within each ROI) and (2) Last ROI (final region before response). Results showed that OAs were significantly slower and less accurate than YAs across all emotions (all $ps < .05$). Repeated-measures ANOVAs revealed significant three-way interactions (Spent Time: $F(4.2, 262.1) = 2.5, p < .05$; Last ROI: $F(2.8, 174.3) = 8.3, p < .01$), indicating that YAs focused more on diagnostic regions, while OAs explored them less. Multiple regression analyses showed that Spent Time predicted faster RTs for all emotions in YAs, replicating previous findings. In OAs, Spent Time predicted faster RTs only for eye-diagnostic emotions: “anger” ($F(1, 28) = 16.00, R^2 = .36, \beta = -49.33, p < .01$), “fear” ($F(1, 28) = 8.71, R^2 = .24, \beta = -63.75, p < .01$), and “sadness” ($F(1, 28) = 10.52, R^2 = .27, \beta = -46.29, p < .01$); and for the eye-and-mouth emotion, “surprise” ($F(2, 27) = 9.95, R^2 = .42$; eyes: $\beta = -39.25, p < .01$; mouth: $\beta = -57.78, p < .05$); but not for mouth-dominant emotions (“disgust” and “happiness”; all $ps > .05$). These findings extend prior research by demonstrating that prioritizing diagnostic facial regions supports emotion recognition efficiency in both age groups, particularly for emotions relying on eye-region cues. OAs’ lack of benefit from mouth-region exploration may reflect an age-related attentional bias, offering insight into mechanisms underlying emotion recognition decline in aging.

Disclosures: S. Kim: None. D. Lee: None.

Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

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Program #/Poster #: PSTR180.04/BB2

Topic: H.04. Emotion

Support: MH125615
MH112558
BCS2318984

Title: Neural Responses to Natural Versus AI-generated Affective Images

Authors: *Y. CHEN¹, R. FANG¹, A. KEIL², M. DING¹;

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Abstract: The International Affective Picture System (IAPS) contains 1,182 well-characterized photographs depicting natural scenes varying in affective content. These pictures are used

extensively in affective neuroscience to investigate the neural correlates of emotional processing. Recently, in an effort to augment this dataset, we have begun to generate synthetic emotional images by combining IAPS pictures and diffusion-based AI models. The goal of this study is to compare the neural responses to IAPS pictures and matching AI-generated images. The stimulus set consisted of 60 IAPS pictures (20 pleasant, 20 neutral, 20 unpleasant) and 60 matching AI-generated images (20 pleasant, 20 neutral, 20 unpleasant). In a recording session, a total of 30 IAPS pictures and 30 matching AI-generated images were presented in random order, where each image was displayed for 3 seconds with neighboring images separated by an interval of 2.8 to 3.5 seconds. Each experiment consisted of 10 recording sessions spread over two days. The fMRI data was recorded on a 3T Siemens Prisma scanner. Pupil responses to image presentation were monitored using an MRI-compatible Eyelink1000 Eyetracker. Our preliminary analysis of the fMRI data (N=10) showed that (1) both the IAPS pictures and the matching AI-generated images activated higher-order visual areas such as OTJ and components of the anterior emotion network such as the insula and (2) in the retinotopic visual cortex including V1, MVPA (Multivariate Pattern Analysis) classifiers built to decode emotional categories from voxel patterns activated by IAPS pictures could be used to decode emotional categories from voxel patterns activated by AI-generated images and vice versa, suggesting that the IAPS pictures and the matching AI images evoked similar neural responses in the brain. Efforts to confirm these findings are underway by recruiting additional participants. Analysis is also being expanded to include the comparison of such measures as functional connectivity and pupillometry.

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Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

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Program #/Poster #: PSTR180.05/BB3

Topic: H.04. Emotion

Title: Emotion-aware generative AI for cognitive behavioral therapy: a neurocomputational framework for simulating affective regulation

Authors: A. ANZER^{1,2}, *S. SINHA^{3,2}, A. ROY², C. DOMINIQUE²;

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Abstract: Affective dysregulation, driven by impaired top-down modulation of limbic structures, is a core mechanism underlying anxiety, depression, and digital addiction. Neuroimaging studies implicate dysfunctional cortico-limbic pathways—particularly between the prefrontal cortex (PFC) and amygdala—in poor emotion regulation. These disruptions reduce the brain's ability to reappraise emotional stimuli, increasing vulnerability to persistent negative affect and maladaptive behaviors. While Cognitive Behavioral Therapy (CBT) is known to

recruit these same neural circuits—especially dorsolateral and ventromedial PFC—through structured cognitive restructuring and behavioral activation, its reach is limited by access to trained clinicians and session frequency constraints. There is thus a critical need for scalable tools that emulate affective regulation mechanisms and provide continuous support between sessions. We present a **neuroscience-guided generative AI system** that simulates CBT dialogue and models emotion regulation dynamics. We are currently developing and validating an AI approach, using clinician-patient therapy transcripts from Alexander Street and the American Psychological Association. We have built a proof-of-concept using an annotated transcript from the Beck Institute (Judith & Abe) as follows. First, 229 therapist-patient exchanges were extracted. Next, each patient response was labeled using a transformer-based emotion classifier (distilroberta-base) and embedded into a fine-tuning prompt with therapist input and emotion context. A GPT-2 model was fine-tuned using Low-Rank Adaptation (LoRA; $r=8$, $\alpha=16$), conditioning language generation on affective state. A real-time dialogue interface was built using Gradio. The fine-tuned model successfully generated emotionally aligned responses reflective of CBT principles such as Socratic questioning, validation, and reframing. Model perplexity improved from 4.39 to 2.31 post-fine-tuning. An affect trajectory plot showed converging emotional resolution across multi-turn conversations. A crisis detection module flagged sequences with escalating negative affect (e.g., ≥ 2 turns of sadness or anger), with 96% precision on simulated escalation cases. Human review confirmed clinical coherence in 83% of AI responses. This work shows that generative AI, when guided by affective neuroscience, can simulate regulated emotional dialogue. The model provides a proof-of-concept for emotion-aware therapeutic co-agents and supports future integration of neurophysiological inputs for real-time affect modeling.

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Poster

PSTR180: Human Emotion

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Topic: H.04. Emotion

Support: JSPS KAKENHI 24H00810
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JSPS KAKENHI 24KK0189
JST PRESTO JPMJPR20C6

Title: Individual differences in AI anxiety are reflected in shared neural responses to AI-related movies across distributed cortical regions

Authors: J. WANG, *S. NISHIDA;

Ctr. for Information and Neural Networks (CiNet), Advanced ICT Res. Inst., Natl. Inst. of Information and Communications Technol. (NICT), Suita, Osaka, Japan

Abstract: The growing spread of artificial intelligence (AI) technology in our society has dramatically enhanced the convenience of our lives. At the same time, it has raised various human concerns about AI, collectively referred to as AI anxiety, such as fears that “AI will be out of control”, “AI will dominate us”, or “AI will replace our jobs”. Since AI anxiety can hinder the integration of AI into society, it is crucial to understand its neural basis to eliminate it fundamentally. However, this neural basis remains largely unclear. To gain important insights into the neural basis of AI anxiety, the present study investigated how individual differences in AI anxiety influence shared neural responses to AI-related information. We collected fMRI data from 56 participants while they viewed a series of AI-related movies. We assessed AI anxiety using a dedicated scale, along with other types of anxiety: generalized anxiety (State-Trait Anxiety Inventory), social anxiety (Liebowitz Social Anxiety Scale). In addition, participants provided preference ratings for each movie. We computed voxelwise inter-subject correlation (ISC) to assess shared neural responses during movie viewing and performed brain-behavior correlation analyses to examine the relationship between ISC patterns and individual traits and preferences. To identify the unique influences of AI anxiety on shared neural responses, independent of other anxiety traits and preferences, we conducted conjunction analyses between AI anxiety and the other measures. Our results showed that individual differences in AI anxiety scores were uniquely associated with shared neural responses in distributed cortical regions. These included the precuneus, posterior cingulate cortex, the lateral occipital cortex, and temporal regions, which are involved in various cognitive functions, such as visuospatial processing, episodic memory, and self-referential cognition. These findings provide novel insights into neural mechanisms underlying AI anxiety and contribute to the development of human-centered AI systems that are more broadly accepted by society.

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Poster

PSTR180: Human Emotion

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Topic: H.04. Emotion

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Title: Cortical thickness differences in auditory-reward regions between musically anhedonic and hedonic individuals

Authors: *S. HOMMA¹, S. HONDA^{1,2}, K. TAKAHASHI¹, T. ETANI^{3,5,6}, Y. TOBARI¹, Y. MIMURA¹, M. WADA^{1,7}, M. TAKANO^{1,8}, S. KOIKE⁹, M. MIMURA¹, H. UCHIDA¹, S. NAKAJIMA^{1,10}, S. FUJII⁴;

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Abstract: Musical reward refers to the pleasurable, emotionally positive, and motivational experiences evoked by music. Prior research has emphasized the role of auditory-reward system interaction in musical reward processing, including the superior temporal gyrus (STG), orbitofrontal cortex (OFC), nucleus accumbens, and insula. However, it remains unclear whether individual differences in musical reward may be related to the local neuronal structure of the auditory-reward system. Therefore, this study aimed to examine the association between musical reward and cortical thickness of the regions involved in the auditory-reward system. One-hundred-two individuals (47.6±16.4 years, 46 female [45%]) underwent T1-weighted magnetic resonance imaging scanning. Cortical thickness was estimated using Freesurfer, and normative modeling based on nonlinear regression of age and sex from 2312 healthy participants in a multi-site dataset was applied. Musical reward sensitivity was assessed using the Barcelona Music Reward Questionnaire (BMRQ). Based on the BMRQ scores, participants were classified as either the musical hedonic group (n = 47 [46%]) or the musical anhedonic group (n = 55 [54%]). We compared the age- and sex-adjusted cortical thickness of the predefined regions of interest (ROIs) (bilateral STG, lateral OFC, medial OFC, rostral anterior cingulate cortex, insula, nucleus accumbens, caudate, and putamen) between the groups using the analysis of covariance, controlling for musical training years. Additionally, we conducted partial correlation analyses between the BMRQ scores and cortical thickness both within each group and across all the participants, adjusting for musical training years. The results showed greater cortical thickness in the musically hedonic group compared to the anhedonic group in the bilateral STG ($F(1,99) = 6.74, p = .044$), the bilateral lateral OFC ($F(1,99) = 5.82, p = .047$), and the bilateral insula ($F(1,99) = 6.78, p = .044$) after a false discovery rate correction. However, no significant correlations were found between the BMRQ scores and cortical thickness in any of the ROIs. These findings suggest that people with higher musical reward sensitivity may exhibit enhanced structural development in brain regions involved in auditory-affective integration and reward evaluation.

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Poster

PSTR180: Human Emotion

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Program #/Poster #: PSTR180.08/BB6

Topic: H.04. Emotion

Title: Modulation of reward prediction errors by negative emotion

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Abstract: Reward prediction errors (RPEs)—the difference between expected and actual outcomes—are central to reinforcement learning and adaptive decision-making. They are typically encoded by midbrain dopaminergic neurons and reflected in activity across target sites in the striatum and prefrontal cortex. While the role of RPEs in guiding behavior through reward learning is well established, less is known about how emotional context—particularly task-relevant negative emotional information—influences this process. Studying how negative emotion shapes RPE processing is important for uncovering mechanisms underlying affective disorders, where reward learning is frequently impaired. In this fMRI study (N=32; 14 F; Age: 23.2±2.8 years), we investigated the modulation of RPE-related brain activity by negative emotion. We hypothesized that this modulation could be driven either by the valence or the salience of negative stimuli relative to neutral. Participants performed a guessing task in which they could win monetary reward. By design, each trial had either a high (80%) or a low probability (20%) of winning reward. Unknown to the participants, the outcomes on each trial were predetermined. In the initial localizer phase, outcome was conveyed via traditional monetary images (coin for reward, gray circle for no-reward) to identify standard RPE signals in the absence of emotional stimuli. In the following main phase, the outcome was indicated by an emotional image—either negative or neutral—mapped explicitly to indicate reward or no-reward outcome, with the mapping reversed across blocks. Trial-wise RPEs were computed using a Rescorla-Wagner model and incorporated into a general linear model as amplitude-modulated regressors for rewarded (positive RPE) and unrewarded (negative RPE) trials. In the localizer phase, replicating previous findings, RPEs elicited robust activation in the bilateral ventral striatum and substantia nigra/ventral tegmental area. Notably, in the main phase, a significant interaction between RPE type (positive vs. negative) and outcome emotion (negative vs. neutral) emerged in a right dorsolateral prefrontal cortex (dlPFC) cluster. In this region, we observed a reduction in the positive RPE related activity and enhancement in the negative RPE related activity when the outcome was signaled by a negative (relative to a neutral) image. These findings suggest that the dlPFC is engaged in the modulation of RPE signals by negative stimuli that is primarily driven by the competing valence between reward and emotional information. Overall, our study contributes to the emerging role of DLPFC in reward learning during affective contexts.

Disclosures: L. Taneja: None. S. Padmala: None.

Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR180.09/BB7

Topic: H.04. Emotion

Support: Natural Sciences and Engineering Research Council of Canada: Canadian Graduate Scholarship - Master's

Title: Imagined distraction regulates differential fear conditioning: Positively valenced distraction in the mind's eye

Authors: *M. A. J. ANDRIES, A. LYONS, V. I. CANTLEY, J. LOEPPKY, H. MAFURU, J. WERMIE, T. HANSON-OLIVEIRA, S. G. GREENING;
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Abstract: From mindfulness practices to imagined exposure, mental imagery is often implicated in the regulation of negative emotion. One empirically supported example is imagined distraction, where the goal-directed generation of a distracting mental image has been shown to inhibit the processing of the emotional stimulus, thus downregulating the emotional response. However, no research has evaluated whether a positively valenced mental image is a more effective distractor than a neutral mental image, or if differences in trait negative affect may alter the efficacy of imagined distraction. To address these gaps in the literature, 103 participants were recruited ($n_{\text{Female}} = 78$, $n_{\text{Male}} = 22$, $n_{\text{Other}} = 3$; $M_{\text{Age}} = 21.24$, $SD_{\text{Age}} = 4.82$). Sex differences were not evaluated. A differential fear association was first created. An Emotion Regulation phase followed, where participants either attended to the stimulus presented or visualized a neutral or positively valenced distractor. We primarily hypothesized that imagining a distracting stimulus would downregulate one's fear response when presented with a threat cue, as measured through the skin conductance response (SCR) and self-reported fear. Additionally, positively valenced imagery was predicted to regulate fear to a greater extent than neutral imagery. Exploratory analyses evaluated group differences in emotion regulation between individuals who scored high in trait negative affect versus controls. Self-reported fear and SCR measures revealed the successful acquisition and persistence of differential fear. Whereas the self-reported fear results supported only positively valenced imagery in the regulation of fear, SCR results revealed that both positively valenced and neutral imagined distraction had downregulated the differential threat response. No direct evidence for the increased efficacy of positively valenced distraction was found. Exploratory group effects proved nonsignificant, suggesting that trait negative affect did not significantly alter emotion regulation efficacy. Together, the present investigation informs the use of an effective emotion regulation strategy for those who struggle with emotion dysregulation.

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Poster

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Program #/Poster #: PSTR180.10/BB8

Topic: H.04. Emotion

Support: Robert W. Fuhrman Endowed Award for Student-led Research Fall 2024

Title: Does the predictability of threat cues influence REM sleep's effect on fear learning?

Authors: *J. WOOLRIDGE¹, A. KUNWAR², S. SANCHEZ^{1,1}, I. LERNER³;

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Abstract: Sleep, particularly Rapid Eye Movement (REM) sleep, plays a pivotal role in emotional regulation and fear memory consolidation. However, fear-conditioning studies show contradictory findings regarding whether REM sleep enhances or diminishes fear response during tests of fear recall and generalization. These discrepancies highlight the need to clarify how REM sleep modulates fear memories. In our previous study (Lerner et al., 2021), we have shown preliminary evidence that the degree to which neutral cues predict an upcoming threat could determine whether REM sleep will increase or decrease fear responses. However, this has not yet been studied by directly manipulating threat predictiveness. In the current study, a novel experimental paradigm was designed to investigate if REM sleep differentially affects fear responses for cues that are highly predictive of threat versus cues that are moderately predictive of threat. Healthy university students underwent a fear exposure session consisting of cues (colored shapes) that predicted an aversive image and sound with a reinforcement rate of 0% (CS-), 50% (CS+), and ~83% (CS++). Participants were then assigned to one of three groups: a sleep group, in which participants spent a full EEG-monitored night asleep at the lab prior to undergoing a fear recall testing session upon waking; a wake-delayed group, where participants spent the same amount of time awake prior to testing; and a wake-immediate group, where they were administered the testing session 10 minutes following exposure. During the testing session, participants were prompted to provide fear expectancy ratings to cues similar to the ones presented during exposure (without aversive stimuli applied). Preliminary analyses of fear expectancy ratings revealed that, unlike the wake groups who showed graded fear response from CS+ (highest) to CS- (lowest), the sleep group showed a similar degree of fear response to CS++ and CS+, both higher than CS-. Moreover, analysis of the associations between sleep stages and fear ratings revealed a trend towards a negative correlation between the percentage of time spent in REM sleep and fear recall to highly predictive cues. This pattern of results suggests that REM sleep may be decreasing fear response particularly to the highly predictive cues while having less impact on moderately predictive cues. We discuss the implications of these findings in terms of

recent models that propose REM sleep acts as a modulator of signal-to-noise ratio within memory representations.

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Poster

PSTR180: Human Emotion

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Program #/Poster #: PSTR180.11/BB9

Topic: H.04. Emotion

Support: SECIHTI: Beca Nacional #814473

Title: Resting-state eeg signatures reflect anxiety-social support interactions in young adults.

Authors: *D. NAVARRO NOLASCO¹, L. BELTRAN-PARRAZAL², L. LOPEZ-MERAZ³, A. MARTÍNEZ⁴, F. A. GARCÍA-GARCÍA⁵, C. MORGADO-VALLE⁶;

¹Inst. de Investigaciones Cerebrales - Univ. Veracruzana, Xalapa, Mexico; ²Univ. Veracruzana, Xalapa-Enriquez, Mexico; ³INSTITUTO DE INVESTIGACIONES CEREBRALES, Univ. Veracruzana, Xalapa, Mexico; ⁴Inst. de Neuroetología, Univ. Veracruzana, Xalapa, Veracruz, Mexico; ⁵Biomedicina, ⁶Univ. Veracruzana, Xalapa, Mexico

Abstract: Anxiety is an evolutionarily conserved emotion that can become maladaptive when regulatory mechanisms, including those of the medial prefrontal cortex (mPFC), fail. While perceived social support (PSS) acts as a behavioral buffer against anxiety, its neurophysiological correlates remain underexplored. This study investigates whether resting-state electroencephalography (EEG) power spectral density (PSD) patterns reflect the interaction between anxiety and PSS in healthy young adults. We hypothesize that distinct PSD profiles are associated with varying levels of anxiety and PSS, thereby indicating underlying neural mechanisms of emotional resilience. Resting-state EEG was recorded from 25 healthy adults (ages 20-24) using 21 electrodes arranged according to the international 10-20 system during 10-minute sessions with eyes open and eyes closed. Participants completed the Beck Anxiety Inventory (BAI) and the Multidimensional Scale of Perceived Social Support (MSPSS). After artifact correction via independent component analysis (ICA), PSD was computed across delta, theta, alpha, and beta frequency bands. Individuals with high BAI and low MSPSS scores exhibited left frontal delta asymmetry and right temporal attenuation in the alpha and beta bands. Participants with balanced BAI and MSPSS scores showed bilateral temporal activity across all frequency bands. Principal component analysis (PCA) accounted for 82.3% of the variance in the eyes-open condition and 78.9% in the eyes-closed condition. Linear mixed models confirmed significant interactions between BAI, MSPSS, and EEG clusters (R^2 range: 0.80-0.67). These findings suggest that resting-state EEG PSD patterns reflect specific interactions between anxiety and perceived social support, supporting a modulatory role of the mPFC in cortical dynamics underlying emotional resilience.

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Poster

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Location: SDCC Halls B-H

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Program #/Poster #: PSTR180.12/BB10

Topic: H.04. Emotion

Title: Brain metabolic networks related to pain, depression, and anxiety in cancer patients

Authors: *R. ITO¹, W.-Y. LIN², Y. ONO¹;

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Abstract: Cancer patients commonly experience pain and physical discomfort, especially pain and emotional distress. The coordinated activity within a brain network plays an important role in the perception of pain and psychological symptoms. The goal of this study is to identify the complex brain network of interconnected regions that may yield unique biomarkers for pain treatment. This study used glucose PET imaging to identify brain regions associated with these symptoms in 167 patients with head and neck or esophageal cancer. Patients were classified into three groups: the AP group, who experienced pain despite receiving analgesics; the AG group, who had good pain control with analgesic treatment; and the N group, who did not experience pain and were not receiving treatment. We investigated cortical activity and metabolic connectivity patterns to differentiate the AP group from the other two groups. We performed a one-way ANOVA followed by multiple comparisons on mean glucose uptake across the groups. Regions with significant differences were anatomically subdivided using AAL labels and defined as regions of interest for metabolic connectivity analysis. Significant group differences in glucose uptake were found in the right middle frontal gyrus (MFG), the bilateral middle cingulate cortex (MCC), the precuneus, the left amygdala and hippocampus, the bilateral cerebellum, and the pons. These results suggest hyperactivity in limbic and brainstem regions, as well as reduced activity in the default mode network (DMN) and central executive network (CEN), in patients with cancer pain. Metabolic connectivity analysis revealed coupling between the right superior frontal gyrus (SFG) and the right precuneus exclusively in the AP group. Additional couplings were observed in both the AP and AG groups: the bilateral cerebellum with the bilateral precuneus and right middle cingulate cortex (MCC), the right cerebellum with the left MCC, the right MCC with the right middle frontal gyrus (MFG) and SFG, the right MFG with the bilateral precuneus, and the left amygdala and the hippocampus with the right MFG and SFG. These patterns were absent in the N group. Altered connectivity between the cerebellum and the DMN/CEN, as well as changes in limbic-CEN coupling, have been reported in patients with pain or affective symptoms. Our findings confirmed similar network alterations in cancer patients with pain. The MFG or SFG may be a biomarker that can be therapeutically modified.

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Poster

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Program #/Poster #: PSTR180.13/BB11

Topic: H.04. Emotion

Support: National Natural Science Foundation of China under grant number 82272116.

Title: Unveiling Directional Cortical and Subcortical Brain Network Dynamics and Gamma Oscillation Signatures in Emotional Processing: A Multi-Center sEEG study

Authors: *Y. XU¹, B. WANG², J. LI², Z. WU³, L. CHEN⁴;

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Abstract: Emotion processing involves complex neural mechanisms across multiple brain regions. Despite a wealth of research on emotion processing, the spatiotemporal dynamics of emotional stimuli and the interaction between cortical and subcortical brain regions remain unclear. This study aimed to explore dynamic brain activity related to emotional stimuli in patients with stereoelectroencephalography (sEEG) recordings. Conducted across 4 centers in China, the study used emotional images to provoke positive, neutral, and negative emotions in 7 patients. The study focused on identifying region-specific neural dynamics and interregional connectivity in the thalamus, amygdala subregions, and visual cortex using event-related potentials (ERP), time-frequency analysis, and functional network connectivity. ERP analysis showed no significant differences in thalamus, basal nucleus, lateral nucleus, and paralamina nucleus in response to emotional stimuli. The thalamus exhibited N300 and P600 components, while amygdala subregions showed N300 components. Time-frequency analysis revealed enhanced gamma energy in the thalamus, basal nucleus, and lateral nucleus at 100 ms post-stimulus under negative emotional conditions, with no significant differences under positive or neutral conditions. V1 in the occipital lobe showed increased gamma energy at 300 ms for positive and negative stimuli. Beta energy showed minimal variation across conditions. The left hemisphere V1 exhibited minimal gamma response, while the right showed stronger enhancement. SVM decoding of occipital lobe activity yielded 67% accuracy. Feature extraction from emotional images via ResNet showed no clustering, indicating emotional responses were not confounded by visual features. Network analysis using PLV and DCM revealed strong connectivity between the occipital lobe and other regions at 300 ms, with bidirectional flow between the occipital lobe and paralamina nucleus, and unidirectional flow from the basal nucleus to the lateral nucleus. This study provides insights into the neural processes of emotion

processing, highlighting the role of the occipital lobe, thalamus, and amygdala subregions, and offering new pathways for future studies on emotion decoding and brain network interactions.

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Poster

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Topic: H.04. Emotion

Support: MOST 111-2410-H-A49 -049 -MY3

Title: Effects of multimodal integration on empathy for emotional communication in naturalistic social situations

Authors: R.-J. HUNG¹, Z.-R. CHEN¹, P. WANG¹, H. YEH¹, Y.-S. CHEN², *L.-F. CHEN¹;

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Abstract: Social interactions rely heavily on the triggering of empathic responses by visual and/or auditory cues; however, it remains unclear whether audiovisual emotional information elicits stronger empathic responses than auditory information alone. This study employed naturalistic communication tasks among friends to investigate the impact of audiovisual information on empathy for both positive and negative emotions. We initially recruited 40 friend dyads. Data from 13 dyads in the Audio-Visual group (5 males; mean age = 23.5 ± 3.26 , range = 20-35) and 17 dyads in the Audio-Only group (14 males; mean age = 23.44 ± 3.42 , range = 20-34) were retained for analysis. In the Audio-Visual group, each dyad sat face-to-face with the ability to see and hear one another. In the Audio-Only group, each dyad sat face-to-face with a plastic board positioned between them. Each dyad completed the task under two feedback conditions, administered in separate sessions: Feedback (FB) and No Feedback (NoFB). During the FB visit, the Empathizer was allowed to provide brief feedback. During the NoFB visit, the Empathizer listened in silence. Electroencephalographic (EEG) data were recorded using two 32-channel elastic caps during emotional communication tasks (Happy, Sad, and Neutral). The cortical activation of the preprocessed EEG signals was estimated using the standardized LORETA. Behavioral results revealed that audiovisual cues enhanced the accuracy of empathic accuracy, but only in the context of sadness ($p = 0.022$). The benefits of audiovisual information were also evident when empathizers had the opportunity to provide feedback ($p = 0.024$). Neural results revealed significant interactions among modality, emotion, and feedback only in the right temporal pole ($F(1, 58) = 14.83$, $p = 0.013$) and the right anterior fusiform gyrus ($F(1, 58) = 11.96$, $p = 0.045$), where alpha power was significantly lower under the Sad-NoFB condition than under the Happy-NoFB condition, but only when presented Audio-Visual cues. Moreover, alpha power was lower under the Sad-NoFB condition than under the Sad-FB condition, but only

when presented with Audio-Visual cues. These results suggested that the right ventromedial anterior temporal lobe is involved in the integration of multimodal information and empathic processing. This study highlights the importance of multimodal integration on empathy and its association with emotional and cognitive factors.

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Poster

PSTR180: Human Emotion

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Program #/Poster #: PSTR180.15/BB13

Topic: H.04. Emotion

Support: Aligning Science Across Parkinson's ASAP-020-519
R01-MH134000 (R.C.L.)

Title: High-resolution cardiac contractility tracks subjective emotion and the neural correlates of sympathetic arousal

Authors: *J. E. STASIAK¹, J. WANG¹, N. M. DUNDON¹, E. J. RIZOR², S. T. GRAFTON¹, R. C. LAPATE¹;

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Abstract: The sympathetic nervous system plays a central role in orchestrating autonomic responses to emotionally salient experiences, yet common sympathetic indices of emotion—such as electrodermal activity (EDA)—have relatively dispersed time courses, potentially obscuring rapidly unfolding processes underlying subjective emotion. Prior work has identified cortical and subcortical regions involved in sympathetic control in emotional contexts, including amygdalar and cerebellar nuclei and medial prefrontal areas (James et al., 2013; Henderson et al., 2012; Macefield et al., 2016; Critchley et al., 2000). Yet it remains unclear whether this circuitry modulates emotion-dependent changes across distinct sympathetic channels, or whether neural correlates of each channel track self-reported emotional intensity similarly. Here, we examined the neural correlates of sympathetic activity using two arousal indices: EDA and cardiac contractility measured via transradial electrical bioimpedance velocimetry (TREV; Stump et al., 2024), a measure of beat to beat cardiac sympathetic drive with comparatively faster temporal resolution and MRI compatibility (Bernstein et al., 2012). Participants (n = 67) completed a naturalistic emotion-induction paradigm involving an extended (18s) countdown to unpleasant or mild electric shock while TREV derived cardiac contractility, EDA, emotional intensity ratings, and fMRI data were collected. Cardiac contractility was positively associated with EDA ($p < 0.001$) and predicted subsequent emotional intensity ratings ($p < 0.001$), supporting its validity as a sympathetic marker that reflects subjective emotional arousal. During anticipation of

unpleasant (vs. mild) threat, increased contractility was associated with higher activation in regions previously implicated in sympathetic control, including the middle frontal gyrus, angular gyrus, and cerebellar lobules VI, Crus I, and Crus II (cluster corrected $z > 2.3$, $p < .05$; Henderson et al., 2012; Critchley et al., 2000)—effects not observed for EDA. Moreover, overlap between activation associated with greater contractility and subjective emotional intensity during anticipation of unpleasant (vs. mild) threat was found in the angular and supramarginal gyri, regions implicated in integrating sensory input with emotionally salient contextual features (Gottlieb, 2007; Ramanan et al., 2018; Beissner et al., 2013). Together, these findings suggest that cardiac contractility uniquely tracks shared physiological and experiential emotion processes and support TREV as a promising tool for noninvasively capturing dynamic arousal with high temporal specificity.

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Poster

PSTR180: Human Emotion

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Topic: H.04. Emotion

Support: JSPS KAKENHI (grant number 17K12063)

Title: Neural mechanisms underlying the counting auditory desensitization technique for dental fear: a functional magnetic resonance imaging study

Authors: *H. KARIBE¹, M. KOEDA², S. TANAKA¹, Y. KATO¹;
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Abstract: Background: Dental fear remains a prevalent condition, with approximately 80% of individuals in Japan reporting some degree of fear, leading to avoidance of treatment. Among the various triggers, auditory stimuli, such as the sounds of the high-speed handpiece and vacuum suction, are particularly aversive. In clinical settings in pediatric dentistry, the “counting method”—a psychological approach in which the dentists count from one to 10 during drilling procedures—has been employed to mitigate anxiety. However, neurobiological evidence supporting its efficacy is lacking. The present study investigated the neurofunctional correlates of auditory stimuli related to dental procedures and objectively evaluated the cognitive modulation induced by the counting method. Methods: Nineteen right-handed healthy adults (9 women and 10 men; average age, 33.9 years) participated in a functional magnetic resonance imaging (fMRI) study. All individuals had previously undergone a dental treatment experience. Three auditory conditions—drilling sound alone, counting sound alone, and drilling sound combined with counting—were presented in a block design paradigm. Brain activities during the presentation of these sounds were evaluated by contrast fMRI BOLD signals. Emotional

responses were assessed post-hoc using a visual analog scale measuring valence, arousal, aversiveness, fear, and perceived pain. Results: The fMRI analyses demonstrated that, while the drilling sound alone elicited minimal activation in the left superior temporal gyrus (STG), the counting sound and the combined condition elicited significantly greater bilateral STG activation (one-way analysis of variance [ANOVA], $p < 0.001$). Notably, the combined condition demonstrated attenuated emotional responses compared to the drilling sound alone, particularly in the fear and pain measures (one-way ANOVA, $p = 0.041$ and 0.002 , respectively), suggesting a potential recontextualization of the auditory input via cognitive engagement. Conclusions: These findings provide the first functional neuroimaging evidence that counting modulates auditory processing in a manner that may reduce emotional reactivity to aversive stimuli. Such modulation may serve as a cognitive coping mechanism that promotes attentional redirection and emotional desensitization. Future studies are warranted to explore its application in clinical populations with dental phobia and further elucidate its long-term efficacy and neural mechanisms.

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Poster

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Topic: H.04. Emotion

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UCSF RAP 7504825

Title: Unique brain activations based on awe type

Authors: *Z. NAEEM^{1,2,3}, M. ALI^{1,2}, J. TOWNSEND^{1,2,3,4}, A. T. VU^{1,2,3};

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Abstract: Awe is a self-transcendent emotional experience known to dampen default-mode network activity, increase prosocial behavior, and improve overall well-being. Emerging functional magnetic resonance imaging (fMRI) studies on awe have relied exclusively on natural scenes to trigger the emotion. However, recent research has identified 8 highly salient awe types, with the top five being moral beauty, collective effervescence, nature, music, and visual design (Keltner 2024). The neural response to distinct awe types remains unknown, raising questions about how the brain processes differential self-transcendent experiences, and which types elicit greater prosocial behavior. Our study aims to fill this gap by examining the brain's response to category-specific awe stimuli. We catalogued videos (41s) from collective effervescence (CE), universe (UNI), visual design (VD), and nature (NAT) categories, which were then rated using a

shortened version of the AWE Experience scale (n=7 raters). Awe videos showed a significant difference in awe intensity compared to neutral videos ($p < .0001$). After choosing the top 4 awe-inducing clips per category, we used fMRI to probe brain representations of each awe type (n=3, 1 participant excluded for motion). During the scan, participants watched randomized awe clips from the 4 categories, and were also presented with a neutral and blank condition (TR/TE: 1000/30ms; 2.4x2.4x2.4mm³ voxel size; 60 slices; FOV: 216x216x144mm³; multiband 5). To enhance awe immersion, we used a custom projector screen that increased the visual field of view by over 50% (25°x45°). Z maps were calculated using FMRIB Software Library's generalized linear model. Clusters were thresholded at $Z > 2.0$ with a corrected cluster significance threshold of $p = 0.05$. Preliminary results across all 3 subjects show that CE activated the middle temporal gyrus (MTG), an area linked to facial emotion and motion processing, and deactivated frontal pole regions. UNI stimuli elicited significantly less overall brain activity than its neutral contrast, hinting at awe quieting the brain. Similarly, VD and NAT produced less overall activity, with NAT's neutral contrast activating frontal regions absent during awe. All awe types versus neutral showed significant bilateral occipital activation and reduced frontal lobe activity. Taken together, these results paint the first neural portrait of awe's distinct activation profiles. Current work includes increasing our sample, including physiological data, and investigating functional activation and connectivity differences between awe types.

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Poster

PSTR180: Human Emotion

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Program #/Poster #: PSTR180.18/CC1

Topic: H.04. Emotion

Support: Academy of Nutrition and Dietetics

Title: Assessment of Academic Stress, Eating Behaviors, and Dietary Intake in Graduate and Health Professional Students

Authors: *P. R. BURGHARDT;
Wayne State Univ., Detroit, MI

Abstract: Background: A binary relationship has been proposed between psychological stress and maladaptive eating behaviors leading to weight gain and obesity (Bremner, 2020). Yet this interaction has not yet been elucidated in graduate and health professional students, a population known to have high academic stress and poor diet quality. **Methods:** Thirty graduate and health professional students from Wayne State University completed the Perception of Academic Stress (PAS) questionnaire and the Three Factor Eating Questionnaire (TFEQ-18) to assess academic stress and eating behavior, respectively. Energy intake (EI) was calculated from 3-day food logs that included 2 weekdays and 1 weekend day. We are currently collecting data at end of Winter

semester to examine the interactions between stress induced eating behaviors and diet intake over the course of the academic year. **Results:** At the start of Fall semester, we found that high Emotional Eating scores associated with increased EI ($P=0.02$). Controlling for sex revealed that female students with high academic stress also reported high EE scores ($P=0.03$) and male students with high academic stress reported increased EI ($P=0.03$). **Conclusion:** Our preliminary results suggest that academic stress may promote emotional eating potentially perpetuating increased energy intake in graduate and health professional students. These relationships appear to be influenced by sex as females who reported lower academic stress also reported less emotional eating, whereas high academic stress in males associated with increased EI without changes in EE. Understanding the relationship between stress, eating behaviors, and dietary intake have important implications for uncovering the relationship between stress and obesity.

Disclosures: P.R. Burghardt: None.

Poster

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Program #/Poster #: PSTR180.19/CC2

Topic: H.04. Emotion

Support: NIH R01-MH127006

Title: The Mood-Sensitive Brain: Aperiodic Slope Mirrors Negative Affect

Authors: *Y. Y. REED¹, M. MOCCHI², B. A. METZGER³, R. MATHURA¹, B. PASCUZZI⁴, S. PULAPAKA⁵, L. S. MATTAR¹, A. J. WATROUS¹, E. BARTOLI¹, J. ADKINSON¹, V. KRISHNAN¹, A. MAHESHWARI¹, L. LIN¹, C. D. HACKER⁶, X. FAN¹, K. BIJANKI¹; ¹Baylor Col. of Med., Houston, TX; ²Univ. of Iowa, Iowa City, IA; ³Swarthmore Col., Swarthmore, PA; ⁴Virginia Commonwealth Univ., Richmond, VA; ⁵Univ. of the Cumberlands, Williamsburg, KY; ⁶Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Objective: Mood disorders significantly reduce quality of life and are often difficult to monitor using self-report alone. Identifying reliable neurophysiological markers of affective symptoms is a critical goal for improving clinical assessment and guiding targeted interventions. Prior work in treatment-resistant depression (TRD) found that a flatter aperiodic 1/f slope in the affective salience network (ASN) corresponds to lower depression severity. The current study examined whether this relationship generalizes to a broader population and whether positive and negative affective scores are differentially associated with aperiodic neural activity across the ASN. Methods: Seventeen adult participants (ages 18-54; 9 female/8 male) undergoing intracranial monitoring completed two mood inventories: the Computerized Adaptive Test for Depression Inventory (CAT-DI) and the Positive and Negative Affect Schedule (PANAS). Resting state electrophysiological recordings were obtained, and aperiodic slope was extracted from regions within the ASN, including the ventromedial prefrontal cortex (vmPFC), and

amygdala. Correlational analyses were performed between slope and mood scores. Results: A flatter 1/f slope in the vmPFC was significantly associated with lower depression severity (CAT-DI; $p = 0.001$). The vmPFC slope was also significantly associated with PANAS negative affect ($p = 0.011$). Amygdala slope was not associated with CAT-DI or PANAS positive affect but was significantly correlated with PANAS negative affect ($p = 0.018$), consistent with the amygdala's role in negative affective processing. Conclusion: These findings support the generalizability of aperiodic slope as a neural correlate of mood-related brain states, extending prior work beyond TRD to a broader sample. The relationship between slope and negative affect highlights its potential as a noninvasive mood biomarker. As a next step, we plan to investigate whether specific high-arousal PANAS descriptors (e.g., "jittery," "upset") show stronger associations with slope variation in salience-related regions, offering a more fine-grained view of how affect is encoded in the brain.

Disclosures: **Y.Y. Reed:** None. **M. Mocchi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent Pending: 63/592,453. **B.A. Metzger:** None. **R. Mathura:** None. **B. Pascuzzi:** None. **S. Pulapaka:** None. **L.S. Mattar:** None. **A.J. Watrous:** None. **E. Bartoli:** None. **J. Adkinson:** None. **V. Krishnan:** None. **A. Maheshwari:** None. **L. Lin:** None. **C.D. Hacker:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent Pending: 63/592,453. **X. Fan:** None. **K. Bijanki:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); US Patent Pending: 63/592,453.

Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR180.20/CC3

Topic: H.04. Emotion

Title: Evaluating predictive models of affective processes across multiple affective domains

Authors: ***M. KWON**¹, P. A. KRAGEL², T. D. WAGER¹;

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Abstract: Machine learning-based neuroimaging models ("brain signatures") have emerged as powerful tools for predicting mental states and behaviors, serving as potential objective metrics for subjective experiences. While numerous signatures have been developed for specific affective processes, significant questions remain about how these signatures perform across different contexts and what they tell us about how affective processes are represented in the brain. Addressing these questions requires systematic evaluation across diverse contexts and examination of the neural representations these models capture. This study systematically evaluated 28 published brain signatures across pain, appetitive, aversive, and cognitive control

domains using a large-scale dataset from the Affective Neuroimaging Consortium (N=990). We calculated signature responses (cosine similarity between signatures and individual fMRI contrast maps) to assess within-domain consistency and cross-domain specificity. We then reconstructed activation patterns from decoding weights using structure coefficients (Haufe et al., 2014) and applied multidimensional scaling to analyze their representational similarity, characterizing the neural organization underlying different affective processes. Results revealed domain-dependent variation in signature performance. Pain signatures (e.g., Neurological Pain Signature; Wager et al., 2013) showed high within-domain generalizability across different pain subtypes. In contrast, aversive signatures demonstrated low specificity, responding to appetitive stimuli, and limited within-domain generalizability. Multidimensional scaling of reconstructed activation patterns revealed that pain and appetitive signatures formed tight, distinct clusters, while aversive signatures showed greater heterogeneity, subdividing based on stimulus modalities (e.g., visual, auditory). Our findings suggest fundamental differences in neural organization across affective domains: pain appears to have a more consistent neural implementation across contexts and individuals, while aversive processes show greater variability and context-dependence. These results demonstrate the importance of rigorously establishing boundary conditions for brain signatures and suggest that some affective processes show more intrinsically coherent neural constructs than others, potentially due to their more direct sensory basis or more consistent implementation across studies.

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Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR180.21/CC4

Topic: H.04. Emotion

Title: Taming Mind and Body: Mindfulness Training Buffers Stress and Mood Reactivity While Protecting Cognitive Functioning

Authors: *G. BATCHALLI MARUTHY¹, A. M. CAMPOS¹, G. CUMMING¹, S. RODRIGUEZ¹, S. RAMAKRISHNAN¹, B. RYPMA²;

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Abstract: Mindfulness-based interventions (MBIs) have become increasingly popular in treatment of physical and emotional disorders, but their mechanisms of action remain elusive. Given that stress impairs emotional and cognitive functioning, we aimed to assess how MBIs may promote resilience to stress-related challenges. We hypothesized that MBIs might exert palliative effects upon one's ability to process and regulate emotions induced by environmental stressors. Furthermore, we aimed to understand how cognitive control and inhibition mechanism may be linked to emotion regulation after training. Participants were divided into either a

training group that received mindfulness training for a period of 8 weeks or an active control group that received relaxation training wherein they listened to instrumental classical music for the same duration. Both groups performed attention tasks before and after the 8 weeks of training or music listening. To assess the effects of mindfulness training on preservation of mood and attention control, both groups of participants were subjected to stress by mood induction procedures. Negative affect was induced through a combination of somber music and self-referential prompts. Trait mindfulness was assessed using both the Five-Facet Mindfulness Questionnaire (FFMQ; measures mindfulness as a multidimensional construct) and the Mindfulness Attention and Awareness Scale (MAAS; measures mindfulness as a unidimensional construct). Forty-eight participants were recruited. Analyses focused on 20 participants (19 - 81 years; 3 males and 17 females) who completed all sessions. Paired t-tests were performed to examine within group differences after mindfulness training and the active control. In general, the mindfulness trained group had a reduction in symptoms of depression (p -value = 0.016). They also had more positive affect (p -value = 0.054) and had minimal or no changes to mood reactivity suggesting a buffering effect of training on negative affect. Mindfulness-trained participants also had improved orienting (p -value = 0.061) compared to control participants. These results suggest that mindfulness training, specifically focused attention training, exerts beneficial stress-buffering effects on attention mechanisms.

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Poster

PSTR180: Human Emotion

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Program #/Poster #: PSTR180.22/CC5

Topic: H.04. Emotion

Support: P20GM13044701A1
Program of Excellence Funds

Title: Alpha Amylase Reactivity in Response to Virtual Trier Stress Test Across Adulthood

Authors: *J. N. BEADLE¹, D. E. WARREN²;

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Abstract: Neuroendocrine-based stress reactivity to in person social situations has been established in healthy adult populations by measuring cortisol and alpha-amylase. However, less is known about hormonal stress reactivity to social stressors in a response to virtual social interactions across the adult lifespan. Furthermore, it is unknown how social emotions, such as empathy, affect alpha-amylase stress reactivity in response to a virtual social stressor across the adult lifespan. The present study utilized a new virtual version of the Trier Social Stress Test

(vTSST) conducted over an online video conferencing platform. The study examined a sample across the adult lifespan and included healthy adults aged 19-86 (N=54; Mage=55.85; Medu=16.09; 64.8% female). We examined their social emotions (empathy) in the moment and their alpha-amylase reactivity to the vTSST. We found that their empathic responses to vTSST were positively correlated with their average alpha-amylase levels across the Trier ($r(50)=.41$, $p=.004$). We conducted a linear regression and found that average empathic concern was positively associated with average alpha amylase responses to the vTSST (Overall model: $p=.005$; $R^2=.24$; empathy $\beta=.32$; $p=.02$; age $=.29$; $p=.03$). This relationship remained after accounting for gender and age. Individuals with higher empathic responses to the vTSST had higher alpha-amylase levels, suggesting a more reactive stress responses to this social situation. It may be that individuals with higher social emotional reactivity may experience greater stress in response to situations involving a social stressor. Future studies may investigate whether this extends to in person social stressors.

Disclosures: J.N. Beadle: None. D.E. Warren: None.

Poster

PSTR180: Human Emotion

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Program #/Poster #: PSTR180.23/CC6

Topic: H.04. Emotion

Support: NIMH Grant R01MH122431

Title: Medial-excitatory and lateral-inhibitory networks in the human brain control emotion-related sympathetic outflow

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Abstract: The neural mechanisms underlying changes in sympathetic nervous system outflow during emotions are not well understood. While human neuroimaging studies have advanced neural network models that produce autonomic outflow, non-invasive brain recordings have limited temporal resolution. Here, we use high temporal resolution intracranial recordings from nine participants to investigate the functional organization of the sympathetic control network subserving human emotion. In this work, participants watched a series of emotion-eliciting video clips chosen to evoke amusement, disgust, awe, fear, sadness, or nurturant love (mean video-clip number = 132 ± 91 SD) while skin conductance, a sympathetic measure, was monitored. We used fronto-temporo-insular activity to generate network-level models that predicted continuous skin conductance on the millisecond timescale with high accuracy (mean correlation coefficient = 0.38 ± 0.15 SD). The network model weights show medial nodes exhibit excitatory control, while lateral nodes exhibit inhibitory control of skin conductance. Additionally, electrical

stimulation mapping in five participants shows medial node stimulation generates skin conductance while lateral node stimulation suppresses skin conductance. Overall, these findings show a medially distributed excitatory network and a laterally distributed inhibitory network that reciprocally controls emotion-related sympathetic outflow.

Disclosures: P.W. Hullett: None. Q.R. Greicius: None. A. Lin: None. E.F. Chang: None. V.E. Sturm: None.

Poster

PSTR180: Human Emotion

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Program #/Poster #: PSTR180.24/CC7

Topic: H.04. Emotion

Title: Mapping Well-Being's Neural Architecture: Functional Connectivity and Small-World Topology Dissociate Happiness, Meaning, Psychological Richness, and Distress

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Abstract: Subjective well-being—hedonic happiness, eudaimonic meaning, and psychological richness (PR, a life rich in novelty and perspective change)—lacks clear neural differentiation. We analyzed Human Connectome Project resting-state fMRI (n=915 adults, 22-35 y, mixed sex) to map functional connectivity (FC) and small-world topology of these dimensions plus anxiety and depression. PR was a five-item composite indexing experiential diversity and cognitive exploration (NEO Openness, reverse Risk-Avoidance, Self-Efficacy, Dimensional-Change Card-Sort, Penn Matrix Reasoning; z-scored, $\alpha=.72$). Happiness was indexed by NIH Positive Affect, with NIH Life Satisfaction (LS) secondary. Happiness, meaning (NIH Meaning-Purpose), PR, anxiety, and depression (DSM scales) were predicted using connectome-based predictive modeling and nested 10-fold Lasso (Schaefer-400 atlas, $p<.01$). Automated CPM/Lasso ensured no bias. PR sub-indices were examined: Experiential Diversity (Openness + Risk) and Cognitive Exploration (Self-Efficacy + Card-Sort + Matrices). Small-worldness (σ), clustering, path length computed from 15%-density graphs. Preprocessing used ICA-FIX and motion censoring (FD<0.2 mm). FC predicted outcomes (R^2 , SE $\approx$.02: happiness .08, meaning .10, PR .07, anxiety .09, depression .08). Happiness mapped to salience-executive (SN-ECN) coupling; meaning to modular default-mode (DMN); PR to distributed DMN-ECN-SN integration; LS, secondary, shared SN-ECN coupling. Experiential Diversity linked to SN-ECN ($R^2=.06$); Cognitive Exploration to ECN-DMN ($R^2=.06$). PR correlated with happiness ($r=.35$, $p<.01$) and meaning ($r=.40$), with neural overlap (cosine=.46, .58). Adding σ improved PR and happiness predictions ($\Delta R^2\approx.02$, SE $\approx$.01, $p<.05$); clustering/path length were negligible. Anxiety/depression showed limbic-control dysconnectivity. Split-half replication confirmed results. Findings reveal dissociable neural signatures of well-being and distress; PR integrates happiness/meaning via

flexible connectivity, with sub-indices distinguishing experiential/cognitive roles, guiding neurofeedback.

Disclosures: C. Liu: None.

Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

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Program #/Poster #: PSTR180.25/CC8

Topic: H.04. Emotion

Support: SNI program CVU 2013153
DGAPA-PAPIIT IN207923
DGAPA-PASPA

Title: Cognitive and socioemotional domains in family members of femicide victims in Mexico

Authors: *A. PIÑA HERNÁNDEZ, I. ESPINOSA MÉNDEZ, D. ATILANO-BARBOSA, F. A. BARRIOS;
Inst. de Neurobiología, UNAM, Querétaro, Mexico

Abstract: Not only are the direct victims of femicide affected, but their loved ones also endure profound and lasting consequences. Despite this, little is known about the mental health impacts on the family members and close companions of the victims. These families must cope with devastating loss while simultaneously confronting the harsh reality of widespread impunity. Furthermore, they often face inefficient, retraumatizing legal processes and inadequate mental health services (Guerrera F., 2018). In 2024 alone, 1,212 femicides were recorded in Mexico. Of these cases, only 0.3% have resulted in a sentencing. Many of these particularly violent crimes are unlikely to ever be fully prosecuted or punished. Currently, there is no official record of the number of indirect victims of femicide in Mexico, but we can estimate approximately 4,363 individuals as indirect victims. Some research suggests that at least three people are deeply affected by a violent crime such as homicide, while other estimates suggest that between three and ten individuals may experience significant psychological and emotional impacts—though not all to the same extent (Connolly & Gordon, 2015; Redmond et al., 1989). In this context, it is crucial to understand how the emotional and cognitive mental health of family members is affected in order to advocate for specialized legal support and state-provided therapeutic interventions that are sensitive to their specific needs. A total of 8 family members of victims of femicide (VIF) were compared with 36 control participants using the cognitive and emotional batteries of the NIH Toolbox (version 1.28.7225, Spanish edition); a two-tailed t-test was performed and p-values were adjusted for multiple comparisons using the Benjamini-Hochberg method, revealing significant differences between groups in the following domains: Anger-

Affect ($p = 0.0230$), Fear-Affect ($p = 0.0230$), Fear-Somatic Arousal ($p = 0.0397$), Friendship ($p = 0.0230$), Perceived Stress ($p = 0.0230$), and Sadness ($p = 0.0425$).

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Poster

PSTR180: Human Emotion

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR180.26/CC9

Topic: H.04. Emotion

Support: FECHAC
ITESM

Title: Psychosocial Context Evaluation of the City of Delicias

Authors: *D. AQUINO PÉREZ¹, F. PROO ORTÍZ², R. LOERA-VALENCIA³, A. FLORES⁴; ¹ELPAC-UCC, Chihuahua, Mexico; ²ITESM, Chihuahua, Mexico; ³Karolinska Inst., Chihuahua, Mexico; ⁴Inst. Tecnológico y de Estudios Superiores de Monterrey, Querétaro, Mexico

Abstract: In 2016, the UN established Health and Well-being (3) and Sustainable Cities (11) as global priorities. Evaluating psychosocial contexts helps identify the risks and needs of communities for intervention design. Chihuahua had 190.55 depression cases per 100,000 in 2023 (INEGI), but Delicias lacks specific mental health statistics (Samuel Guerrero, CEPAPSI). This project aims to collect data in a cross-sectional observation to promote evidence-based practices, uncovering issues affecting Delicias' adult population: violence exposure, depression, anxiety and stress. To evaluate the psychosocial status of adults near "Parque Vida," Delicias, across dimensions of: a) violence exposure, b) depression, anxiety, c) quality of life, and stress. A quantitative, cross-sectional observational study used the CEV, DASS-21, and WHOQOL-BREF on Delicias residents in October 2023 and April 2024. Only the second evaluation ($n=75$, ages 18-60, convenience sampling) is reported. The sample was 70.6% male ($n=53$) and 29.3% female ($n=22$), with diverse marital statuses and education levels. 84% ($n=63$) reported no physiological/psychological conditions; 16% ($n=12$) had diagnoses (hypertension, type 2 diabetes, depression, ADHD, bipolarity). Non-parametric tests (Mann-Whitney U, Spearman correlation in SPSS v25) were used due to non-normal data. No significant gender differences were found in stress, anxiety, depression, or quality of life across severity ranges. However, women tended to report higher mild-severe anxiety, while men reported more extreme anxiety. Men showed a higher prevalence of mild to extreme depression; women reported more severe depression symptoms. Strong correlations were found between depression and anxiety ($r = 0.850$, $p < 0.01$), depression and stress ($r = 0.920$, $p < 0.01$), and stress and anxiety ($r = 0.901$, $p < 0.01$). Delicias' adults face challenges in mental health detection and treatment. Gender may

influence symptom reporting. Men showed more extreme symptoms, highlighting their mental health needs. Intervention strategies based on the collected data are presented.

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Poster

PSTR181: Human Imaging: Mood

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.01/CC10

Topic: H.05. Mood Disorders

Title: Predicting Suicidal Attempts Using Resting-State fMRI and Psychosocial Data: A Machine Learning Study from the ABCD Cohort

Authors: *G. AHN¹, J. D. E. GABRIELI²;
²Dept Brain/Cognit Sci., ¹MIT, Cambridge, MA

Abstract: Background Suicide is a leading cause of death in youth, yet most predictive studies focus on adults. Early identification of children at high risk could enable timely intervention. **Methods** Using the Adolescent Brain Cognitive Development (ABCD) cohort, we extracted resting-state functional-connectivity matrices and 77 psychosocial variables spanning anthropometrics, psychopathology, neurocognition, and family environment. Suicide-attempt status was derived from the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS). A discovery sample was split 80 %/20 % for training and internal validation (stratified by case status), and an independent replication sample comprised 10 healthy controls (HC) and 10 children with a documented suicide attempt (SA). We compared a transformer-based tabular foundation model (TabPFN) with an L1-regularized logistic-regression classifier and an unsupervised anomaly-detection approach (Isolation Forest). **Results** Combining functional-connectivity features with psychosocial measures substantially improved discrimination relative to either modality alone in TabPFN model. Combined model showed 87% AUROC while the psychosocial variables and neuroimaging showed 84% and 50% AUROC. The sparse logistic-regression model achieved 100 % sensitivity on the internal validation set and outperformed TabPFN at identifying SA cases. Isolation Forest correctly flagged all SA cases in the replication cohort, yielding 100 % positive predictive value. **Conclusions** A lightweight, interpretable linear model leveraging whole-brain connectivity and routine psychosocial assessments can accurately detect pre-adolescent suicide attempts, and an anomaly-detection framework maintains perfect precision on unseen participants. These findings underscore the utility of multimodal markers for pediatric suicide-risk stratification and lay the groundwork for prospective survival analyses and transfer-learning applications across independent neuroimaging datasets.

Disclosures: G. Ahn: None. J.D.E. Gabrieli: None.

Poster

PSTR181: Human Imaging: Mood

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Topic: H.05. Mood Disorders

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Title: Feedback-related negativity during reward consumption in major depression and anxious depression

Authors: *X. REN¹, E. WHITE^{1,2}, R. KUPLICKI¹, M. P. PAULUS^{1,2}, M. IRONSIDE^{1,2}, R. L. AUPPERLE^{1,2}, J. L. STEWART^{1,2};

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Abstract: Anhedonia, the diminished ability to experience pleasure, is a core symptom of major depressive disorder (MDD) that often persists despite treatment and is associated with impairments in reward processing. Although previous studies have identified alterations in reward anticipation, less is known about neural responses to reward outcomes, specifically feedback-related negativity (FRN), in MDD with and without comorbid anxiety (anxious depression; AD). We examined FRN amplitudes during reward consumption in 199 participants: MDD (n=53) or AD (n=108), and healthy controls (HC; n=38), who completed the Monetary Incentive Delay (MID) task during simultaneous EEG-MRI recording. FRN was analyzed using a mixed analysis of variance (ANOVA) with group (MDD, AD, HC) as the between-subjects factor, and feedback (gain, loss) and electrode (Fz, Cz, FCz) as within-subjects factors. A significant gender x group interaction was observed ($F=8.87$, $p < .001$). Female participants with MDD exhibited larger (more negative) FRN amplitudes than HC ($t = -0.83$, $p = .04$), whereas male participants with MDD showed smaller (less negative) FRN than HC ($t = 1.19$, $p = .03$). No significant FRN differences were found between AD and HC. To assess medication effects, a follow-up analysis within the clinical groups revealed a marginal gender x medication x group interaction ($F = 3.72$, $p = .05$). Unmedicated females with MDD showed the largest (negative) FRN amplitudes. In this group, smaller FRN amplitudes at baseline were associated with greater depression at baseline ($\rho = 0.47$, $p = .04$), 3 months ($\rho = 0.60$, $p = .03$), and 9 months ($\rho = 0.92$, $p < .001$). Conversely, in medicated female MDD participants, smaller FRN amplitudes at baseline were associated with lower depression scores at 9 months ($\rho = -0.48$, $p = .05$). These findings suggest that FRN during reward consumption may serve as a gender- and treatment-sensitive neural marker in MDD. Enhanced FRN in unmedicated females predicts persistent symptoms,

while the opposite pattern in medicated females may reflect adaptive neural changes with treatment. The absence of FRN differences in AD suggests distinct pathophysiological mechanisms. Overall, these results support the utility of FRN as a potential biomarker for tracking symptom trajectories and guiding individualized treatment in depression.

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Poster

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Program #/Poster #: PSTR181.03/CC12

Topic: H.05. Mood Disorders

Support: NIH ZIA NR000020-06

Title: Associations between growth differentiation factor 15 and fatigue symptoms - a secondary analysis of two cross-over clinical trials

Authors: *T. GOTO¹, J. ZHAO², L. SALIGAN²;

¹Cizik Sch. of Nursing at UTHealth Houston, Houston, TX; ²Natl. Inst. of Nursing Res., Bethesda, MD

Abstract: Fatigue is a distressing symptom reported by up to 90% of individuals with chronic medical illness, significantly impairing quality of life. Emerging evidence suggests that mitochondrial dysfunction is a key contributor to fatigue symptoms. Growth Differentiation Factor 15 (GDF15), a protein linked to mitochondrial disorders, has been suggested as a potential biomarker for fatigue symptoms. A previous study has demonstrated that blocking a GDF15 receptor mostly prevented fatigue-like behaviors in an animal model. In this study, therefore, we aimed to explore the relationship between fatigue symptoms and circulating GDF15 levels in patients who participated in two randomized, cross-over clinical trials assessing the effects of ketamine versus midazolam as an active comparator on fatigue (NCT02317341 and NCT04141696). Fatigue was assessed using visual analog scale, and plasma GDF15 levels were measured by Luminex system at baseline, 120 min, 230 min, 3 days, and 7 days post intervention. Demographic and clinical variables were also included in the analyses. Ten participants (3 males, 7 females; mean age = 52.1 ± 13.0) with chronic fatigue (>6 months) were included. Participants were either cancer survivors, had fibromyalgia, myalgic encephalomyelitis/chronic fatigue syndrome, or systemic lupus erythematosus. Four participants received ketamine followed by midazolam, and six received the reverse sequence. Linear mixed-effects modeling revealed no evidence of carryover effect. We did not detect statistically significant association between plasma GDF15 levels and fatigue scores over time. However, intraindividual analysis showed that some participants exhibited strong within-subject correlations between GDF15 and fatigue scores across timepoints. These findings suggest that

while GDF15 may not universally be correlated with fatigue in all individuals, it could be a relevant biomarker for fatigue in specific subgroups. Further investigation in larger cohorts is warranted to validate these individual-level associations and explore their clinical utility.

Disclosures: **T. Goto:** A. Employment/Salary (full or part-time): UTHealth Houston. **J. Zhao:** A. Employment/Salary (full or part-time): National Institutes of Health. **L. Saligan:** A. Employment/Salary (full or part-time): National Institutes of Health.

Poster

PSTR181: Human Imaging: Mood

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.04/CC13

Topic: H.05. Mood Disorders

Support: Regional Alliance for Promoting Liaison Psychiatry

Title: Development of Machine and Deep Learning-Based Predictive Model for Objective Assessment of Depressive, Euthymic, and Hypomanic States in Bipolar Disorder Using Activity and Sleep Information

Authors: *X. LI^{1,2};

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Abstract: *Bipolar Disorder (BD)* is a chronic illness characterized by recurring episodes of hypomania, mania, and depression, interspersed with periods of remission, with a lifetime prevalence of approximately 0.7% across both type I and type II. Accurate assessment of mood states is crucial for timely interventions and relapse prevention; however, differentiating bipolar depression from unipolar depression and distinguishing mild hypomanic states from usual mood fluctuations remain diagnostic challenges. In this study, 113 patients with BD and 99 healthy controls recorded daily activity (steps, calories, distance, seated time, and time in light, moderate, and high-intensity activity) and sleep metrics (bedtimes, sleep onset, interruptions, and stages) over 6- or 9-month periods, alongside daily mood self-assessments on an 11-point scale (-5 to +5). Weekly manic and depressive states were assessed using the Altman Self-Rating Mania Scale (ASRM) and the Quick Inventory of Depressive Symptomatology (QIDS-J), respectively, and each objective dataset was labeled with the corresponding mood rating to create a training dataset. Multiple machine learning and deep learning models, including Random Forest (RF), Gradient Boosting Tree (GBT), eXtreme Gradient Boosting (XGBoost), LightGBM (LGBM), Fully Convolutional Network (FCN), Recurrent Neural Network (RNN), Long Short-Term Memory (LSTM), and Gated Recurrent Unit (GRU), were employed to predict current and future (up to one week ahead) mood states, using the area under the curve (AUC) as the primary evaluation metric. Ensemble methods (RF and LGBM) demonstrated superior performance (accuracies up to 0.74, sensitivities 0.74, F1 scores 0.71, and AUC values 0.74 and 0.73),

followed closely by other gradient-boosting algorithms (XGBoost and GBT). At the same time, LSTM led among deep learning models (accuracy 0.71, AUC 0.73). Traditional techniques like Decision Trees, k-Nearest Neighbors, and Logistic Regression showed moderate effectiveness, whereas Naïve Bayes and Support Vector Machines performed less robustly. SHapley Additive exPlanations (SHAP) and Multimodal Analysis revealed that activity features predominated in short-term predictions, while sleep features became increasingly influential in longer-term forecasts. These findings highlight that wearable-based data can help monitor mood changes and support early intervention and relapse prevention.

Disclosures: X. Li: None.

Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.05/CC14

Topic: H.05. Mood Disorders

Support: Taipei Veterans General Hospital VTA112- V1-8-1
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Ministry of Health and Welfare MOHW-YFH-11357
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Ministry of Science and Technology, Taiwan MOST112-2321-B-A49 - 021
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Title: Glymphatic Dysfunction Across Psychiatric Disorders: Brain Structural and Cognitive Correlates Using the Diffusion Tensor Imaging Along the Perivascular Space (DTI-ALPS) Index

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Abstract: The glymphatic system is crucial in maintaining brain homeostasis, clearing metabolic waste, and distributing vital molecules throughout the central nervous system. Recent studies have suggested that glymphatic system dysfunction may contribute to the pathophysiology of various psychiatric disorders. The diffusion tensor imaging-along the perivascular space (DTI-ALPS) index is an indirect yet informative marker of glymphatic function. However, comparative research examining DTI-ALPS indices across different psychiatric disorders is limited, as is our understanding of the associations between these indices and neuroanatomical or clinical features. This study aimed to assess differences in DTI-ALPS indices between

psychiatric disorders and to explore their relationship with gray matter volume, cognitive performance, and symptom severity. Participants were recruited from the Taiwan Aging and Mental Illness cohort, comprising 130 healthy controls, as well as those 130 with schizophrenia (SZ), 93 with bipolar disorder (BD), and 65 with major depressive disorder (MDD). Group differences in DTI-ALPS indices were tested using a one-way analysis of variance. General linear regression models were performed to explore the relationship between DTI-ALPS indices and gray matter volume (GMV). Additionally, Spearman correlation analyses were conducted to examine the associations between DTI-ALPS indices, cognitive function, and symptom severity. All psychiatric groups showed significantly lower DTI-ALPS indices compared to healthy controls, with the most pronounced reduction observed in the SZ group. In the SZ group, higher DTI-ALPS indices were positively associated with greater GMV in the bilateral cerebellum and fusiform gyrus, as well as with better cognitive performance. In the BD group, DTI-ALPS indices showed positive correlations with hippocampal volume and cognitive test scores and negative correlations with the severity of depressive and anxiety symptoms. In the MDD group, lower DTI-ALPS indices were linked to cognitive impairment, although no significant changes in GMV were detected. Glymphatic system dysfunction may represent a potential biomarker for psychiatric disorders. The DTI-ALPS index reflects alterations in brain structure, cognitive function, and symptom severity. Therefore, it could be a potential target for therapeutic strategies to alleviate clinical symptoms and improve cognitive function.

Disclosures: J. Zhu: None. A. Yang: None. S. Tsai: None.

Poster

PSTR181: Human Imaging: Mood

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Program #/Poster #: PSTR181.06/CC15

Topic: H.05. Mood Disorders

Support: Canadian Institutes of Health Research PJT-148840

Title: Repetitive transcranial magnetic stimulation (rTMS) for the treatment of MRI-defined vascular depression

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Abstract: Background: Vascular depression (VD) is a proposed subtype of late-life depression (LLD) linked to cognitive impairment and cerebrovascular pathology, most notably white matter hyperintensities (WMHs) on magnetic resonance imaging (MRI). VD may account for up to 50% of LLD cases and is often resistant to pharmacological treatment. Preliminary evidence suggests that repetitive transcranial magnetic stimulation (rTMS) may be an effective treatment option for patients with VD. This study explored the comparative efficacy of rTMS in LLD patients with

MRI-defined VD versus patients with non-vascular depression (non-VD). **Method:** We analyzed data from 94 participants with LLD enrolled in the FOUR-D study (ClinicalTrials.gov identifier: NCT02998580). Pre-treatment MRI scans were visually evaluated for WMHs using the Fazekas scale, and participants with a deep WMH score ≥ 2 were classified as having VD. Cognitive performance, including executive function, processing speed, verbal learning and memory, as well as treatment outcomes to bilateral rTMS targeting the dorsolateral prefrontal cortex, were compared between groups. **Results:** Forty-one participants met criteria for VD. Compared to non-VD patients, those with VD were significantly older and demonstrated poorer performance on executive function tasks, specifically response inhibition and task switching. No significant differences in treatment outcomes to rTMS were observed between groups. Remission was achieved by 47.4% of VD patients and 30.8% of non-VD patients. **Conclusion:** A substantial proportion of the sample met neuroimaging criteria for VD, and these patients showed poorer executive function. Despite this, patients with VD responded similarly, or numerically slightly better, to rTMS treatment. This contrasts with the typically poorer outcomes observed with pharmacotherapy in VD. These findings support the potential utility of rTMS in VD, although further investigation is warranted.

Disclosures: K. Göke: None. J. Ramirez: None. S. Nestor: None. D. Blumberger: None.

Poster

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Program #/Poster #: PSTR181.07/DD1

Topic: H.05. Mood Disorders

Support: Financiamiento de Proyectos de Investigación para la Salud 2024 (Grant FPIS2024-INR-4943)

Title: Biomarkers of the gut microbiome for mental disorders in Mexicans with obesity

Authors: *L. SANCHEZ-CHAPUL¹, M. SAMUDIO-CRUZ², D. CERQUEDA-GARCÍA⁵, E. CABRERA-RUIZ⁶, C. LANDA-SOLIS³, A. LUNA⁷, P. CARRILLO-MORA⁴, K. ANDRADE⁸, V. ANDRADE⁹, E. RANGEL-LOPEZ¹¹, J. RIOS MARTINEZ¹², J. VALENCIA LEÓN¹³, M. GONZALEZ PRIETO¹⁰;

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Ciencias de la Salud, ¹³Dirección Gen. Adjunta de Sanidad Naval, Secretaría de Marina Armada de México, Mexico City, Mexico

Abstract: In Mexico, the taxonomic profile of the gut microbiota in obese adults and its relationship with depressive and anxiety symptoms is still unexplored. The aim of this study was to characterize the signature of the gut microbiota of Mexican adults with obesity and its association with depression and anxiety. We characterized the gut microbiota of 106 Mexican adults with obesity (BMI $\geq$ 30) stratified by mental health status: no symptoms (OCG, n=79), depression (OD, n=7), anxiety (OAx, n=8) or both (ODAx, n=12) using 16S rRNA sequencing (V3-V4 region, Illumina MiSeq) and the LEfSe bioinformatics study. Alpha diversity was assessed using an independent-samples t-test, and beta diversity was analyzed using PERMANOVA. LEfSe identified taxa with different frequencies and associations between bacterial genera and clinical variables were analyzed using the Maaslin2 library. There were no significant differences in alpha and beta diversity between groups. The *Bacteroidota* dominated (46.9%) over the *Firmicutes* (33.3%), with *Fusobacteriota* showing differences between groups (p=0.001), making the *Bacteroidota* the most common phylum and the *Prevotella* the predominant enterotype. Thirty taxonomic biomarkers defined the gut microbiota between groups; 4 biomarkers from OCG belong to the phylum *Firmicutes*, 5 from OD to the phylum *Firmicutes* and *Bacteroidota*, 13 from OAx to the phylum *Firmicutes*, *Bacteroidetes*, *Fusobacteroidota* and *Proteobacteria* and 8 from ODAx to the phylum *Firmicutes*. Our study is the first to identify the signature of the gut microbiota in Mexican adults with obesity and depressive and anxiety symptoms. The 30 taxonomic biomarkers differentiate between obese individuals with and without these symptoms and offer potential clinical utility for the diagnosis and treatment of depression and anxiety in obese individuals.

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Poster

PSTR181: Human Imaging: Mood

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Program #/Poster #: PSTR181.08/DD2

Topic: H.05. Mood Disorders

Support: NIH Grant R01MH134973

Title: Intrinsic neural timescales in treatment resistant depression and their modulation by ketamine

Authors: *E. ALCANTARA¹, K. WENGLER²;

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Abstract: Major depressive disorder is one of the leading causes of disability worldwide and approximately a third of patients develop treatment resistant depression (TRD). Cognitive impairments are a hallmark feature of depression and greatly impact quality of life. However, current treatment options do not target cognitive impairments. Ketamine is an effective treatment for TRD that modulates the excitation/inhibition balance (E/I). Relatedly, intrinsic neural timescales (INT) are a resting state fMRI measure thought to be sensitive to the strength of recurrent excitation and reflective of E/I. Additionally, recurrent excitation is a canonical microcircuit property that is responsible for information processing and relevant for several aspects of cognition. Therefore, disruptions of E/I in canonical microcircuits may be responsible for the cognitive deficits in TRD and ketamine's therapeutic effect may be linked to this pathway. Resting-state fMRI data were analyzed from 89 TRD patients and 34 controls from the Perturbation of the TRD Connectome by Fast-Acting Therapies project. A subset of patients (n=60) received four serial ketamine infusions that were administered 2-3 times weekly. The timepoints for data collection were: (1) baseline (pre-treatment), (2) 24hrs post first infusion, (3) 24hrs post last infusion, and (4) 5 weeks post treatment (or at time of relapse). INT maps for 188 brain regions (HCP-MMP1.0; averaged across hemispheres) were estimated using guidelines by Goldberg et al. (Imaging Neuroscience, 2024). Linear regressions were used to investigate relationships between regional INT and three phenotypes: (1) patient vs control group (diagnosis), (2) depression severity, and (3) cognitive performance. INT were shorter in TRD (33 significant brain regions; FWE-p = 0.0001), particularly in the insula (all $t < -2.25$, $p < 0.037$) and cingulate (all $t < -2.35$, $p < 0.019$). Additionally, shorter INT were related to worse depression severity throughout the brain (39 significant brain regions; FWE-p = 0.0001), most notably in the insula (all $t < -2.40$, $p < 0.043$) and cingulate (all $t < -2.51$, $p < 0.048$). Lastly, longer INT related to increased processing speed performance (33 significant regions; FEW-p = 0.0001), markedly in the insula (all $t < 3.18$, $p < 0.001$) and cingulate (all $t < 2.20$, $p < 0.028$). Given these findings, the effect of ketamine on INT is currently being evaluated. We identified shorter INT throughout the brain in TRD with greater INT shortening relating to worse depression severity and worse cognition. E/I alterations offer a target mechanism underlying TRD, potentially explaining the effectiveness of ketamine.

Disclosures: E. Alcantara: None. K. Wengler: None.

Poster

PSTR181: Human Imaging: Mood

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Topic: H.05. Mood Disorders

Support: ZonMw Grant 537001005

Title: Neural correlates of positive future-oriented thinking related to recent suicide attempts, suicidal ideation, and hopelessness in individuals with psychopathology

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Cognitive Neurosci. Ctr., Univ. Med. Ctr. Groningen, GRONINGEN, Netherlands

Abstract: Wenrui Deng¹, Justine Dickhoff¹, Esther M. Opmeer², Jan-Bernard C. Marsman¹, André Aleman^{1,3}, Marie-José van Tol¹ 1Cognitive Neuroscience Center, Department of Biomedical Sciences, University Medical Center Groningen, The Netherlands 2Hogeschool Windesheim, Zwolle, The Netherlands 3Faculty of Behavioral and Social Sciences, University of Groningen, Groningen, The Netherlands. Suicide risk is high in individuals with psychiatric disorders and has been associated with deficits in thinking about future positive outcomes. Whether the ability to vividly think of positive future and its underpinning neural mechanisms can explain the propensity to engage in suicide attempts is unclear. Therefore, the vividness and brain activation during positive future-oriented thinking of individuals who recently attempted suicide were compared to individuals who never attempted suicide. Functional MRI data and vividness ratings acquired during envisioning self-relevant positive and neutral future events were compared between psychiatric patients who recently attempted suicide (SP, N=23; median recency <1 month, maximum six months), psychiatric patient controls without attempts (PC, N=22), and non-psychiatric controls (NPC, N=23). Associations with suicidal ideation, hopelessness, and depressive severity scores were explored. No differences in vividness and brain activation during positive versus neutral imagination were observed between SP and PC, though both patient groups showed less vivid imagination and higher activation of fronto-opercular brain regions during both positive and neutral imagination than NPC. Hopelessness related more strongly to suicidal ideation in SP than in PC, and to lower activation in the medial orbitofrontal cortex (mOFC) and left frontopolar cortex during positive versus neutral imagination across patient groups. Mediation analyses revealed that the mOFC and left frontopolar cortex activation during positive versus neutral imagination related to higher suicidal ideation via hopelessness, specifically in SP. Blurred images during envisioning future events and strong recruitment of cognitive control regions associated with the construction and maintenance of mental representations do not appear to directly explain the propensity to attempt suicide. Instead, hypoactivation of regions involved in reward and emotion processing when envisioning future events relates to a higher suicidal risk through its pertinence to hopelessness. This study provides evidence of the complex interplay between the neural underpinnings of future-oriented thinking and symptomatology underlying suicide.

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Poster

PSTR181: Human Imaging: Mood

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Topic: H.05. Mood Disorders

Support: Internal RNI Funding

Title: Resilience of Nucleus Accumbens Functional Connectivity During Residential Treatment for Opioid and Stimulant Co-Use: A Longitudinal Resting-State fMRI Study

Authors: *R. THURN^{1,5}, D. THOMPSON-LAKE⁵, T. A. MCGAUGHEY⁶, G. K. ADAMS², M. V. CHERKASOVA³, J. J. MAHONEY, III⁵, P. WORHUNSKY⁵, J. MARTON⁵, D. FARMER⁴;

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Abstract: Despite over 60% of individuals with opioid use disorder (OUD) also reporting stimulant (e.g., methamphetamine) use, co-occurring substance use disorders (coSUD) are understudied. Standard of care treatment for OUD includes medications for opioid use disorder (MOUD; e.g., buprenorphine, buprenorphine-naloxone, methadone) which reduce opioid cravings. Prior research in OUD suggests reductions in both cue-induced and non-cue induced (i.e., tonic) craving over the first 10 months of MOUD treatment. These reductions are negatively correlated with increases in resting state functional connectivity (FC) between the nucleus accumbens (NAc) and cortical regions. Building on these findings, we hypothesize that in individuals with coSUD, NAc-corticolimbic FC (anterior/posterior cingulate cortex, insula, dorsolateral/ventromedial/orbitofrontal cortices) will progressively increase throughout the course of treatment, reflecting reduced salience of internal states (e.g., tonic craving). Eleven individuals enrolled in residential coSUD treatment (5 female; age = 33.1±9.0 [mean±SD] years; years of use = 11.1±9.6 [opioid]; 11.8±9.2 [stimulants]) completed resting-state fMRI after initiating treatment (baseline) and 14 and 30 days post-baseline. All participants were prescribed and compliant with, MOUD for the duration of this study. Image processing and analyses were completed in AFNI. FC between ROIs (Z-scores) were entered into repeated-measures ANOVAs and corrected for multiple comparisons (FWE, $\alpha = 0.05$). Contrary to our hypothesis, we observed no significant increase in NAc-corticolimbic FC or reductions in tonic craving (scale: 0-10; baseline = 4.0±2.3 [mean±SD]; day 14 = 4.0±2.6; day 30 = 3.1±3.0) at either 14 or 30 days. Current literature suggests a link between NAc-corticolimbic FC and craving. In our study, both tonic craving and FC between the NAc and a priori corticolimbic regions remained stable over four weeks of residential treatment. These results suggest support for the association between NAc-corticolimbic FC and craving, and provide preliminary evidence towards differences in treatment response between those with OUD and coSUD. Data collection is ongoing and incorporates an additional three-month timepoint to explore the longer-term progression of biobehavioral associations and clinical outcomes in coSUD.

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Poster

PSTR181: Human Imaging: Mood

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Program #/Poster #: PSTR181.11/DD5

Topic: H.05. Mood Disorders

Title: Linking Magnetoencephalography Dynamics to Reward-based Decision Processes in Pediatric Epilepsy

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Abstract: Background: Epilepsy is one of the most common neurological disorders in youth and is frequently comorbid with depression. Although these conditions often co-occur, their interactive effects—particularly on reward processing—are not well understood. Reward processing deficits are well-documented in depression but remain underexplored in epilepsy. Objective: This study aimed to investigate reward learning in adolescents with epilepsy using a behavioral and computational approach. Methods: A probabilistic reward task (PRT) was administered to adolescents aged 10-19, including typically-developing (TD) controls (n = 24) and adolescents diagnosed with epilepsy (EPI; n = 24). Response bias and reaction time were assessed behaviorally. Drift diffusion modeling (DDM) was applied to evaluate underlying cognitive processes related to decision-making and reward learning. Magnetoencephalography (MEG) was used to measure active neural connectivity during an affective regulation task. Results: EPI participants exhibited significantly slower reaction times compared to TD controls (p = .008). The EPI group showed significantly lower boundary separation (p = .02), suggesting reduced cognitive control and less adaptive decision-making compared to the TD group. Additionally, non-decision time was significantly longer in the EPI group (p = .04), indicating slower sensory or motor processing. There were significantly lower values for drift rate in the rewarded condition for the EPI group (p = .03), suggesting a slower learning rate for rewarded stimuli as compared to the TD group. A significant negative association was found between non-decision time and connectivity strength between the left precentral and postcentral gyri in the TD group (p = .02), indicating that faster sensory encoding and motor response were associated with stronger connectivity in sensorimotor regions. Conclusion: Relative to TD, EPI participants showed differences in reward-based decision-making processes, with blunted sensory-motor processing being linked to connectivity in sensory-motor brain areas. This suggests that reward processing in EPI should take into account the separate aspects of this form of decision-making.

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Poster

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Topic: H.05. Mood Disorders

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Title: A Wearable Platform for Closed-Loop Auditory Stimulation During Sleep with High-Density Scalp and Intracranial EEG

Authors: *U. TOPALOVIC¹, M. BAYDA², M. VALLEJO¹, M. SEEGER², C. ORAGWAM¹, R. MUSTAPHA², J. BAHAM², S. HILLER², N. HASULAK⁴, J.-P. LANGEVIN², V. R. RAO⁵, I. FRIED⁶, D. ELIASHIV², B. J. KNOWLTON³, N. A. SUTHANA¹;
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Abstract: Abstract:

Closed-loop auditory stimulation during slow-wave sleep is a promising method to modulate memory consolidation and neural dynamics. We present a wearable platform integrating high-density scalp EEG, chronic intracranial EEG (via the RNS System), and real-time closed-loop auditory stimulation targeting slow- and delta-wave phases during sleep. This system includes a desktop PC for signal detection and audio delivery, a GUI for configuration and monitoring, and Raspberry Pi for synchronizing scalp and iEEG streams via simultaneous marker pulses, and a compact flexible head-mounted coil. Building on our prior wearable system for synchronized scalp EEG and iEEG¹, we improved the hardware for comfort and stability during sleep. The flexible coil, made from polyimide flex PCB (0.26 mm thick, 86 mm diameter), houses three coils: two for telemetry and one for synchronization pulses, enabling millisecond alignment across devices. We tested components in 10 participants during 2-hour sleep sessions, including individuals with chronic hippocampal electrodes. Sleep staging and slow- and delta-wave detection were performed in real time using signals from three frontal scalp EEG channels. Auditory stimulation was delivered precisely at the rising phase of slow waves and delta waves, as detected in real time. Latency measurements confirmed a mean detection-to-stimulation delay of 24.5 ± 5.9 ms ($n=100$), ensuring timely phase-locked stimulation. Real-time sleep staging used an adapted offline algorithm, yielding $89.03 \pm 3.57\%$ agreement with offline scoring. In real-time operation, slow-wave detection accuracy was $88.5 \pm 5.4\%$, and delta-wave detection was $83.1 \pm 6.7\%$, compared to offline analyses. Stimulation occurred at a mean phase offset of $14^\circ \pm 11^\circ$ for slow-waves and $17^\circ \pm 24^\circ$ for delta waves (mean $\pm$ circular standard deviation) relative to target scalp EEG peaks. These results demonstrate the feasibility and precision of this wearable multimodal platform for closed-loop auditory stimulation during sleep. Given that thousands of individuals already have chronically implanted devices like the RNS System, our platform offers translational potential to study and enhance sleep-dependent memory consolidation in naturalistic environments over extended periods.

References:

1. Topalovic, U., Aghajan, Z. M., Villaroman, D., Hiller, S., Christov-Moore, L., Wishard, T. J., Stangl, M., Hasulak, N., Inman, C. S., Fields, T. A., Rao, V. R., Eliashiv, D., Fried, I., Suthana, N. (2020) *Wireless and Programmable Recording and Stimulation of Deep Brain Activity in Freely Moving Humans*. Neuron 108, 322-334.e9

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Poster

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Topic: H.05. Mood Disorders

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Title: Fatigue-driven inflation of physical effort assessment in major depressive disorder

Authors: *V. LOOI^{1,2}, G. E. STEWARD^{1,2}, V. S. CHIB^{1,2,3};

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Abstract: Motivational impairments characterize Major Depressive Disorder (MDD), yet the role of subjective effort assessment in driving these impairments remains poorly understood. This study addresses this gap by examining how MDD influences physical effort assessment. 30 participants with MDD (Mean age = 22.9, SD = 4.6, 6 M, 24 F) and 31 healthy control participants (Mean age = 24.8, SD = 4.8, 9 M, 22 F) completed a grip force task using a hand dynamometer. After learning the mappings between numeric effort levels (normalized to their maximum voluntary contraction) and force output, they completed an assessment phase in which they exerted force to fill a visual bar without explicit effort targets, then retrospectively rated perceived effort. For each trial in the assessment phase, we quantified mean exertion (ME) as average exerted force, exertion variability (EV) as the standard deviation of exerted force, and assessment error (AE) as the difference between perceived effort and ME for each trial. Linear mixed-effect models were used to evaluate group differences. Trial number served as a proxy for accumulating fatigue, allowing us to examine its role in exertion performance and effort assessment.

Despite comparable ME across goal levels between the two cohorts, MDD participants exhibited greater EV ($p = .006$) after accounting for ME. They also consistently rated their exertions as more effortful than the effort goals and assessments of healthy controls ($p < .001$). To examine differences in effort assessment accuracy, we modeled AE as a function of EV normalized to ME ($EVN = EV/ME$). The model confirmed the significant effect of EVN on AE ($p < .001$), with higher EVN predicting larger AE in both cohorts, yet a significant cohort effect of MDD ($p = .023$) remained, indicating that heightened AE in MDD is attributable not only to their greater EVN but also to a cohort-specific distortion in effort assessment. We further assessed the effects

of accumulating fatigue on EV and AE by incorporating the interaction between trial number and cohort as a predictor. While the relationship between EV and repeated trials did not significantly differ between cohorts ($p = .214$), MDD exhibits a more pronounced increase in AE with repeated exertion ($p = .004$). These results reveal a heightened sensitivity to fatigue in MDD that is not captured by differences in motoric mean exertion levels or exertion variability alone. This inflation in subjective effort may in turn contribute to impaired assessment accuracy and undermine motivation. Our findings provide a novel behavioral account suggesting that fatigue symptomatology in MDD may drive motivational impairments by amplifying perceived effort costs.

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Poster

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Title: Frontolimbic functional connectivity is associated with the antidepressant effect of 24-hour sleep deprivation in individuals with major depressive disorder

Authors: *H. YUN^{1,3}, S. WILLIAMS^{1,5}, H. FISHER^{1,6}, Z. YANG^{1,6}, S. ANAKWE⁶, D. CHEN^{1,4}, E. BELDZIK^{1,4}, L. D. LEWIS^{1,4,6,2};

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Abstract: Sleep deprivation can paradoxically cause rapid improvements in mood in some individuals with major depressive disorder (MDD). The neural mechanisms underlying why some patients exhibit this antidepressant effect (responder) while others do not (nonresponder) remain unclear. In this study, we investigated associations between fMRI signals and mood scores before and after sleep deprivation. We collected simultaneous EEG-fMRI data from 68 participants (MDD: N=42; healthy controls: N=26) under two conditions: after a night of normal

sleep (well-rested session) and after 24-hours of sleep deprivation (sleep-deprived session). We hypothesized that connectivity of the amygdala may relate to changes in mood. Using the bilateral amygdala as the seed, whole-brain functional connectivity analysis was conducted on time series from the Emotional Face Matching Task, after regressing out task and motion effects. At the well-rested session, responders exhibited significantly stronger amygdala connectivity with the mediodorsal thalamus and posterior cingulate compared to non-responders (unpaired t-test, $p < 0.05$, FWE-corrected). Under sleep-deprived conditions, no significant group differences emerged (unpaired t-test, $p > 0.05$ N.S.). Next, we tested whether pairwise functional connectivity between 15 salience and frontolimbic regions—identified in literature to be linked to sleep and depression—is associated with participants' depression scores (modified Montgomery-Åsberg Depression Rating Scale). A total of 105 ROI pairs were tested using mixed linear regression models. Stronger connectivity between anterior cingulate cortex (ACC)-putamen, pallidum, thalamus, insula-hippocampus, and caudate-pallidum was significantly associated with better mood in MDD patients across sessions ($p < 0.00048$, Bonferroni-Holm corrected). In healthy controls, worse mood score was associated with stronger connectivity among the ACC-caudate, pallidum, frontal medial-insula, inferior frontal gyrus pars opercularis-pars triangularis, and caudate-thalamus ($p < 0.00048$, Bonferroni-Holm corrected). Notably, increased ACC-thalamus connectivity (mean increase=23.43%, SD=34.96%; $p < 0.001$, paired t-test, $n=42$) correlated with mood improvement in MDD patients ($r=0.43$, Pearson correlation, $p < 0.05$, Bonferroni-corrected), but not in healthy controls. Connectivity changes in other ROI pairs did not significantly relate to mood change. These results suggest that individual differences in connectivity between salience and sensory networks are linked to mood response to sleep deprivation in depression.

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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.15/DD9

Topic: H.05. Mood Disorders

Title: Intact emotional responses to music in major depressive disorder

Authors: A. PITNER¹, A. KORNIYENKO², *P. WALLISCH³;

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Abstract: Anhedonia - diminished capacity to experience pleasure - is a hallmark of major depressive disorder (MDD). Prior work from our group (Poincot et al., 2019) surprisingly showed that self-reported enjoyment of music was unrelated to Beck Depression Inventory (BDI) scores. We (i) replicated this finding in a well-powered sample, (ii) examined whether MDD

modulates specific music-evoked emotions beyond global liking, (iii) validated results with the PHQ-9, and (iv) assessed music-specific anhedonia. Research participants (n > 1000) listened to 400 short, genre-balanced excerpts while reporting felt emotions, liking, and arousal. Depression severity was assessed with BDI-II and PHQ-9. We used machine learning methods to probe whether depression scores predicted liking or emotion ratings, controlling for age, sex, and musical training. The design was well powered to detect small effects. BDI and PHQ-9 were strongly associated with lower current mood but showed no relation to music-evoked emotions or liking. Instead, felt emotion valence robustly predicted liking independent of depression severity. We conclude that individuals suffering from MDD report blunted mood yet retain intact, emotion-driven appreciation of music. These findings suggest that music engagement provides a spared and direct hedonic channel that could be leveraged in interventions targeting affective disorders.

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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.16/DD10

Topic: H.05. Mood Disorders

Support: UC Irvine 2024 Summer Undergraduate Research Fellowship

Title: Expression of circadian and stress response genes in clinical blood of patients with depression

Authors: *B. NGUYEN¹, R. KUBA¹, F. MAMDANI¹, A. SEQUEIRA²;

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Abstract: The goal of this exploratory study was to determine whether circadian and stress response gene expression differences are observed in blood samples of individuals with major depressive disorder (MDD), and to investigate whether MDD subjects experiencing sleep disturbances display greater perturbations in gene expression. The circadian rhythm, influencing physiological processes like sleep patterns, appetite, digestion, and temperature, is regulated by clock genes including BMAL1, PER1, PER2, PER3, CRY1. Previous research by our group has shown significant alterations in the expression of these genes in post-mortem brain samples of individuals with major depressive disorder (MDD). Stress response genes such as FKBP5 and NR3C1 also play a role in MDD and have also been shown to be dysregulated in MDD. Clinical blood samples were first collected from 207 subjects, comprising two groups: 100 control subjects and 107 MDD subjects. The presence of sleep disturbances was measured using the Hamilton Depression Rating Scale. RNA was extracted, converted to cDNA, and amplified using quantitative real-time PCR to measure gene expression. Gene expression changes were determined using analysis of covariance (ANCOVA). Specific gene expression alterations in

MDDs compared to controls were explored and also the correlation between clock gene alterations and sleep disturbances. MDDs experienced greater instances and variations in sleep disturbances compared to controls. Additionally, the FKBP5, PER1, PER2, and PER3 genes were significantly upregulated in MDDs ($p \leq 0.001$). Ultimately, these results may contribute not only to the development of a biomarker predicting MDD and facilitating timely interventions, but in particular for sleep disorders among MDDs.

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Poster

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Program #/Poster #: PSTR181.17/DD11

Topic: H.05. Mood Disorders

Support: NIH Grant MH096889

Title: Decoding of neural activation across wake and sleep reveals affective processing and correlates with depression symptoms in humans

Authors: X. LIN¹, M. CHO², K. A. PALLER¹, *E. SCHECHTMAN²;

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Abstract: During sleep, brain networks supporting cognitive functions are activated, leading to improved cognitive performance. We hypothesize that networks involved in affective processing are likewise active during sleep, and that their activity governs mental well-being in health and disease. We investigated this process using multivariate EEG decoding across wake and sleep. We further examine the relationship between activation patterns during sleep and individual differences in depression and anxiety symptoms as assessed by standardized questionnaires. EEG was recorded from 64 channels in 52 healthy participants during an emotional-picture-viewing task (positive vs negative images) and during a subsequent nap. Using time-domain decoding analyses, we show that affective activation during sleep and restful wake correlated with depression symptoms, measured using Beck's Depression Index (BDI-II). An additional time-frequency-resolved decoding analysis revealed that the frequency of positive activation during sleep — particularly in the theta and alpha bands — was negatively correlated with depression symptoms (BDI-II) and anxiety symptoms (MASQ), and positively associated with post-sleep mood improvements (POMS difference). These findings suggest that the spontaneous activation of affective networks during sleep reflects stable inter-individual differences in affective traits and contributes to mood regulation. This study offers insight into the neural mechanisms underlying affective processing during sleep and wakeful rest, with implications for how this implicit processing impacts psychological well-being, and highlights the potential of combining EEG decoding with psychological assessments to better understand individual differences in sleep-related affective processing. Taken together, these results provide evidence that

spontaneous affective processing during sleep contributes to day-to-day mood, with potential implications for identifying sleep-related biomarkers of affective disorders.

Disclosures: X. Lin: None. M. Cho: None. K.A. Paller: None. E. Schechtman: None.

Poster

PSTR181: Human Imaging: Mood

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Program #/Poster #: PSTR181.18/DD12

Topic: H.05. Mood Disorders

Support: NIMH Grant K01MH117442
NIMH Grant R01MH083784

Title: Sex moderates the effect of peripheral BDNF on rostral Anterior Cingulate Cortex thickness differently in adolescents and adults with Major Depressive Disorder

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Abstract: Peripheral brain-derived neurotrophic factor (BDNF) has been linked to Major Depressive Disorder (MDD) and antidepressant responsiveness (Brunoni et al., 2008). Structural alterations in the rostral anterior cingulate cortex (rACC), a region implicated in emotion regulation, are observed in adolescents with MDD (Jamieson et al., 2022). Furthermore, sex-specific relationships have been shown between rACC thickness and the course of depression in adults with MDD (Wu & Baeken, 2024). Lower BDNF levels (Na et al., 2006) and BDNF gene polymorphisms (Shen et al., 2020) have also been linked to lower rACC thickness in adults with MDD. Due to emerging evidence that these biomarkers have sex-specific effects on treatment response (Smit et al., 2024) and MDD, we tested whether associations between peripheral BDNF and rACC thickness are moderated by sex in two developmental samples. Linear regression models were conducted in two MDD samples with BDNF and MRI data: adolescents from the Teen Inflammation Glutamate Emotion Research (TIGER) study (K01MH117442; aged 13-18, n=49, 68% female) and adults from the Cell Aging in Major Depression (CAN-D) study (R01MH083784; aged 19-65, n=45, 55% female), examining a BDNF sex interaction on rACC cortical thickness (left, right), controlling for age, BMI, and contraceptive/psychiatric medication use. BDNF was assayed from dried blood spots obtained via finger prick (TIGER; Luminex 62-plex) and serum samples obtained via blood draw (CAN-D; ELISA); BDNF outliers (± 1.5 IQR; 1 in TIGER; 3 in CAN-D) were removed. rACC thickness was extracted from high-resolution T1-weighted MRI (Freesurfer v.6.0). Adolescents showed a significant BDNF and sex interaction on left rACC thickness ($\beta = -0.69$, $p = .02$), whereby higher BDNF was associated with greater rACC thickness in females but lower thickness in males. In adults, an opposite pattern

emerged ($\beta=0.33$, $p=.05$), whereby higher BDNF was associated with greater left rACC thickness in males with no association in females. No statistically significant BDNF by sex interactions were observed for the right rACC in either sample (all $\beta s \geq 0.27$, all $p s \geq 0.13$), though adults showed a pattern consistent with left rACC findings. These results suggest that hemisphere- and sex-specific neurobiological mechanisms in MDD may shift over the course of MDD (adolescence to adulthood), with peripheral BDNF potentially influencing distinct neurodevelopmental and emotion regulation outcomes. Although limited by varying BDNF assay methods across samples, these findings support further exploration of developmental differences in neuroplasticity or hormonal regulation underlying MDD.

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Poster

PSTR181: Human Imaging: Mood

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.19/DD13

Topic: H.05. Mood Disorders

Title: How Reliable Are Early Warning Signs? Sensitivity and Specificity of Early Warning Signs as Markers to predict Depressive and Hypomanic/Manic State of Patients with Bipolar Disorder

Authors: *K. IWABUCHI;

Dept. of Psychiatry, Tohoku Univ. Grad. Sch. of Medicine, Sendai, Japan., Sendai/Miyagi, Japan

Abstract: Bipolar disorder (BD) is life disturbing and recurrent mood disorder. High relapse rates are related with worse prognosis, lower social functioning, and higher mortality rate due to suicide. Mood instability in BD remains high even with good medical treatment. In clinical practice, it is recommended to monitor mood and lifestyle changes to detect early warning signs (EWSs) of relapse and thus prevent relapse and obtain early intervention. However, the accuracy of each EWS is not fully studied nor understood. To answer this question, we conducted observational research at the Tohoku University Hospital and other eight hospitals in Japan from December 2021 to March 2023. The inclusion criteria were (1) bipolar I disorder (BD-I) or bipolar II disorder (BD-II), (2) age ≥ 18 years, and (3) outpatients or voluntarily hospitalized patients. A total of 117 patients were recruited and four patients did not meet inclusion criteria. A List of candidate EWSs for depressive and hypomanic/manic states was established. Participants selected the two most frequently appeared depression and hypomanic/manic EWSs from the list and self-reported the presence and absence of their EWSs on a daily basis. Altman Self-Rating Mania Scale (ASRM) and quick inventory of depressive symptomatology Japanese version (QIDS-J) were also self-reported on weekly basis. The data were accumulated through smart phone application for six months. We calculated true positive rate (TPR) and false positive rate (FPR) from our data to make receiver operating characteristics (ROC) curve. We have

determined threshold, the frequency of EWSs in five to nine days, and calculate most adequate sensitivity, specificity, and cut-off point for each EWSs. There is a significant difference in Mann-Whitney test, which shows depression EWSs have higher sensitivity than hypomanic/manic EWSs ($p < 0.001$). The mean rank of specificity is higher in hypomanic/manic EWSs than depression EWSs. As depression EWSs, “difficulty in speech”, “easily get tired”, and “feel I am no good” have high sensitivities, 88.9%, 89.5%, and 88.5%, respectively. As hypomanic/manic EWSs, “feel extremely joyful”, “lose focus”, “make an aggressive effort to housework” have high specificity, 89.1%, 89.1%, and 89.5%, respectively. Our results give insights for clinical symptoms’ diagnostic accuracy, which are less invasive with zero cost. These are powerful clinical tool in clinical setting for treating BD. Our study provided initial evidence to support the usability of EWSs for predicting depressive and hypomanic/manic state of BD patients, and propose practical way of using EWSs for maintaining patients’ mood condition.

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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.20/DD14

Topic: H.05. Mood Disorders

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Title: Ketamine-induced functional connectivity changes in patients of suicidal ideation

Authors: *C. YU¹, W.-C. LI¹, G.-J. SHE¹, L.-K. CHENG², M.-H. CHEN², L.-F. CHEN¹;
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Abstract: Suicide is a critical health issue due to its high mortality rate. Ketamine has shown efficacy in reducing depressive symptoms and suicidal ideation, yet its neurobiological mechanisms remain unclear. In the current study, we aimed to investigate neural network alterations associated with ketamine treatment in patients with suicidal ideation using whole-brain region-to-region functional connectivity (FC) analysis. Forty-three MDD patients were randomly assigned to receive either 0.5 mg/kg ketamine (n=20) or 0.045 mg/kg midazolam (n=23, control). Resting-state fMRI scans were obtained prior to infusion and on day 3 post-infusion. Suicidal ideation and behavior were assessed using the Columbia Suicide Severity Rating Scale (CSSRS). The brain was parcellated into 289 regions to calculate pairwise FC. Two-way repeated-measures ANCOVA was conducted to assess FC changes, controlling for age and sex (cluster-level uncorrected $p < 0.001$). For significant group $\times$ time interactions, paired and two-sample t-tests were performed for post comparison ($p < 0.05$, Bonferroni corrected). Partial correlation analyses examined associations between FC and CSSRS changes ($p < 0.05$). Results showed ketamine increased FC between bilateral pericalcarine cortex and right superior frontal gyrus, and the increment was positively correlated with suicidal ideation improvement. Pericalcarine cortex composes a part of visual network. Previous research reported decreased connectivity between the visual networks and the dorsal attention network in MDD patients (Chen et al., 2019). The increased FC in the pericalcarine cortex observed in our study may reflect a normalization effect related to the antidepressant action of ketamine. Furthermore, reduced FC between the right superior frontal cortex and striatum in treatment-resistant depression has been reported (Chen et al., 2020), and ketamine has been found to normalize prefrontal global connectivity in MDD at 24 hours post-treatment (Abdallah et al., 2018). Our findings highlight a potential role for visual-frontal connectivity in suicidal ideation after ketamine treatment.

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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.21/DD15

Topic: H.05. Mood Disorders

Support: R01AG070227

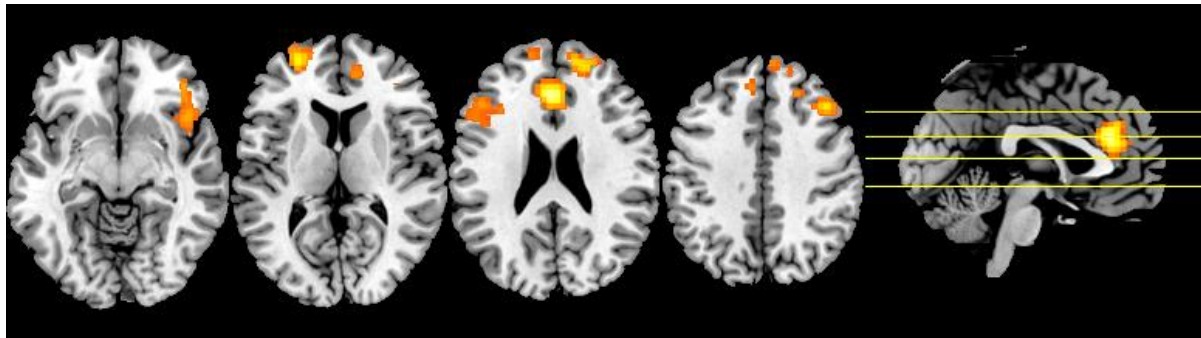
Title: Increased brain entropy in the executive control and salience network in major depressive disorders

Authors: E. WANG¹, A. WANG², *Z. WANG³;

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Abstract: Background and hypothesis: Resting state fMRI-derived brain entropy (BEN) indicates the irregularity of brain activity. In healthy adults, lower BEN in dorso-lateral prefrontal cortex (DLPFC) and prefrontal cortex (PFC) correlates with better cognitive control and executive function. Major depressive disorder (MDD) is associated with impaired emotional regulation and diminished sensitivity to rewarding stimuli, suggesting increased functional dysregulation in brain regions responsible for affective control and salience processing. This postulation can be translated into a new **hypothesis:** MDD has higher BEN than controls in the executive network and the salience network. **Methods:** Preprocessed resting state fMRI (rsfMRI) data were downloaded from 1081 young healthy subjects from the Human Connectome Project. BEN maps were calculated from the rsfMRI data using BENtbx (<https://cfn.upenn.edu/~zewang/BENtbx.php>). 34 subjects had a major depressive episode in their lifetime diagnosed based on DSMIV. 34 age, sex matched controls were identified. Two-sample t-test was performed to assess the MDD patients vs control BEN difference. Age, sex, and education years were included as covariates. Statistical significance was defined by $p < 0.001$. Multiple comparison correction was performed with the permutation-based cluster size correction method. The cluster size was > 150 ($q < 0.5$). **Results:** Higher BEN was found in DLPFC, PFC, rostral anterior cingulate cortex (rACC) and insula. DLPFC and PFC are part of the executive control network, while rACC and insula are part of the salience network. **Conclusion:** These findings prove truth of our hypothesis. Increased BEN in these areas may reflect heightened irregularity and reduced efficiency of intrinsic brain activity, consistent with impaired emotional regulation and executive dysfunction observed in MDD. These results highlight the potential utility of BEN as a neuroimaging marker for altered neural dynamics in depression, offering new insight into the disorder's pathophysiology.



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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.22/DD16

Topic: H.05. Mood Disorders

Title: Race, Cytokines, and Depression: The Role of the Exposome

Authors: *W. WYCHE¹, A. KUMAR², G. N. PANDEY^{3,4}, X. REN², O. A. AJILORE⁴;
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Abstract: Previous studies have shown that racial discrimination and the perceived stress of racism are associated with elevated pro-inflammatory cytokines. Given the established link between these cytokines and major depression - central to the inflammatory hypothesis of depression - this study examined racial differences in the inflammation-depression relationship using a secondary analysis of an ethnically diverse dataset.

A total of 121 subjects were recruited as part of a larger research program on major depressive disorder (MDD) at the University of Illinois at Chicago (UIC). Forty-six were African American (21 healthy, 25 with MDD), and 75 were White (34 healthy, 41 with MDD). Depressed participants met a minimum score of ≥ 15 on the Hamilton Rating Scale for Depression. Depression severity was also assessed using the Center for Epidemiological Studies-Depression Scale.

Plasma/serum levels of C-reactive protein (CRP) and pro-inflammatory cytokines (IL-1 β , IL-6, TNF- α) were measured using enzyme-linked immunosorbent assay (ELISA) with commercially available Quantakine® kits (R&D Systems, Minneapolis, MN).

Among non-depressed participants, African American participants had significantly higher CRP than White participants ($F = 4.48$, $p = .04$). No such group difference was seen among those with depression. After adjusting for neighborhood factors (e.g., household poverty, food access, unemployment), CRP differences in the non-depressed group were no longer significant ($p = .69$), indicating these factors may account for racial disparities in CRP.

We conducted a post-hoc neuroimaging analysis of right amygdala volume. After adjusting for age and sex, depression severity was positively associated with amygdala volume, driven largely by White participants ($r = .314$, $p = .014$), but not significant among Black participants ($r = .282$, $p = .163$). A positive association between CRP and right amygdala volume emerged in depressed Black participants ($r = .608$, $p = .016$), but not Whites ($r = .156$, $p = .232$). In non-depressed Black participants, this relationship was negative ($r = -.328$, $p = .389$), suggesting better-than-expected amygdala volume given inflammation. These results underscore the need to consider social determinants of health when examining racial differences in biological correlates of inflammation.

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Poster

PSTR181: Human Imaging: Mood

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Topic: H.05. Mood Disorders

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Title: Multiomic profiling identifies critical regulatory programs in major depressive disorder

Authors: *L. REN¹, A. KOZLENKOV², J. JUNG³, Z. DUREN⁴, S. DRACHEVA⁵;

¹Dept. of Med. and Mol. Genet. and Ctr. for Computat. Biol. and Bioinformatics, Indianapolis, IN; ²Dept. of Psychiatry, Icahn Sch. of Med. at Mount Sinai, New York, NY; ³Friedman Brain Institute, Icahn Sch. of Med. at Mount Sinai, New York, NY; ⁴Dept. of Med. and Mol. Genet. and Ctr. for Computat. Biol. and Bioinformatics of Indiana Univ. Sch. of Med., Indianapolis, IN; ⁵Dept. Psychiat, Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Major depressive disorder (MDD) affects over 300 million individuals worldwide and is a leading cause of disability. To investigate its molecular underpinnings, we performed shallow (5×) whole-genome DNA sequencing, as well as RNA sequencing of astrocyte (ASTR) and microglia (MG) nuclei isolated from the frontal cortex (BA10) of autopsy specimens from 112 MDD donors and 60 control donors with no documented psychiatric diagnoses (a total of 172 donors). Autopsied brain tissues were obtained from the Douglas - Bell Canada Brain Bank, Suicide Brain Bank, Dr. Gustavo Turecki, Director. Notably, all MDD donors died from suicide. Cell type-specific nuclei were isolated using fluorescence-activated nuclear sorting (FANS). Additionally, we generated single-nucleus (sn)RNA-seq and snATAC-seq data from a subset of donors (N = 44; 22 MDD, 22 control) using the 10x Genomics multiome assay, identifying nuclei corresponding to six major brain cell types—excitatory neurons, inhibitory neurons, oligodendrocytes, astrocytes, microglia, and oligodendrocyte precursor cells (OPCs)—as well as 18 distinct subpopulations. An additional 32 multiome samples are currently being processed (N = 32). Bulk RNA-seq analysis of FANS-isolated astrocytes (ASTR) and microglia (MG) identified approximately 800,000 significant eQTLs (545,000 in MG and 544,000 in ASTR), with only ~35% shared between the two cell types, highlighting substantial cell-type specificity. eQTL analysis of the snRNA-seq data detected, on average, ~100,000 significant eQTLs across the six major brain cell types, uncovering numerous novel regulatory associations. We also performed differential expression and chromatin accessibility analyses comparing MDD and control samples. Integrative MAGMA and sLDSC analyses of the differentially expressed genes revealed significant enrichment of MDD GWAS loci in astrocyte-specific genes and open chromatin regions. Leveraging single-cell multiomic data with LINGER, we constructed gene regulatory networks and identified cell-type-specific transcriptional regulators and gene modules potentially involved in MDD pathophysiology. Together, these findings offer a valuable resource for understanding cell-type-specific regulatory mechanisms underlying MDD.

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Poster

PSTR181: Human Imaging: Mood

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Program #/Poster #: PSTR181.24/EE2

Topic: H.05. Mood Disorders

Support: Korea Advanced Institute of Science and Technology

Title: Modulation of Heartbeat-Evoked Potentials (HEP) following a compassion-based interoceptive training in individuals with depression.

Authors: *A. ANZOLIN¹, S. ELLIS¹, E. KIM², B. CAHN³, D. JOSS⁴, F. MARIN⁴, V. NAPADOW¹, Z. SCHUMAN OLIVIER⁴;

¹Physical Med. and Rehabil., Spaulding Rehabil. Hospital, Harvard Med. Sch., Charlestown, MA; ²Ctr. for contemplative science, Korea Advanced Inst. of Sci. and Technol., Dajeon, Korea, Republic of; ³Univ. California San Diego, La Jolla, CA; ⁴Cambridge Hlth. Alliance, Harvard Med. Sch., Boston, MA

Abstract: Purpose: Depression is one of the most prevalent mental health disorders in the United States, typically characterized by self-critical thoughts and decreased interoceptive awareness. Therefore, integrative therapies targeting self-compassion and awareness of physiological signals inside the body may be beneficial. Heart-Smile Training (HST) is an interoceptive compassion-based behavioral intervention designed to cultivate bodily awareness around the heart area. By integrating the cardiovascular and neural systems, HST aims to encourage whole-body sensations originating from a warming sensation at the heart. This study utilized electroencephalography (EEG) to investigate the neural and neurocardiac mechanisms utilized during HST in depression patients. **Methods:** Patients (N=25) with mild to moderately severe depression (as determined by a CAT-MH score) were randomized into a 4-week HST intervention group or a waitlist control group. Participants enrolled in the HST group participated in a 3-day intensive retreat, followed by four weekly group meetings, and a final 1-day retreat. This HST program integrates core virtues such as wisdom, gratitude, and focused attention with compassion, loving-kindness, and empathy with a focus on specific mental and interoceptive states that accompany each meditation practice. Depression and anxiety scores were collected weekly throughout the study intervention and EEG was conducted before and after HST or the waitlist period. **Results:** A significant reduction in depression severity (CAT-DI) assessed at 6 weeks from baseline was observed in the HST group but not in the waitlist (WL) control group (Wilcoxon rank-sum test, $p=0.02$ for HST, $p=0.20$ for WL). A similar trend was observed in the anxiety score (CAT-ANX) from baseline to post (Wilcoxon rank-sum test, $p=0.07$ for HST, $p=0.65$ for WL). From a neurophysiological perspective, a significant change in heart-beat evoked potential (HEP) amplitude, assessed while meditating, was observed in the HST group but not in the control group (Student t-test, $p=0.015$ for HST, $p=0.47$ for WL), suggesting enhanced interoceptive processing following the intervention. **Conclusion:** These findings suggest that HST may play a role in the decrease of depression symptoms, as well as the increase in HEP amplitude. The proposed intervention may help increase interoceptive awareness, thereby effectively integrating cardiovascular and neural systems.

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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.25/EE3

Topic: H.05. Mood Disorders

Support: NIH BRAIN Initiative UH3NS103550
Hope for Depression Research Foundation
Dana Foundation
GE Healthcare

Title: Functional and structural remodeling of treatment-resistant depression with subcallosal cingulate deep brain stimulation

Authors: *J. CHA¹, H. SONG¹, M. FIGEE¹, J. SHIN², S. BANERJEE², P. RIVA-POSSE³, B. KOPELL¹, H. S. MAYBERG¹, K. CHOI¹;

¹Icahn Sch. of Med. at Mount Sinai, New York, NY; ²GE Healthcare, New York, NY;

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Abstract: Recent advances in understanding MRI safety in DBS patients have enabled increasing use of MRI-based neuroimaging studies in this population. While prior research demonstrated that subcallosal cingulate cortex (SCC) DBS induces long-term metabolic changes in corticolimbic circuits, longitudinal structural and functional MRI alterations using 3.0T MRI remain unknown. This study examined 6-month longitudinal changes in brain structure and function following SCC DBS for treatment-resistant depression (TRD). Seven TRD patients with fully implanted SCC DBS devices underwent 3.0T MRI (GE Signa Architect) at preoperative baseline and after 1, 3, and 6 months of chronic stimulation. For each session, high-resolution T1-weighted, diffusion-weighted, and resting-state fMRI images were acquired within a 30-minute scan time. Image analyses were conducted using Freesurfer, FSL, and AFNI. Cortical thickness was computed at each vertex, and mean thickness for 400 cortical regions was extracted. Tract-Based Spatial Statistics (TBSS) assessed white matter integrity using Fractional Anisotropy (FA) in the forceps minor, bilateral cingulum bundles, and bilateral uncinate fasciculus. Regional neural activity was evaluated using normalized Amplitude of Low-Frequency Fluctuations (ALFF) within gray matter. ALFF values of 17 functional networks were extracted. Linear mixed models, with random intercepts for individual variability, examined longitudinal changes. Significant structural changes in cortical thickness were found in the bilateral midcingulate cortex, medial frontal, inferior frontal, inferior temporal, and right middle temporal regions, with notable increases following chronic stimulation. White matter analysis showed increased FA in the bilateral cingulum bundle and right uncinate fasciculus. Additionally, local neural activity within the default mode network (DMN) increased postoperatively, peaking at 3 months, then declining. This study reveals significant longitudinal effects of SCC DBS on structural and functional brain features, particularly within the DMN and salience network-associated regions. Structurally, increased cortical thickness and enhanced

white matter integrity were observed within DMN and salience network pathways. Functionally, local DMN neural activity showed dynamic postoperative changes. These results suggest that SCC DBS induces functional and structural remodeling of DMN- and salience network-related neural architecture and activity, underscoring their central role in mediating antidepressant effects.

Disclosures: **J. Cha:** None. **H. Song:** None. **M. Figuee:** F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation and Medtronic. **J. Shin:** A. Employment/Salary (full or part-time); GE Healthcare. **S. Banerjee:** A. Employment/Salary (full or part-time); GE Healthcare. **P. Riva-Posse:** F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation, LivaNova, Janssen Pharmaceuticals, and Motif Neurotech. **B. Kopell:** F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation and Medtronic, and ClearPoint Neuro. **H.S. Mayberg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Abbott Laboratories. F. Consulting Fees (e.g., advisory boards); Abbott Laboratories. **K. Choi:** F. Consulting Fees (e.g., advisory boards); Abbott Neuromodulation.

Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.26/EE4

Topic: H.05. Mood Disorders

Support: Rohini Nilekani Philanthropies CBM grant

Title: The Centre for Brain and Mind: A longitudinal family-based cohort and biobank of major psychiatric illnesses in India

Authors: ***B. VISWANATH**, S. BUDDHA NAYOK, P. JAYASANKAR, C. CONSORTIUM; Natl. Inst. of Mental Hlth. and Neurosciences, Bangalore, India

Abstract: Major psychiatric illnesses are highly heritable, yet the search for replicable genetic and neurobiological mechanisms has proven highly challenging. One of the major reasons for this non- replicability is the focus on discrete clinical disease constructs, as categorized in current classificatory systems. Studying large numbers of multiplex families with affected members having several psychiatric illnesses, and unaffected relatives, would provide the most statistically robust method for the identification of neurocognitive endophenotypes that cut across traditional diagnostic boundaries.

The Centre for Brain and Mind (CBM) is such an attempt to develop a family-based longitudinal cohort and biobank of major psychiatric illnesses in India. CBM has longitudinal family cohorts of schizophrenia, bipolar disorder, obsessive-compulsive disorder, addiction and Alzheimer's dementia, along with their unaffected first-degree relatives (FDR) and population healthy controls. All individuals undergo detailed clinical assessments, and a blood sample is drawn to

isolate DNA and peripheral blood mononuclear cells. Genetic studies are conducted in parallel with deep endophenotype assessments (cognition, brain imaging, psychophysics and electroencephalogram) and induced pluripotent stem cell (iPSC) generation to develop a comprehensive understanding of the biology of these disorders.

So far, we have screened ca. 5000 families and recruited 850 families (2700 individuals) with multiple affected members, and 300 population healthy controls. Deep endophenotype assessments have been performed in 600 families (1600 individuals) and 250 population healthy controls. Whole exome sequencing (N=300) and iPSC generation (N=115) have been performed for a subset of individuals.

We identified general factor of cognition as a transdiagnostic endophenotype. Minor physical anomalies and gaze fixation abnormalities were found to be specific for psychotic disorders (schizophrenia and psychotic mood disorders). Adverse childhood events were found to worsen the cognitive deficits in FDRs. Whole exome sequencing identified rare damaging variants in several genes related to neurodevelopment, and subsequent studies in iPSC derived neural precursors and cortical organoids identified cell migration deficits.

Overall, we find various interesting leads about the biology of major psychiatric illnesses using the CBM study sample in India. Correlating deep clinical assessments, genomic variations, and phenotypes at various levels (cell, tissue, organ and system) may help us understand the biological links related to disease mechanisms in psychiatry.

Disclosures: B. Viswanath: None. S. Buddha Nayok: None. P. Jayasankar: None. C. Consortium: None.

Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.27/EE5

Topic: H.05. Mood Disorders

Support: Rohini Nilekani Philanthropies #G-202303-00559

Title: Clinical, cellular and genetic dissection of severe mental illnesses: A Centre for Brain and Mind study

Authors: *S. PALCHAUDHURI^{1,2}, C. CONSORTIUM^{1,2};

¹Ctr. for Brain and Mind, Natl. Ctr. for Biol. Sci., Bangalore, India; ²Ctr. for Brain and Mind, Natl. Inst. of Mental Hlth. and Neurosciences, Bangalore, India

Abstract: Introduction: Severe mental illnesses (SMIs) pose a heavy burden on global health; ~14% of the world population, or 1.1 billion people are suffering (GBD 2021). Despite such prevalence, accurate clinical diagnoses and the study of genetic and environmental factors contributing to disease etiology has been a challenge. The Centre for Brain and Mind (CBM) is a collaborative, multi-institutional platform to employ a multi-tier investigation of brain alteration

in SMIs that will help improve disease identification and management.

Strategy: A majority of SMIs are neurodevelopmental, with genetic and environmental contributions to their etiology. However, traditional clinical diagnoses fail to identify disease-specific clinical features; in addition, genes critical to disease phenotype have been hard to identify given the polygenic basis of SMIs. This 20-yr study analyses a prospective cohort of clinically dense families. We use a multi-dimensional approach to map the evolution of SMIs in patients and healthy individuals using (a) clinical and endophenotype evaluations that include cognitive, neuroimaging and clinical electrophysiology assessments, (b) whole exome sequencing and (c) generation of stem cells for detailed analyses. This continues to generate a rich longitudinal dataset of brain phenotypes and a biorepository to aid the discovery of genetic, cellular and electrophysiological contributions to altered biology in SMIs.

Results: A total of 2138 subjects were recruited to the study (Phase I) that include patients of selected SMIs (schizophrenia, bipolar, obsessive-compulsive or substance-use disorders, dementia), and their first-degree unaffected relatives for clinical, endophenotype assessments and sample collection. The cohort also includes a set of population controls (N=327). Repeated evaluations conducted every 2 years are ongoing. For the generation of stem cell lines for each SMI, 2 patients and 1 family control lines were generated, totaling 130 lines to date. Exome sequencing of 489 individuals from the cohort has been completed. Lastly, all data is ported to CALM-Brain data resource to enable accessibility and further analyses with advanced computational methods.

Disclosures: S. Palchaudhuri: None. C. Consortium: None.

Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.28/EE6

Topic: H.05. Mood Disorders

Support: Irish Research Council Postgraduate Scholarship, Health Research Board Grant No. HRA-POR-324
The ENIGMA Bipolar Initiative (NIH R01 MH129742)
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NeuRA/UNSW

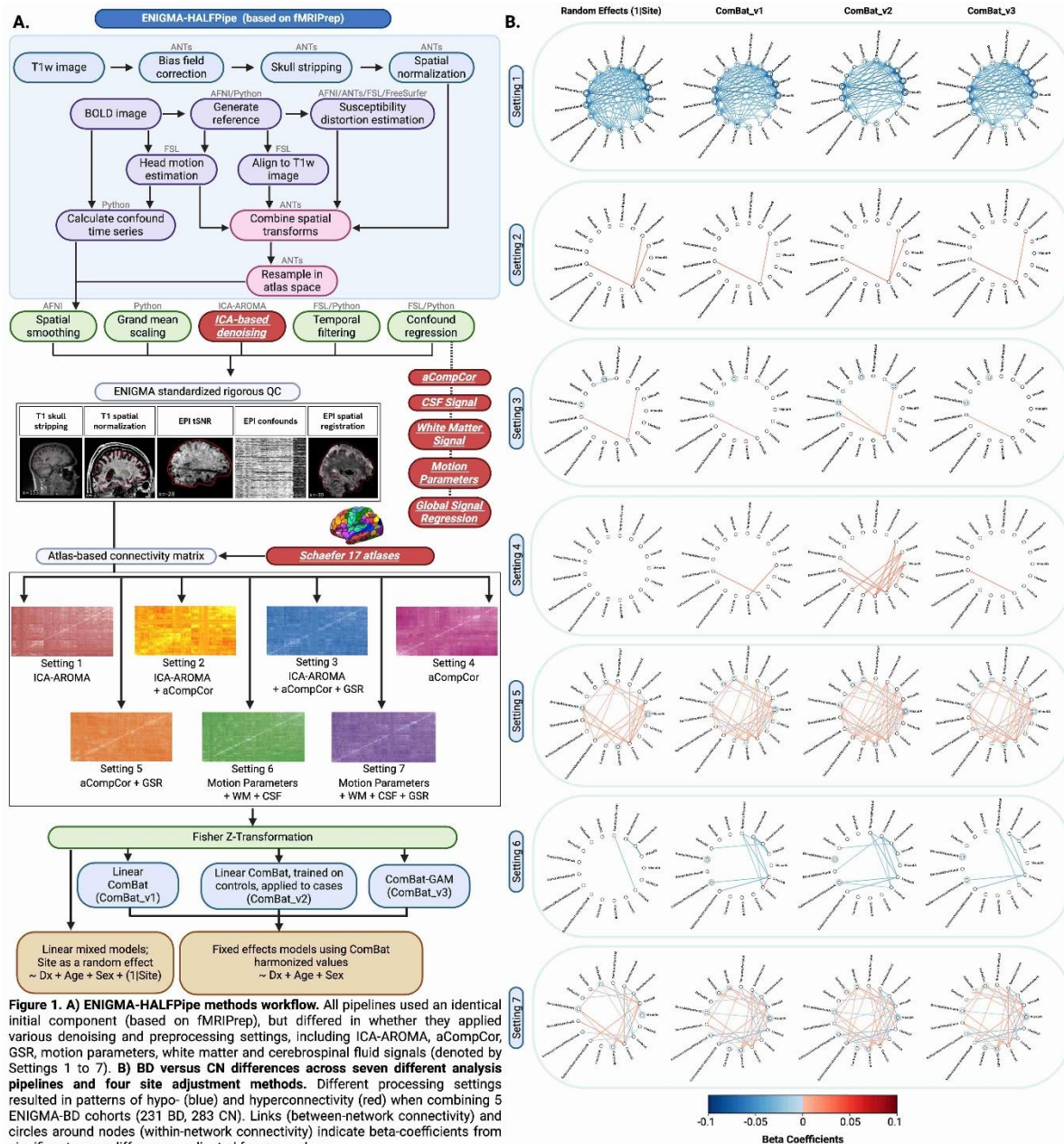
Title: A scalable framework for multisite functional MRI analyses of mental illness: Insights from ENIGMA Bipolar Disorder Working Group

Authors: *M. KANG¹, L. NABULSI¹, S. I. THOMOPOULOS¹, Y. IM¹, D. CANNON², J. C. SOARES³, G. ZUNTA-SOARES³, B. MWANGI³, M.-J. WU³, J. M. FULLERTON⁴, P. MITCHELL⁵, G. ROBERTS⁵, L. KLAHN⁶, M. LANDÉN⁷, E. VILAJOSANA⁸, C. MOREAU⁹, J. RADUA⁸, L. WALLER¹⁰, I. VEER¹¹, O. A. ANDREASSEN¹², P. M. THOMPSON¹, C. CHING¹;

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Abstract: Resting-state functional MRI (rsfMRI) studies of mental illness often apply various data processing and analysis techniques to small single site samples, making it challenging to assess generalizability. Standardized data processing and site adjustment methods are needed to pool existing study samples and improve the predictive power of rsfMRI features for mental illness.

We pooled data from 5 ENIGMA-Bipolar Disorder (BD) Working Group sites (231 BD, 283 controls (CN), ages 13-81, 57% female) to evaluate the effects of 7 preprocessing pipelines and 4 site harmonization methods on BD vs. CN functional connectivity features, using ENIGMA-HALFpipe - a scalable framework for large-scale rsfMRI studies (Figure 1A). Site effects were adjusted using 1) linear mixed-effect models (with site as a random effect), 2) linear ComBat applied to the whole sample, 3) linear ComBat trained on CN then applied to BD, and 4) non-linear ComBat-GAM. Combinations of seven common processing settings were tested: ICA-AROMA, aCompCor, global signal regression (GSR), motion parameters, and physiological regressors. All results were adjusted for age, sex, and multiple comparisons (FDR; $q < 0.05$). BD vs. CN connectivity differences varied across choice of settings (Figure 1B). Hypoconnectivity within Default Mode A and within Dorsal Attention A networks was consistently observed in settings 1, 3, 5, and 7. Settings 2, 3, 5, and 7 demonstrated hyperconnectivity across Dorsal Attention B and Frontoparietal Control C networks. The application of GSR increased the detection of within and between network connectivity alterations in BD. Linear and non-linear ComBat methods resulted in more group differences, than modeling site as a random effect. In this preliminary analysis, variations in rsfMRI processing influenced the detection of functional connectivity differences between BD and CN. ENIGMA-HALFpipe provides a standardized framework for combining multisite rsfMRI data to boost statistical power and search for more generalizable rsfMRI markers for BD and other mental illnesses.



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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.29/EE7

Topic: H.05. Mood Disorders

Title: Reward and Resilience

Authors: *C. A. MIKKELSEN;
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Abstract: A critical question in mental health research seeks to address why some individuals who experience stressors remain seemingly unscathed, while others develop increased psychopathology symptoms. Previous work has sought to investigate the potential protective effects of reward sensitivity against the development of psychopathology in response to stressful life events. It has been proposed that increased reward sensitivity promotes resilience by helping individuals maintain positive affect, and promoting approach behavior. Due to the increased plasticity of the developing brain, it is particularly important to understand stress responses in children and adolescents. I will present two complementary pre-registered studies using consortium data from the Human Connectome Project in Development (HCP-D) and the Adolescent Brain and Cognitive Development (ABCD) Study that seek to expand our knowledge about how neural sensitivity to reward may promote resilience in the face of stressful life events. Specifically, we investigate how neural activity in response to reward anticipation and reward receipt in the striatum and ventromedial prefrontal cortex (vmPFC) moderate the association between stressful life events and development of internalizing psychopathology in two large samples of youths. In the first study, we utilized neural data collected before the COVID-19 pandemic as part of the HCP-D, and follow-up data collected post-pandemic that inquired as to participants' pandemic-related stressors and their current mental health. We found that activity in the left ventromedial prefrontal cortex for wins vs losses during reward receipt, moderates the association between pandemic stressors and psychopathology. In contrast, activity in the striatum during reward receipt did not moderate this association. In the second study (ABCD), we analyzed data from the Monetary Incentive Delay task which allowed us to investigate neural activity during reward anticipation. Here, we found that both striatal activity and activity in the vmPFC for activity during reward anticipation versus neutral trials moderated the association between life stressors and psychopathology. These results set the stage to explore the distinct roles of the ventromedial prefrontal cortex and the striatum, both critical aspects of the reward processing network, in promoting resilience in the face of stressors.

Disclosures: C.A. Mikkelsen: None.

Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.30/EE8

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

Title: Associations between adverse childhood experiences, family environment, and internalizing symptoms in early development

Authors: *D. LEE¹, B. LEONARD², J. RASMUSSEN¹, M. A. YASSA³;
²Neurobio. and Behavior, ¹Univ. of California, Irvine, Irvine, CA; ³Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Early-life adversity contributes to mental health risk, but the role of family environment in shaping these effects remains poorly understood. While adverse childhood experiences (ACEs) have been widely studied, less is known about exposure to ACEs as it relates to specific aspects of family environment (e.g. supportive/cohesive vs. negative/dysfunctional aspects) as well as internalizing symptoms. Data were drawn from a subsample of Adolescent Brain Cognitive Development (ABCD) study (n = 2,282, 8.9-11 years) with family environment assessed via the Family Environmental Scale (FES) and sorted into 2 principal components: "Family Cohesion" and "Family Dysfunction". Early life adversity was measured by the Adverse Childhood Experiences (ACEs). Internalizing symptoms were measured using parent-reported Child Behavior Checklist (CBCL) internalizing composite scores, reflecting symptoms of anxiety, depression, withdrawal, and somatic complaints. Higher ACEs scores were associated with lower family cohesion ($p < .001$), but not significantly associated with family dysfunction. Higher ACEs scores were also associated with higher internalizing symptoms ($R = 0.291$, $p < .001$). Moderation analyses revealed that Family Cohesion significantly moderated the ACEs-internalizing symptoms association ($p < .01$), such that the association between ACEs and internalizing symptoms was stronger at higher levels of family cohesion. No moderation effect was observed for Family Dysfunction. While higher family cohesion would normally be considered protective, in this sample, it amplified the statistical association between ACEs and internalizing symptoms. This may reflect greater emotional salience of adversity in families with higher cohesion, or bidirectional effects where internalizing symptoms influence perceived family cohesion. Longitudinal studies are needed to clarify directionality and to examine how these factors relate to underlying brain circuits, including functional connectivity between the paraventricular nucleus of the thalamus (PVT) and hippocampus. Ongoing work will also explore potential race and sex differences in these relationships.

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Poster

PSTR181: Human Imaging: Mood

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR181.31/FF1

Topic: I.03. Decision Making

Support: NIMH R01MH12830

Title: Motivational conflict resolution is shaped by early life unpredictability

Authors: *B. LEONARD¹, M. MARTINEZ-ORTIZ², C. A. HARTLEY³, M. A. YASSA⁴, A. BORNSTEIN¹;

¹Univ. of California, Irvine, Irvine, CA; ³Psychology, ²New York Univ., Brooklyn, NY;

⁴Neurobio. and Behavior, Univ. of California Irvine, Irvine, CA

Abstract: Motivational conflict resolution is central to survival. There is growing evidence from rodent and human experiments that brain processes underlying motivational conflict resolution may be interrupted by early life adversity-specifically, unpredictability during childhood (ELU)--and be altered in mood disorders such as anhedonia. However, it is unknown which components of the resolution process in adulthood are altered by elevated adversity. Participants were asked to play "Revenge of the Zorn," a gamified version of a motivational conflict task adapted from Korn & Bach, 2019. Participants played as space explorers trying to survive as many planets as possible (keeping their fuel tank above zero fuel units for a full 5 trials each). On each planet they were asked to decide between 1) playing a game with trial-varying, explicit chance of gaining fuel, losing fuel, or being robbed by a Zorn alien (sudden death), versus 2) paying one fuel point to wait for the next trial (avoidance strategy). The total sample consisted of 111 participants, including: a web-based cohort (Prolific; n = 98, 52 Female, 57 Male, 2 "Other"; 32.7 ± 11.2 years), and an fMRI cohort collected locally (n = 13, 4 Female, 8 Male, 2 "Other"; 28.9 ± 9.47 years). Early life adversity was measured by the Questionnaire of Unpredictability in Childhood (QUIC) and the Adverse Childhood Experiences survey (ACEs). Participants with higher QUIC survived fewer planets ($r = .26$, $p = .008$), consistent with their choices being less likely to follow the optimal policy ($r = -.3$, $p = .002$). This was attributed to greater avoidance in response to threat ($r = -.2$, $p = .03$), despite being marginally more likely to forage in all situations ($r = .19$, $p = .053$). ACEs did not reveal effects of early life adversity on behavioral measures (all $r < .14$, $p > .14$), though ACEs and QUIC were strongly correlated ($r = -.61$, $p < 10^{-12}$). Early life unpredictability has large effects on emotional circuit maturation, cognition, and long-term mental health outcomes. We find that motivational conflict resolution can provide a specific measure of the effects of ELU on behavior, perhaps distinct from other forms of adversity, and with sensitivity to trial-varying task demands that allows for mechanistic investigation using, e.g., fMRI.

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Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.01/FF2

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Hartford Hospital Medical Staff Grant
Jim Bowers and Becky Swanson-Bowers Research Fund
Yale center for clinical investigation (YCCI)

Title: Altered Reward Processing in Individuals Receiving Methadone for Opioid Use Disorder and Individuals Pursuing Metabolic Bariatric Surgery Compared to Community Controls

Authors: *D. KANG¹, V. R. STEELE²;

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Abstract: Opioid use disorder (OUD) and obesity are two critical public health challenges. Both opioids and food are powerful reinforcers, to which repeated exposure hijacks reward neurocircuitry. Whether OUD and obesity have overlapping reward deficit is under debate. Here, we hypothesized a similar monetary reward processing deficit in individuals receiving methadone to treat OUD (MOUD) and individuals pursuing metabolic bariatric surgery (MBS), compared to community controls (CC). We collected event-related potential (ERP) data during a monetary reward task from 30 MOUD participants (43.4% female, mean age 40.6), 12 MBS participants with high food reward sensitivity (66.7% female, mean age 44.8), and 30 CC participants (43.3% female, mean age 24.8). Mean amplitudes of late positive potential (LPP), representing extended reward processing, relative to win/loss feedback type, were extracted from electrodes Cz and Pz. We conducted a repeated measure ANOVA, including group, channel, feedback type (Win/Loss), their interactions, and age as factors in the model and two-sample t-tests to assess simple effects. The repeated measure ANOVA indicated a significant interaction of group by channel ($F(2,255)=3.73, p=0.025$), and main effect of channel ($F(1,255)=86.43, p<0.001$), group ($F(2,255)=22.30, p<0.001$), age ($F(1,255)=4.58, p=0.034$) but not feedback type. MOUD participants exhibited an elevated LPP across all feedback types in Cz ($t(55.4)=4.29, p<0.001$) and Pz ($t(51.9)=2.49, p=0.016$) compared to CC participants. Moreover, MBS participants had elevated LPP in Pz ($t(23.0)=2.14, p=0.043$) but not Cz, compared to CC participants. MOUD participants had larger LPP in Cz ($t(34.2)=3.37, p=0.002$) but not in Pz, compared to MBS participants. Our results indicated a similarly elevated LPP in monetary reward processing in both MOUD and MBS compared to CC, suggesting a hijacked reward system by drugs or food. Interventions targeting these reward processes may be effective for both groups.

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Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

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Program #/Poster #: PSTR182.02/FF3

Topic: H.04. Emotion

Support: NIH Grant MH125615
NIH Grant MH112558
NSF Grant BCS2318984

Title: Role of the Pulvinar in Visual Affective Scene Processing

Authors: ***M. J. LOBEL**¹, L. CUI², Y. LIANG¹, K. BO³, A. KEIL⁴, M. DING⁵;
¹Biomed. Engin., ²Biomed. engineering, Univ. of Florida, Gainesville, FL; ³Dept. of Psychological and Brain Sci., Dartmouth Col., Lebanon, NH; ⁵Biomed. Engin., ⁴Univ. Florida, Gainesville, FL

Abstract: The pulvinar is the largest nucleus of the thalamus. The proposed functions of the pulvinar range from working memory to attention to emotion. In this study, we examined the role of the pulvinar in visual affective scene processing by analyzing two independent fMRI datasets. In the first dataset, simultaneous EEG-fMRI data were recorded from 20 human participants viewing pleasant, unpleasant, and neutral scenes from the International Affective Picture System (IAPS). In the second dataset, fMRI data were recorded from 30 human participants performing an emotion reappraisal task, in which they were cued to anticipate and then viewed unpleasant and neutral scenes from the IAPS. Analyzing single-trial BOLD responses using support vector machine (SVM) and deep neural network (DNN) decoding techniques, we found that linear SVM was not able to consistently detect the differences in neural representations of different categories of affective scenes in the pulvinar (52.53% for Dataset 1 and 66.61% for Dataset 2), whereas a DNN model was able to consistently do so with significantly above-chance decoding accuracies (58.50% for Dataset 1 and 75.00% for Dataset 2). A weight map analysis further revealed that the medial pulvinar is the most important contributor to the DNN decoding performance. These results demonstrated that the pulvinar contributes to the processing of visual affective scenes and AI-inspired techniques can detect neural pattern differences not readily detected by the conventional machine learning methods.

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Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: Wellcome Trust grant 206207/Z/17/Z
Wellcome Trust grant 206207/Z/17/A
Wellcome Trust grant WT 095495
Wellcome Trust grant WT 204811

BBSRC Discovery Fellowship
John Fell Oxford University Press Research Fund

Title: Value coding by primate amygdala neurons complies with economic choice theory

Authors: *F. GRABENHORST¹, W. SCHULTZ³, S. FERRARI-TONIOLO²;

²Dept. of Exptl. Psychology, ¹Univ. of Oxford, Oxford, United Kingdom; ³Univ. Cambridge, Cambridge, United Kingdom

Abstract: Primate amygdala neurons are implicated in coding the value of choice options for decision-making. Recent studies showed that amygdala neurons process and integrate distinct value components such as reward probability and magnitude (Grabenhorst and Baez-Mendoza, 2025). Further, amygdala neurons process these values into economic choices by implementing a view-based decision mechanism (Grabenhorst et al., 2023). However, it remains unclear whether amygdala value signals comply with the notion that decision makers maximize the value of rewards, as formalized by key axioms of economic theory. In particular, the continuity axiom of Expected Utility Theory (EUT) postulates that reward maximization is reflected by a trade-off between reward probability and magnitude. Our experiment tested this trade-off in two male macaque monkeys who subjectively ranked three gambles in choices, thus revealing their subjective value. Axiom compliance was defined by choice indifference between the intermediate gamble and a probabilistic combination of the other two gambles. We found that the animals' choices between safe and gamble options reflected the integration of probability and magnitude into scalar values consistent with the continuity axiom. In a non-choice task, responses of individual amygdala neurons to separate probability and magnitude cues reflected the monkeys' individual preferences: neuronal responses were lower for non-preferred gambles (relative to safe options), higher for preferred gambles and equal at subjective indifference between safe and gamble options. In a choice task, amygdala neurons integrated probability and magnitude into subjective values that reflected individual preferences. In some neurons, value signals transitioned to signals coding the monkey's economic choices and chosen values. These findings identify amygdala neurons as substrates for encoding behavior-matching subjective values according to the continuity axiom of EUT, and for translating these values into economic choices. Dysfunctional processing of values and choices by the amygdala could play a role in psychiatric and behavioral disorders affecting mental health, in which the amygdala is implicated. References Grabenhorst F, Baez-Mendoza R (2025) Dynamic coding and sequential integration of multiple reward attributes by primate amygdala neurons. Nat Commun 16:3119. Grabenhorst F, Ponce-Alvarez A, Battaglia-Mayer A, Deco G, Schultz W (2023) A view-based decision mechanism for rewards in the primate amygdala. Neuron 111:3871-3884 e3814.

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Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.04/FF5

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Sequential Processing of Physical Salience and Subjective Value Prediction Error in Human SN/VTa

Authors: *J.-C. KIM¹, L. HELLRUNG¹, P. N. TOBLER^{1,2};

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Abstract: Neurons in the dopaminergic substantia nigra/ventral tegmental area (SN/VTa) are crucial for processing value prediction errors (VPEs). In non-human primates, prediction error responses are preceded by responses encoding stimulus salience. However, the precise temporal dynamics of these two signals for predictive cues remain unclear in humans. This fMRI study aimed to temporally characterize and dissociate cue-evoked physical salience and subjective VPE signals in the human SN/VTa. Forty-one healthy participants (mean age 22.4 ± 0.43 years; 19 women) performed a Pavlovian task where visually similar cues predicted appetitive, aversive, or neutral liquid outcomes, delivered probabilistically ($p=0, 0.5$, or 1 ; absolute subjective values for valenced liquids were individually matched). Physical cue salience was indexed by trial-by-trial cue-induced pupil diameter decrease (constriction), and subjective cue VPE was operationalized as the difference in pleasantness rating between presented cues and block averages. General linear model analysis of SN/VTa BOLD responses revealed that activity at cue onset significantly correlated with physical cue salience ($p<0.05$, peak-level, SN/VTa small-volume-corrected). At the time of the subsequent volume (2.1 s post-cue), SN/VTa activity significantly correlated with subjective cue VPE ($p<0.05$, peak-level, SN/VTa small-volume-corrected). Crucially, direct statistical comparison demonstrated that physical salience signals at cue onset were significantly stronger than VPE signals, with the inverse being true at the subsequent time step. These temporally distinct physical salience and VPE signals nevertheless colocalized within the SN/VTa. Our findings demonstrate that conditioned stimuli elicit bi-phasic signals in the human SN/VTa, with an initial, rapid coding of physical salience followed by a distinct, later signal representing subjective value prediction error.

Disclosures: J. Kim: None. L. Hellrung: None. P.N. Tobler: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.05/FF6

Topic: H.03. Motivation

Title: Reward-driven cognitive control of emotional conflict

Authors: *S. DEB¹, S. PADMALA²;

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Abstract: Cognitive control refers to the mental processes that help us align our behavior in a goal-directed manner, especially in the face of conflicts. However, exerting control is costly and effortful, and motivational signals such as performance-based monetary rewards can bias the cost-benefit trade-off toward deploying it. As prior work mainly focused on the impact of reward motivation on non-emotional conflicts, whether and how reward incentives modulate control during emotional conflicts remains unexplored. Unlike in the non-emotional conflict scenarios, it is plausible that reward motivation might not be able to counter the impact of potent incongruent emotional distractors when dealing with emotional conflicts. We tested this question using a face-word emotional conflict paradigm during which trial-wise pre-cues signaled a prospect for a monetary bonus (reward) or none (no-reward). In an initial behavioral study (N = 39; 20 F; 23 ± 3 y), we found that reward (vs. no-reward) prospect led to reduced emotional conflict both in terms of RT and accuracy. In a follow-up fMRI study (N = 33; 17 F; 24 ± 3 y), reward (relative to no-reward) pre-cues robustly engaged ventral striatum, prefrontal and parietal cortex regions, consistent with anticipatory (proactive) mobilization of cognitive control circuitry. During the subsequent task phase, a significant *Reward* (reward, no-reward) × *Congruency* (congruent, incongruent) interaction was detected in the right amygdala, indicating reduced emotional conflict-related activity under reward. Furthermore, across participants, reward cue-driven activation in the rostral anterior cingulate cortex (rACC) (region previously implicated in specifically resolving emotional conflict) predicted reward x congruency interaction scores in the amygdala, suggesting that stronger recruitment of rACC under reward motivation led to greater attenuation of emotional conflict-related activity. Finally, rACC activity correlated with ventral striatum activity while processing reward cues, pointing to a striato-rACC circuit through which reward biases proactive control. Overall, these findings demonstrate that reward incentives strengthen the deployment of cognitive control over emotional conflict by coupling valuation signals in the ventral striatum with rACC control mechanisms, leading to reduced emotional conflict-related activity in the amygdala and potentially aiding behavior. Elucidating how reward motivation modulates emotional conflict has implications for leveraging motivational strategies in conditions marked by deficient affect-laden control, including anxiety and mood disorders.

Disclosures: S. Deb: None. S. Padmala: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.06/FF7

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant K99MH137315
NIH Grant 5R01MH118638

Title: Expectancy violations influence affective states

Authors: *D. FOLLONI¹, F. M. STOLL², P. H. RUDEBECK³;

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Abstract: BACKGROUND: Establishing the mechanisms underlying mood-like states is essential to characterize the basis of Major Depressive Disorder. Emerging theories posit that fluctuations in the rate of expectancy violations influence our affective states providing an experimentally tractable approach to the study of moods. Here, we investigated the behavioral impact of repeated reward prediction violations in situations where learning is not required and where changes in reward rate can be controlled. METHODS: Two macaque monkeys were trained to perform two distinct reward-guided tasks. Before either task, they learned the reward probabilities for 90 unique visual stimuli. Ten stimuli were each associated with a different reward probability, starting at 0.1 and increasing by 0.1 up to 0.9. After learning, they performed a two-choice decision-making task, selecting between two stimuli randomly drawn from the pool of 90. This confirmed they reliably chose the higher reward probability stimulus. They then performed an affect induction task where each stimulus was presented once per session. For 10 trials, reward contingencies were briefly altered to increase the rate of either positive (positive induction version) or negative prediction errors (negative induction version) to induce positive and negative affective state changes, respectively, while reducing the influence of reward learning. Either versions of the affect induction task was presented on each day. RESULTS: In the two-choice decision-making task, subjects chose the stimulus with the highest reward probability on nearly every trial, confirming they had learned the reward contingencies. In the affect induction task, we found that during periods with increased negative prediction errors—due to violations of expected high-reward outcomes—animals' RTs increased. This suggests enhanced affective sensitivity to unexpected negative events in familiar contexts. In contrast, positive affective induction did not alter subjects' RTs. CONCLUSIONS: We show that unexpected events, even from a single stimulus, can shift affective states by briefly altering the consequences of actions the monkeys experience. These results suggest that, in familiar contexts with predictable outcomes, negative—but not positive—violations of expectation can transiently influence affect. This mechanism may underlie the unregulated mood fluctuations seen in mood disorders. Future work will examine related brain and autonomic activity.

Disclosures: D. Folloni: None. F.M. Stoll: None. P.H. Rudebeck: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.07/FF8

Topic: H.02. Reward and Appetitive Learning and Memory

Support: BBSRC Discovery Fellowship BB/Z514780/1
Wellcome Trust 206207/Z/17/Z
Wellcome Trust 206207/Z/17/A

Title: Do monkeys have a theory of mind?

Authors: *S. FERRARI-TONIOLO, M. KADOHISA, M. KUSUNOKI, M. J. BUCKLEY, F. GRABENHORST;
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Abstract: Introduction. Understanding others' mental states is a fundamental element of human social cognition and Theory of Mind (ToM). It is unclear to what extent other primate species manifest this sophisticated social ability, which is disrupted in disorders including autism and schizophrenia. While previous studies have shown that macaques can predict other's choices and socially coordinate their actions (Ferrari-Toniolo et al., 2019, J Neurosci; Grabenhorst et al., 2019, Cell; Haroush & Williams, 2015, Cell), it remains unresolved whether these abilities indicate the understanding of mental states of other agents. Here, we investigated whether monkeys exhibit understanding of others' reward preferences — reflecting subjective mental states — when these differ from own preferences. **Methods.** Two macaques faced each other over a horizontal touch-screen, with visual cues indicating different types and amounts of offered reward (fruit smoothies, 0.2 to 1.0 ml). The monkeys alternated between making and observing choices. Some of the rewards elicited opposite preferences between the two animals. The task allowed the animals to observe each other's choices and thus learn each other's preferences. **Results.** To measure understanding of other's preferences, we quantified the probability of looking at the different reward cues before the touch-screen choice on each trial. When making choices, the monkeys looked significantly more at their preferred option. When observing other's choices between the same pair of options, the monkeys spontaneously and without incentive looked at the partner's cues. Importantly, the monkeys did not look at the partner's cues indiscriminately, nor did they look more frequently at the cue indicating their own preferred reward. Rather, they looked significantly more frequently at the option preferred by the other animal, which was demonstrated when using rewards for which the animals had opposite preferences. **Conclusions.** By demonstrating oculomotor social prediction of other's revealed preferences when these differed from own preferences, these results indicate that macaques can learn from observation to understand the reward preferences of social others. This ability may constitute a precursor of human mentalizing capacities, such as ToM. Our paradigm provides a framework for investigating the neurophysiological basis of understanding others' preferences.

Disclosures: S. Ferrari-Toniolo: None. M. Kadohisa: None. M. Kusunoki: None. M.J. Buckley: None. F. Grabenhorst: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.08/FF9

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant DK134804

Title: Weight loss after obesity disrupts cognitive flexibility through sex-specific reinforcement learning strategies

Authors: *Y. LI¹, B. A. MATIKAINEN-ANKNEY²;

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Abstract: Despite the growing market of interventions for people to lose weight, individuals with a history of obesity often suffer from weight regain, and this has demonstrated a need for a better understanding of factors contributing to this relapse. In our study, we focus on the cognitive aspect and test the hypothesis that persistent deficits in cognitive flexibility - specific maladaptive reinforcement learning strategies - undermine decision-making in the post-weight-loss state. Using a mouse model of diet-induced obesity followed by diet-induced weight loss, we investigated alterations in reward-guided decision-making through an 80:20 probabilistic reversal learning task and closed-economy progressive ratio task. Male and female mice (n=7 each) underwent 8 weeks of high-fat diet (HFD)-induced obesity, followed by 6 weeks of chow diet-induced weight loss. Post-weight-loss mice and controls were tested on a modified probabilistic reversal learning (PRL) task to assess cognitive flexibility and a closed-economy progressive ratio (PR) task to evaluate motivation. Reinforcement learning (RL) modeling was applied to dissociate latent decision-making parameters. Both sexes achieved comparable weight loss, but post-weight-loss mice exhibited persistent deficits in PRL performance: males showed reduced efficiency during late-phase reversal learning ($p < 0.001$), while females showed early-phase impairments ($p < 0.05$) but recovered later. RL modeling revealed reduced learning rate in post-weight-loss mice, indicating impaired value updating despite intact motivation. Sex-specific strategies were suggested here, with females compensating for early deficits through dynamic adjustment, whereas males remained inflexible. These findings demonstrate that prior obesity induced long-lasting, sex-divergent cognitive inflexibility, characterized by maladaptive reinforcement learning, which may explain vulnerability to relapse. This demonstrates the need for targeted interventions addressing post-weight-loss cognitive barriers to improve maintenance outcomes.

Disclosures: Y. Li: None. B.A. Matikainen-Ankney: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.09/FF10

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Wellcome Trust 227608/Z/23/Z
Wellcome Trust 206207/Z/17/Z
Wellcome Trust 206207/Z/17/A

Title: Structured Nutrient Encoding in Primate Amygdala During Reward-based Decisions

Authors: *F.-Y. HUANG, F. GRABENHORST;
Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: Sensory and nutrient properties influence behavioral and neural responses to food rewards. Primates exhibit robust preferences for sugar and fat, suggesting these properties are integrated into subjective values that guide food choice (Huang et al., 2021) and reinforcement learning (Huang & Grabenhorst, 2023). The amygdala is critical for value-based decision-making (Grabenhorst et al., 2012; Jezzini & Padoa-Schioppa, 2020) and for regulating appetite and post-ingestive processes (Zimmerman et al., 2025). However, it remains unknown how biologically critical macronutrients—fat, sugar, and protein—organize amygdala reward coding to support nutrient-sensitive food choice. Here, we recorded single-unit activity from 208 amygdala neurons in two adult male rhesus macaques (*Macaca mulatta*) as they repeatedly chose between eight dairy-based liquid rewards varying in nutrient content (fat, sugar) and oral texture (viscosity, sliding friction). On each trial, monkeys viewed two sequentially presented visual cues (CS), each predicting one reward type, then made a touch choice to receive the chosen reward. Mixed-effects logistic regressions ($n = 18,704$ and $22,170$ choices) confirmed that monkeys preferred liquids high in fat and sugar, and that oral texture mediated the influence of fat content on choice (Huang et al., 2021). Neuronal responses were best explained by general linear models that incorporated nutrient and sensory properties, outperforming stimulus-identity models. Significant fractions of neurons encoded nutrient and sensory properties during cue presentation. Surprisingly, these neurons formed six distinct clusters in Gaussian Mixture Models, each tuned to specific nutrient or sensory dimensions. To examine the nutritional structure of reward coding, we modeled firing rates using Poisson regression models with fat-sugar interaction terms and constructed nonlinear ‘nutrient tuning surfaces’ in ‘mixer triangles’ defined by fat, sugar, and protein proportions. We identified 52/208 (25%) neurons with significant nutrient-space tuning using permutation tests. Unlike support-vector machine decoders trained to classify value and choice variables, nutrient and sensory attribute decoders did not generalize across CS sets—demonstrating cue-specific nutrient representations that converged into abstract value and choice signals during decision-making. These findings reveal unrecognized nutritional structures in high-dimensional amygdala reward coding. The nutritional framework offers a new approach to uncovering functioning principles of primate reward systems shaped by nutritional goals for survival.

Disclosures: F. Huang: None. F. Grabenhorst: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.10/FF11

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Wellcome Trust 206207/Z/17/Z
Wellcome Trust 206207/Z/17/A
Economic and Social Research Council [grant number ES/P000649/1]
Wellcome Centre for Integrative Neuroimaging (WIN Seed Grant: Rapid Response Seed Awards - September 2024)

Title: The neural basis of economic trading: reward exchange during social interaction

Authors: *T. TRAUT, F. GRABENHORST;
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Abstract: Economic trading, the mutually beneficial exchange of goods, is a universal behavior necessary for both individual function and societal welfare. From a neuroscience perspective, trading constitutes a paradigm of complex social cognition. The successful completion of a trade requires (i) subjective valuations of available goods (i.e., rewards), (ii) perspective-taking for social trading partners, and (iii) integrating reward valuations for self and other to determine a mutually acceptable exchange. Economic theory provides a basis for quantifying trading behavior: indifference maps, which represent utility at given reward endowments, characterize individual reward preferences and enable estimation of efficient trading outcomes. However, empirical demonstration of predicted optimal trading and identification of underlying neural mechanisms has remained outstanding. Here, we investigate economic trading behavior during social interaction, using foundational economic models as a guiding framework. Human participants traded rewards with varying social partners in dyads (N=112) and groups (N=50). In a subsample (N=37), neural activity was measured using fMRI during dyadic trading. On each dyadic trading trial, participants received a random endowment (of a two-component liquid food reward) and chose to keep or trade their endowment with one of three social partners with cued, varying reward preferences. Trading involved choosing which reward-component to offer the partner, the offer amount, and the amount to request of the other component in return. In the group task, multiple participants engaged in unrestricted trading (of unitless reward vouchers). Individual reward preferences were well-characterized by empirically constructed indifference maps, allowing accurate prediction of trading: participants who preferred a reward-component attempted trades that maximized their endowment of that same component. Despite significant inter-individual differences in reward preferences, a majority of trade offers were successful. Across participants, both dyadic and group trading resulted in overall increases in utility, with trade proposals that generally approximated optimal choices. Analysis of fMRI data will identify brain areas encoding self utility, other utility, and their integration, and will establish the validity of using neural activity to predict participant trading outcomes in naturalistic settings. The findings from this novel paradigm demonstrate patterns in human trading behavior consistent with predictions from economic theory and may provide insights into the cognitive strategies shaping trade decisions.

Disclosures: T. Traut: None. F. Grabenhorst: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.11/FF12

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Wellcome Trust 206207/Z/17/Z
Wellcome Trust 206207/Z/17/A

Title: Social influence from other's motivation

Authors: *T. JOHNSON, F. GRABENHORST;
Dept. of Exptl. Psychology, Univ. of Oxford, Oxford, United Kingdom

Abstract: The quality of one's motivation has long been established as an essential component of goal pursuit, subjective wellbeing, and other life outcomes. However, whether the perceived motivation of social others is similarly important in guiding behaviour remains unexplored. Here, we investigated whether the type of motivation perceived in a social other alters their influence on one's own behaviour. Participants (n = 104) completed a series of experimental tasks in which they were introduced to a range of social partners who varied in terms of their 'motivational type', a well-defined concept used within Self-Determination Theory (Ryan & Deci, 2000) to describe the quality of one's motivation. Participants learned about each partner's motivational type by reading detailed biographical descriptions introducing these partners as health professionals who were motivated to eat healthily for different reasons. Participants rated these partners on socially-relevant characteristics before performing a series of incentive-compatible decision-making and willingness-to-pay auction tasks that measured preferences. Across these tasks, participants: (i) accurately discerned the self-determination of partners, (ii) were more willing to follow the nutritional decisions of self-determined partners, (iii) expressed stronger preferences for self-determined partners, (iv) switched their food preferences more frequently following the advice of self-determined partners, and (v) were more willing to pay for information about the healthy-eating behaviour and motivation of self-determined partners. These effects were not explained by other social characteristics (rated expertise, trustworthiness, likeability, or similarity) or facial characteristics. Across participants, sensitivity to other's self-determination predicted the degree of social influence in a naturalistic food choice scenario. Functional neuroimaging in a subset of these tasks serves to reveal the underlying neural mechanisms. These data demonstrate that an individual's motivation does not only guide their own behaviour but also the behaviour of social others, a phenomenon we term 'Social Influence from Other's Motivation'.

Disclosures: T. Johnson: None. F. Grabenhorst: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.12/GG1

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIDA Grant R21DA057618
Scialog Grant #29077

Title: The reward positivity tracks the change in value to predictive cues during reinforcement learning

Authors: *Y. GAO, M. JONES, M. ZAKI, T. BAKER;
Ctr. for Mol. and Behavioral Neurosci., Rutgers Univ. - Newark, Newark, NJ

Abstract: Reward prediction error (RPE) signals are central to temporal difference learning, enabling earlier cues to acquire predictive value and guide goal-directed behavior. In humans, the event-related potential (ERP) known as the reward positivity (RewP) behaves like an RPE signal, with positive RPEs eliciting a larger RewP than negative RPEs. However, it remains unclear whether the RewP can be elicited by predictive cues that precede outcomes. To address this, we examined ERPs elicited by such cues as participants learned cue-outcome associations through trial-and-error. Participants completed a virtual T-maze task with six training blocks and three interleaved testing blocks. During training, participants made left/right choices to reach a goal location. At the first turn, one of six predictive cues was presented. Each cue predicted a reward (5¢) with a fixed probability (A: 100%, B: 0%, C: 75%, D: 25%, E/F: 50%). Color and shape indicated valence and probability. During testing, participants selected between cue pairs they felt was more likely to yield a reward. We hypothesized that successful learning would yield increased cue-locked RewP amplitude over time. EEG was recorded from 32 electrodes from 47 participants. Based on AB pair accuracy, participants were grouped into slow (SL: <50%), medium (ML: 50-90%), and fast (FL: >90%) learners. ERP difference waves were computed between cues with complementary probabilities (AB, CD, EF) and across early (blocks 1-2), middle (3-4), and late (5-6) blocks. RewP amplitude was extracted from 200-300 ms post-cue at Fz. An ANOVA revealed a main effect of block ($p = .006$), indicating increased RewP amplitude over time. Post-hoc tests showed that the FL and SL groups exhibited greater CD-RewP in the late ($d = 2.67$) and middle ($d = 2.45$) blocks, respectively, vs early blocks. The ML group showed increased AB-RewP in the late vs middle block ($d = 2.11$), and also showed late EF-RewP changes ($d = 2.36$) compared to earlier blocks. Additionally, ML and SL groups showed EF- and CD-RewP enhancements over AB-RewP in the middle block ($d = 2.27$, $d = 2.39$). These results suggest that cue-elicited RewP tracks the updating of reward expectations, support its role as a neural correlate of RPE, and have implications for using RewP as a biomarker of reward learning in clinical populations.

Disclosures: Y. Gao: None. M. Jones: None. M. Zaki: None. T. Baker: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.13/GG2

Topic: H.02. Reward and Appetitive Learning and Memory

Support: F31AA031627

Title: Reward Processing in Early Adolescence: A Large-Scale Latent Variable Modeling Approach

Authors: *A. PORTER, B. FROELIGER, D. MCCARTHY;
Dept. of Psychological Sci., Univ. of Missouri, Columbia, MO

Abstract: Heightened reward-related impulsivity during adolescence is linked to increased engagement in unhealthy risk-taking behaviors, such as substance use and risky sexual activity. Neuroimaging research has shown that reward anticipation and receipt are associated with increased neural activation in striatal and cognitive control regions, which undergo significant maturation during the critical developmental period of adolescence. Latent variable approaches offer a significant advantage over traditional univariate approaches by capturing shared variance across multiple brain regions, thus providing a more integrated representation of the neural reward-related mechanisms underlying adolescent risk-taking behaviors. In this study, we utilized baseline data from the Adolescent Brain Cognitive Development study ($N = 10,749$; 52% Male; Age range 9-10) to examine the latent factor structure of neural activation patterns associated with reward anticipation and reward receipt during the Monetary Incentive Delay (MID) task. Using exploratory and confirmatory factor analyses, we identified three latent reward anticipation factors, characterized by covariation in the ventral and dorsal striatum and the occipital cortex [RMSEA = 0.057 (90% CI 0.054, 0.060), CFI = 0.92, TLI = 0.89], and two reward receipt factors, characterized by covariation within prefrontal cortex regions and between the default mode network and amygdala [RMSEA = 0.028 (90% CI 0.024, 0.034), CFI = 0.87, TLI = 0.81]. These findings provide a foundation for future work examining how reward-related brain activation is associated with impulsivity and risk-related behaviors in early adolescence.

Disclosures: A. Porter: None. B. Froeliger: None. D. McCarthy: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.14/GG3

Topic: H.04. Emotion

Support: National Institute of Neurological Disorders and Stroke (R01NS134944).

Title: Neural correlates of emotional processing in children: A MEG study using the NAPS database

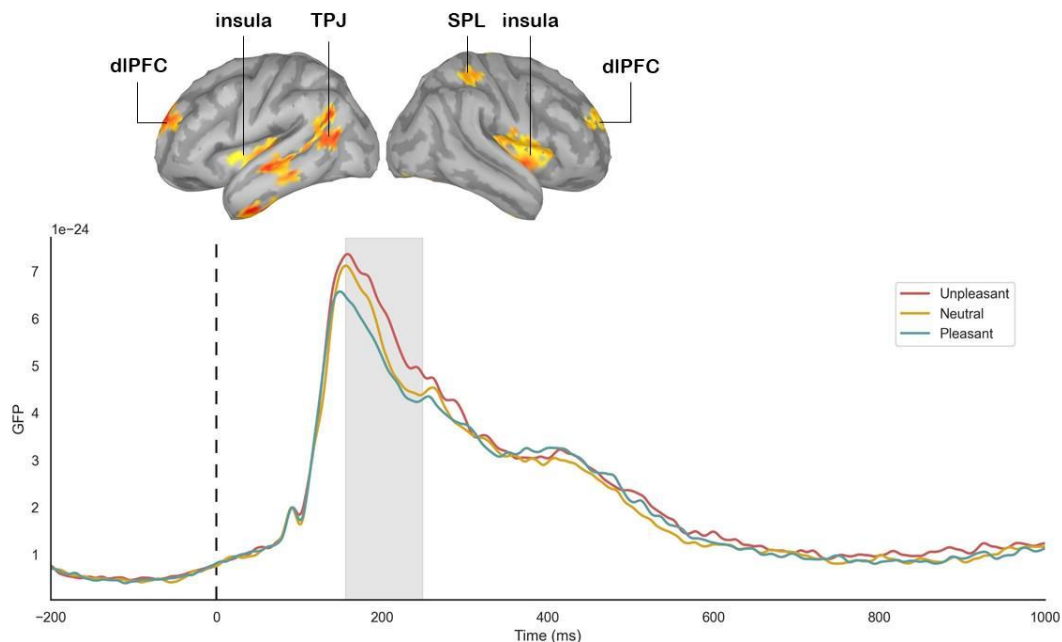
Authors: *I. NTOUMANIS¹, M. TOWNSEND¹, F. KING², C. COOPER³, C. PAPADELIS¹;
¹Cook Children's Hlth. Care Syst., Fort Worth, TX; ²Univ. of Texas at Arlington, arlington, TX, ;
³Cook Children's Med. Ctr., Fort Worth, TX.

Abstract: Understanding how children process emotions remains a key question in developmental neuroscience. Previous studies have mainly used functional magnetic resonance imaging, which has limited temporal resolution, and the International Affective Picture System, which offers limited variability. To address these limitations, we used magnetoencephalography (MEG) and the Nencki Affective Picture System (NAPS), a diverse stimulus set, to characterize the neural correlates of emotional processing in children.

Thirty-eight typically developing children (21 females, aged 5-18 years) underwent MEG while viewing 420 pictures from the NAPS, categorized as pleasant, unpleasant, or neutral. Event-related fields were extracted from -200 to 1000 ms relative to stimulus onset and averaged by category. Global field power was compared across categories using a cluster-based permutation test, and whole-brain source-space analysis was performed to identify brain regions that responded differentially to each category.

Compared to pleasant pictures, unpleasant pictures elicited significantly stronger neural responses from 156 to 250 ms in the insula, dorsolateral prefrontal cortex, temporoparietal junction, and superior parietal lobule (Figure 1). Age and sex correlated with the peak amplitude across categories, with females and younger children showing higher amplitudes ($p = .008$ and $p = .003$, respectively).

Our results show that during childhood, processing of unpleasant emotions engages brain areas implicated in emotion regulation and Theory of Mind as early as 156 ms post-stimulus. This suggests that such affective processes are fast and widely distributed in the brain. We also demonstrate that neural response strength varies by age and sex, underscoring the importance of considering developmental and individual differences in models of affective neuroscience. Our findings may guide future research on the neural basis of emotional development and its disruption in affective and social disorders.



Disclosures: I. Ntoumanis: A. Employment/Salary (full or part-time): Cook Children's Health Care System.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.15/GG4

Topic: H.06. Anxiety Disorders

Title: Examining Directed Forgetting in Emotional Associations

Authors: *D. SINGH¹, J. PACIOS⁴, M. K. ASTHANA^{2,3};

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Abstract: Directed Forgetting is a cognitive strategy of voluntarily disregarding unwanted memories based on the presence of forget cues. While prior studies have majorly focused on the declarative memory performance and isolated piece of information, the current study explores how item-based directed forgetting influences the encoding of emotional associations along with the underlying electrophysiological responses in an auditory conditioning paradigm. Seventeen participants (Age: 18-30 years, Male=10, Female=7) took part in the experiment. In total 44 object line images were used in different phases of experiment. Additionally, half of these images were followed by 1-second beep sound serving as a forget cue. The experiment includes four practice trials followed by the acquisition phase where 24 images were presented for 8 seconds and paired either with an aversive sound (CS+) or with no sound (CS-). Later, all participants were instructed to recall the names of all the images and circle those which they believe were associated with screaming sound, regardless of whether forget cue was presented. Recall test was followed by recognition and liking ratings task. Additionally, 8-channel EEG recordings were taken throughout the experiment. A 2 x 2 repeated-measures ANOVA was performed with Stimuli type (CS+ vs. CS-) and Instructions (Remember vs. Forget) to examine their effects on recall, recognition, and liking ratings. The analysis showed significant main effects of instructions ($F(1,16) = 11.51$, $p < .01$, $\eta^2 = .42$) and stimuli ($F(1,16) = 9.02$, $p < .01$, $\eta^2 = .36$) indicating participants recalled significantly more "remember" items than "forget" items and had higher recall for CS- items compared to CS+ items. Post-hoc analyses revealed participants were more accurate in categorizing "remember" items than "forget" items for both CS+ ($t(16) = 3.06$, $p < .01$) and CS- stimuli ($t(16) = 4.69$, $p < .001$). In contrast, recognition rates had no significant impact. Stimuli and instruction exhibited a significant interaction effect on liking ratings $F(1, 16) = 7.79$; $p = .013$, $\eta^2 = .33$). EEG analysis revealed enhanced delta and beta power peaks between 0-2s and 6-8s for the CS+ relative to the CS- stimulus. Power peaks in alpha and beta band for cue presentation approximately in the 0-2s time window, indicative of encoding suppression. The results may also have therapeutic implications for those struggling with traumatic memories.

Disclosures: D. Singh: None. J. Pacios: None. M.K. Asthana: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.16/GG5

Topic: H.04. Emotion

Title: Affective-cognitive crosstalk in dual-tasking: domain-specific limits of reward-based control

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Abstract: Understanding how affective states interact with cognitive demands during multitasking is important for optimizing performance and ensuring safety in real-world scenarios, from Human Machine Interfacing to UX design. Even in a relatively simpler case of dual-task situations, individuals often experience interference or crosstalk between concurrently activated task representations, which can reflect in performance costs. In the current work, we investigated whether a cognitive conflict-induced affective state can interact with emotion processing in a dual-tasking scenario and how motivational incentives can influence this affective-cognitive crosstalk. In the first experiment, the dual task scenario was achieved by valence categorization of happy or disgust facial expressions (Task 1; T1) followed by a multi-source interference task (MSIT) (Task 2; T2) after a fixed SOA of 100ms. Data from $N=30$ participants (15 F, 18 - 28 Y) showed a significant interaction between T1 valence (positive vs. negative) and T2 cognitive interference level (control vs. incongruent) in reaction times of both T1 and T2, suggesting both backward crosstalk effects (BCE) and forward crosstalk effects (FCE). More specifically, T2 conflict experience impeded the processing of positive T1 stimuli but favored negative T1, suggesting affective compatibility-based BCE. In a subsequent experiment, we tested if rewards contingent on T1 performance can modulate this crosstalk. Specifically, we hypothesized enhanced BCEs when T2's affective dimension favors T1 processing and shielding of interference when T1 and T2 are affectively incompatible, thus leading to a local optimization for T1 performance. Alternatively, it was also hypothesized that reward motivation could lead to a general serialization of task processing by proactive control (i.e., reduced BCE), as suggested by previous studies that investigated reward effects in dual tasking. Contrary to our hypotheses, results from Experiment 2 ($N=30$; 12 F, 18 - 28 Y) showed that rewards did not modulate the BCE, pointing towards the limitation of reward motivation in affective-cognitive processing. To further dissect these dynamics, we plan to conduct drift-diffusion modeling (DDM) to localize domain-specific control mechanisms. The DDM will allow us to determine whether the observed crosstalk effects arise from changes in the rate of evidence accumulation, adjustments in response caution, or shifts in non-decision time. Together, these findings shed light on how affective processing can be modulated by parallel

cognitive processes and delineate the limits of motivational strategies in regulating this interference.

Disclosures: P. Saxena: None. S. Padmala: None.

Poster

PSTR182: New Frontiers in Affective, Computational, and Motivational Neuroscience

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR182.17/GG6

Topic: H.06. Anxiety Disorders

Support: IBRO / Wellcome Trust - IW-6594875598

Title: Cluster-based eeg coherence analysis of anxiety-related functional connectivity

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Abstract: The present study aimed to examine functional connectivity patterns associated with anxiety traits using EEG coherence analysis. Resting-state EEG recordings were collected , under eyes-open and eye-close conditions from 57 participants categorized into high and low anxiety groups using the Generalized Anxiety Disorder 7-item scale (GAD-7). The EEG data were recorded using a 128-channel EGI system. Preprocessing (bandpass filter (1-30 Hz) and ICA analysis), spectral power and coherence analyses were conducted using MNE-Python and K-Means clustering methods. Six clusters of electrodes were identified (e.g., pre-frontal, right frontal, left frontal, right temporoparietal, left temporoparietal and occipital). Power spectral densities (PSD) were computed per subject. Subjects with abnormally high variability were excluded based on the standard deviation of PSD across channels. Spectral coherence was computed for all cluster pairs using magnitude-squared coherence in predefined frequency bands (theta, alpha, beta). Fisher's Z-transformation was applied to normalize coherence values before conducting statistical comparisons between high and low anxiety groups. Significant group differences were found in the alpha and beta bands only in the eye-open condition, particularly in the alpha and beta bands. In the alpha band, as compared with the low-anxiety group, high-anxiety individuals showed increased coherence between right frontal and pre-frontal clusters ($M_{high} = 0.64$, $M_{low} = 0.54$; $t(55) = 2.26$, $p = .03$), right frontal and right temporoparietal clusters ($M_{high} = 0.40$, $M_{low} = 0.34$; $t(55) = 1.99$, $p = .05$) as well as between the left frontal and right temporoparietal clusters ($M_{high} = 0.95$, $M_{low} = 0.81$; $t(55) = -2.66$, $p = .01$). In the beta band, high-anxiety individuals showed decreased coherence between the left temporoparietal and right frontal ($M_{high} = 0.60$, $M_{low} = 0.68$; $t(55) = -2.45$, $p = .02$) and left temporoparietal and pre-frontal clusters ($M_{high} = 0.43$, $M_{low} = 0.49$; $t(55) = -2.79$, $p = .01$)

when compared with the low-anxiety group. These findings suggest distinct functional connectivity profiles associated with anxiety levels, particularly in frontoparietal networks. This work contributes to understanding the neurophysiological basis of anxiety and highlights the utility of EEG coherence as a potential biomarker. This evidence could be complemented with low resolution tomography analysis (LORETA) and a source level analysis.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.01/GG7

Topic: H.03. Motivation

Support: K. Lisa Yang Brain-Body Center
McGovern Institute for Brain Research at MIT

Title: Intracolonic optogenetic stimulation of vagal innervations increases exploratory behaviors in freely moving mice

Authors: *K. PANG¹, S. SELVARAJI², R. MONDAL³, M. SLOWIKOWSKI⁴, G. EBERLY³, E. VARGAS PANIAGUA², A. SAHASRABUDHE², P. ANIKEEVA¹;

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Abstract: Up to 40% of the world's population suffer from functional gastrointestinal (GI) disorders and up to a third of these patients experience anxiety symptoms. The vagus nerve (VN), a major peripheral nerve connecting the brain and the GI tract, modulates motivated behaviors like reward and anxiety. While studies suggest that the VN is required for both colitis-induced anxiety and the anxiolytic effects of probiotics in mice, whether and how colon-vagus-brain interactions contribute to this bidirectional modulation of anxiety by the VN remain unclear. To address this, we (a) investigated the role of colonic vagal innervations in anxiety-like behaviors using wireless intracolonic optogenetics and (b) mapped the central circuits of vagal afferents in the proximal colon using transneuronal viral tracing. We developed flexible multifunctional devices for optogenetic manipulation and temperature monitoring in the mouse proximal colon. Optogenetic stimulation of colonic vagal terminals increased exploratory behaviors in adult Phox2b-Cre;Ai32 mice in the elevated plus maze and the open field test, without affecting stress-induced hyperthermia. These results indicate that colon-innervating vagal neurons modulate anxiety-like behaviors independently of physiological stress responses. Using the real-time place preference test, we found that colonic vagal stimulation was neither aversive nor preferred, suggesting that modulation of motivated behaviors by the VN is input-specific. To identify the brain regions that mediate this anxiolytic effect, we performed

anterograde transneuronal circuit mapping by injecting a Cre-dependent herpes simplex virus (H129ΔTK-TT) into the proximal colon of adult Phox2b-Cre mice. Five days post-injection, virus-mediated fluorescent protein tdTomato expression was present in vagal sensory neurons in the nodose ganglia but not in dorsal root ganglia neurons. tdTomato labelling extended to the caudal medullary regions, including the dorsal vagal complex. By 6 days, tdTomato⁺ neurons were present in medullary and pontine reticular formations, locus coeruleus, parabrachial nucleus, hypothalamus and other central locations. In summary, we present novel technology enabling region-specific optogenetic manipulation of the colon. Our findings suggest that colon-VN stimulation facilitates exploratory behavior and that this effect may be mediated by the central targets of colonic vagal afferents. Future work investigating how vagal activity modulates the function of brain regions receiving colon viscerosensory signals may offer further insights into the shared etiology of GI diseases and affective disorders.

Disclosures: K. Pang: None. S. Selvaraji: None. R. Mondal: None. M. Slowikowski: None. G. Eberly: None. E. Vargas Paniagua: None. A. Sahasrabudhe: None. P. Anikeeva: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroBionics Inc..

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.02/GG8

Topic: H.06. Anxiety Disorders

Title: A molecularly defined amygdala- independent tetra-synaptic forebrain-to- hindbrain pathway for odor-driven innate fear and anxiety Received: 28 April 2023 Accepted: 14 December 2023 Published online: 12 February 2024 Check for updates

Authors: *L. CUI;
Zhejiang Univ., Hangzhou, China

Abstract: Fear-related disorders (for example, phobias and anxiety) cause a substantial public health problem. To date, studies of the neural basis of fear have mostly focused on the amygdala. Here we identify a molecularly defined amygdala-independent tetra-synaptic pathway for olfaction-evoked innate fear and anxiety in male mice. This pathway starts with inputs from the olfactory bulb mitral and tufted cells to pyramidal neurons in the dorsal peduncular cortex that in turn connect to cholecystokinin-expressing (Cck⁺) neurons in the superior part of lateral parabrachial nucleus, which project to tachykinin 1-expressing (Tac1⁺) neurons in the paraventricular nucleus. Notably, the identified pathway is specifically involved in odor-driven innate fear. Selective activation of this pathway induces innate fear, while its inhibition suppresses odor-driven innate fear. In addition, the pathway is both necessary and sufficient for stress-induced anxiety-like behaviors. These findings reveal a forebrain-to-hindbrain neural substrate for sensory-triggered fear and anxiety that bypasses the amygdala.

Disclosures: L. Cui: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.03/GG9

Topic: H.06. Anxiety Disorders

Support: Grant from VIEP-BUAP 2025 to the Academic Body in Neuroendocrinology (BUAP-CA-288)
FI is a fellow of the SECIHTI fellowship No. 4024719.

Title: Anxiety-like behavioral changes following consumption and withdrawal of a 10% sucrose solution.

Authors: *F. ISLAS¹, C. CORTES², J. R. EGUIBAR, Sr.³;

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Abstract: Repeated sugar consumption activates the dopaminergic reward system, promoting compulsive intake and loss of control. Prolonged exposure induces neural and molecular changes associated with emotional dysregulation, addictive behaviors, and heightened anxiety, which may also be exacerbated by sugar abstinence. Two sublines from Sprague-Dawley (SD) strain which differ in their spontaneous yawning frequencies were obtained at the Institute of Physiology. High-yawning (HY) rats had 20 yawns per hour (y/h), while low-yawning (LY) rats yawn only 2 y/h. These sublines also differ in their behavioral responses to different psychobiological tests, such as the open field test (OFT), in which LY rats exhibit increased anxiety-like behavior, whereas HY rats are resilient to stressors. These biomodels are a valuable framework for evaluating behavioral responses to experimentally induced stress. The aim of this work was to evaluate the effect of chronic consumption and withdrawal of a sucrose solution on anxious behavior in young adult HY and LY male rats. The OFT was conducted three times to assess anxiety levels in rats of each subline at every stage of the sucrose addiction. The first test evaluated basal anxiety at 100 ± 1 postnatal days (PND). After a 30-day period of a 10% sucrose solution consumption, they were exposed to the OFT. Following a 14-day withdrawal period, a third OFT was tested. The amount of thigmotaxis time was used to evaluate anxiety levels. Thigmotaxis time was used as an indicator of anxiety-like behavior. LY rats exhibited a 15% increase in basal thigmotaxis time compared to HY rats ($P = 0.054$). After sucrose consumption, this difference decreased to just 4%, but following the abstinence phase, LY had 21% more thigmotaxis with respect to HY male rats. Additionally, LY rats also spent less time in the center of the open field after the abstinence of sucrose, supporting higher anxiety display. In conclusion, sucrose intake reduced anxiety in LY rats but during craving they had the highest anxiety; while HY are resilient, supporting they had non-anxious phenotype.

Disclosures: F. Islas: None. C. Cortes: None. J.R. Eguibar: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.04/GG10

Topic: H.06. Anxiety Disorders

Support: Grant in Aid for Scientific Research (C) 22K11796

Title: Long-term L-ornithine administration alleviates stress responses in socially isolated mice

Authors: *Y. HAYASHI;

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Abstract: L-ornithine has anxiolytic and anti-fatigue effects. However, most previous studies are based on single-dose administration. The functionality of amino acids as food components should be evaluated based on long-term administration. This study investigated the anti-stress effects of long-term L-ornithine administration in socially isolated mice, a model of psychosocial stress, compared to group-housed mice, using behavioral analyses. Male BALB/c mice (20-24 g) were used. L-ornithine monohydrochloride was dissolved in tap water. Mice, under both group-housed and isolated conditions, were divided into three groups and received L-ornithine solutions ad libitum from water bottles for at least 2 weeks: a low-dose group (0.3 mg/mL), a high-dose group (1 mg/mL), and a control group (tap water). Solution intake and body weight were measured periodically. Behavior was assessed using the elevated plus-maze (EPM), open field (OFT), stress-induced hyperthermia (SIH), and pentobarbital-induced sleep (PIS) tests. L-ornithine intake did not cause any abnormal behaviors or diarrhea, and mice remained healthy. No significant differences in body weight were observed due to L-ornithine dosage. However, rearing conditions affected body weight gain, with socially isolated mice exhibiting a lower rate of gain compared to group-housed mice. In socially isolated mice, L-ornithine administration decreased locomotor activity and increased the time spent in the center zone in the OFT. Furthermore, it prolonged sleep duration in the PIS test. No effects of L-ornithine were observed in the EPM or SIH tests in isolated mice. Conversely, L-ornithine showed no effects in group-housed mice across all behavioral tests. Long-term L-ornithine administration has stress-alleviating effects in socially isolated mice, which are presumed to be experiencing high stress levels.

Disclosures: Y. Hayashi: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.05/GG11

Topic: H.06. Anxiety Disorders

Support: NIH DA059646
New Jersey Health Foundation

Title: The neuropeptide receptor GPR83 regulates anxiety-like behavior

Authors: H. LANGKAMER-SMITH¹, A. YADAV², P. PATEL¹, S. JOHNSON¹, *A. K. FAKIRA³;

¹Biomed. Sci., Cooper Med. Sch. of Rowan Univ., Camden, NJ; ²Rowan Univ., Camden, NJ;

³Cooper Med. Sch. at Rowan Univer, Glassboro, NJ

Abstract: In our society there is a growing feeling of isolation and loneliness despite our perceived connectivity via social media and smart phones. This isolation has resulted in sharp increases in anxiety amongst adolescents, especially among young girls. Loneliness and social isolation during the critical developmental period of adolescence is likely to have long-lasting impacts on brain chemistry and connectivity. In fact, there are reports, both preclinical and in patients, indicating that isolation in adolescence has significant effects on overall health, feelings of anxiety, nicotine and alcohol intake, as well as motivation for heroin. GPR83, whose endogenous ligand is a neuropeptide called PEN, was first identified as a protein regulated by the glucocorticoid dexamethasone, indicating that this receptor may play a role in stress-responses. In fact, when mice are treated with corticosterone or dexamethasone, GPR83 expression is reduced in the amygdala. Moreover, GPR83 knockdown in the BLA increases anxiety-related behaviors in female mice. We have recently identified small molecule ligands for GPR83 based on a homology model and in silico screening. Compounds were tested for binding and signaling through GPR83 identifying Cpd 1 as an agonist for the receptor. The goal of the current study is to determine whether our small molecule agonist could regulate anxiety-related behaviors in a model of adolescent social isolation in mice. In addition, we sought to determine whether GPR83 expression was regulated in the brain following this model. Overall, we find that treatment with Cpd1 alleviates anxiety-related behaviors in a dose-dependent manner in female mice. This may be linked to increased expression of GPR83 following adolescent social isolation. Future studies will investigate the functional consequences of social isolation on GPR83 function in neurons and the overall impact on opioid abuse liability.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.06/GG12

Topic: H.03. Motivation

Support: NIH Grant MH123495
NIH Grant MH058883
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NIH Grant MH137593

Title: Ventral pallidal GABAergic neurons encode approach and avoidance during motivational conflict

Authors: *C. E. MARÍA-RÍOS¹, A. DELGADO², J. PEREZ-TORRES², A. M. RIVERA HERNÁNDEZ², P. D. PEREZ-VAZQUEZ², V. RIVERA², C. BRAVO-RIVERA^{1,2};

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Abstract: Balancing appetitive and aversive drives is essential for adaptive decision-making. The ventral pallidum (VP) plays a key role in motivation, such that GABAergic neurons (VP_{GABA}) promote approach and counter threat avoidance in non-conflict scenarios. However, their role in approach/avoidance conflict remains unclear. We used the platform-mediated avoidance (PMA) task, where mice nose-poke for light-signaled 20% sucrose rewards. A 20-second tone signals a co-terminating 2-second, 0.1 mA foot-shock. Mice learn to avoid the shock by stepping onto a safety platform located far from the reward port. We tested mice in two conflict contingencies: low conflict (LC), where rewards were available both during safe periods and warning tone presentations, and high conflict (HC), where rewards were only available when the light (reward) and tone (threat) cues were co-presented. Fiber photometry recordings in Gad2-Cre mice showed that in LC, VP_{GABA} neurons exhibited excitatory tone responses that diminished with training ($p = 0.0177$), suggesting these cue responses may decrease as avoidance becomes habitual. In HC, VP_{GABA} neurons showed excitatory cue responses that increased with training ($p = 0.0275$), and the response to tone-light co-presentation was significantly greater than to tone ($p = 0.0021$) or light alone ($p = 0.0019$), suggesting motivational conflict strongly engages these neurons. VP_{GABA} also exhibited excitatory anticipatory responses prior to nose-poking or stepping on the platform in conflict, but not in non-conflict contingencies (light-cue or tone-cue only). Finally, optogenetic activation of VP_{GABA} impaired avoidance in LC ($p = 0.0072$), but accelerated avoidance in HC ($p = 0.0233$). These findings reveal that VP_{GABA} neurons have a more nuanced and dynamic role in shaping approach and avoidance behavior than previously thought, flexibly guiding action depending on motivational context. This insight has implications for understanding maladaptive decision-making in disorders such as addiction, anxiety, and depression, where internal drives are misaligned or in conflict.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.07/GG13

Topic: H.06. Anxiety Disorders

Support: NIH Intramural Grant

Title: Effects of GPR110 on Neurobehavioral Outcomes in Mice

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Abstract: GPR110, an adhesion GPCR involved in neurodevelopment, is activated by N-docosahexaenoyl ethanolamine (synaptamide), a metabolite of the omega-3 fatty acid docosahexaenoic acid (DHA). This study investigated how GPR110 receptor expression affects behavioral outcomes in mice through two complementary approaches.

GPR110 knockout (KO) and wildtype (WT) mice were used to examine the role of receptor expression in behavioral outcomes. GPR110 KO mice displayed trends toward worsened memory (novel object recognition) and heightened anxiety-like behaviors (elevated plus maze, marble burying). The overexpression of the receptor in Nestin containing cells, a marker for neurogenesis, and in glutamatergic cells led to improvements in anxiety-like behaviors. Proteomic analysis of hippocampal tissue from KO mice showed reduction in synaptic, glutamatergic, and mitochondrial proteins. These findings underscore the critical roles of GPR110 in cognitive and emotional regulation.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.08/GG14

Topic: H.06. Anxiety Disorders

Support: NSTC 113-2320-B-A49-004 (National Science and Technology Council, Taiwan)
AA0313 (Ministry of Education, Taiwan)

Title: A traditional medicine formula treatment ameliorates FKBP51 deficiency-associated inflammatory anxiety

Authors: L. CHEN¹, Y.-P. KANG¹, P.-C. HSU², C.-C. HUNG¹, Y.-L. GAN⁴, S. FU³, C. HSU³, *Y.-H. LEE¹;

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Abstract: The FK506-binding protein (FKBP51), encoded by the FKBP5 gene, acts as a negative cochaperone of the glucocorticoid receptor, regulating stress responses through the hypothalamic-pituitary-adrenal (HPA) axis. Our previous studies have demonstrated the physiological role of FKBP51 in mediating stress adaptation via mitigating inflammation-induced anxiety. Clinical evidence suggests that COVID-19 survivors with robust innate immune responses show an increased risk of anxiety disorders. JWF, a traditional medicine formula with stress-reducing properties, may alleviate post-COVID brain fog. However, its mechanism in inflammation-associated anxiety remained unclear. This study investigated whether the JWF alleviates post-inflammation anxiety established in FKBP5-deficient mice (Fkbp5-KO). Wild-type (WT) and Fkbp5-KO mice received lipopolysaccharide (LPS) or saline injections, followed by JWF treatment (0.4 g JWF/day) or regular water for four days. We found that JWF mitigated body weight loss in LPS-injected Fkbp5-KO mice and alleviated anxiety-like behaviors observed on day 7. Furthermore, we examined inflammation- and neurotransmission-related markers in the hippocampus and found that JWF reduced the mRNA expression of LPS-induced Fkbp5, as well as the pro-inflammatory cytokines in WT mice. It also increased the expression of anti-inflammatory cytokines mRNA, which mitigated the innate immunodeficiency in Fkbp5-KO mice. Hyperactive glutamatergic signaling contributes to anxiety disorders. Notably, LPS-injected Fkbp5-KO mice exhibited a reduced hippocampal NR2A/NR2B protein level, which was reversed by JWF treatment. LPS injection also decreases p-CREB levels, a downstream signaling component of the NMDA receptor that is associated with anxiety-related behaviors, in both WT and Fkbp5-KO mice. However, JWF reversed this effect only in Fkbp5-KO mice. In conclusion, our findings suggested that JWF alleviates post-inflammation anxiety in FKBP5 deficiency mice by normalizing the NR2A/NR2B protein level in the NMDA receptor signaling pathway. This conclusion supports the use of JWF for treating post-inflammatory anxiety.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

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Program #/Poster #: PSTR183.09/GG15

Topic: H.06. Anxiety Disorders

Title: Characterisation of GABA2/3 positive allosteric modulators (PAMs) in tests of anxiety and side effect.

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Abstract: Benzodiazepines (BZs), exemplified by diazepam (DZP) have been effective clinical treatments for forms of epilepsy and anxiety for decades, although issues such as sedation, tolerance and dependence restrict their value. BZs exert their effects via non-selective

modulation of GABA_ARs containing either an α 1, α 2, α 3 or α 5 subunit and the emergence of GABA_AR subtype selective PAMs, notably for α 2- and α 3 subunit-containing GABA_ARs represents an opportunity to provide therapeutic improvement both in terms of efficacy and tolerability, side-effect profile. The present study was designed to profile the α 2/ α 3-GABA_AR PAMs darigabat (DGB), and TPA023B and the α 3-GABA_AR-selective PAM SAN711 in the conditioned emotional response (CER) test of anxiety, and the 5-choice serial reaction time task (5-CSRTT) to study attention and reaction time. Adult, male, SD rats were trained to stable performance in an operant CER task. Rates of responding for food reinforcement was compared between a 2min light/tone 0.3mA shock-paired conditioned stimulus (CS), with a 2min non-CS immediately preceding the CS. In trained rats, response rates reliably declined during the CS period, resulting in a suppression ratio (SR) score of 0.1-0.3. Pretreatment with DGB (0.3-3mg/kg p.o), TPA023B (0.1-3mg/kg p.o) and SAN711 (1-10mg/kg p.o) resulted in a dose-related increase in lever pressing during the CS, indicative of an anxiolytic effect (e.g., SR Veh:0.25 $\pm$ 0.07, DGB(3):0.50 $\pm$ 0.07; P<0.05). In contrast to DZP, rates of lever pressing were not reduced by the subtype-selective GABA_AR PAMs over these doses. Separate cohorts of male, LE rats trained to 5-CSRTT task conditions of 0.75s SD, 5s ITI, 100 trials were treated with equivalent doses of each α 2/ α 3- or α 3-GABA_AR PAM. Consistent with the CER profile, no negative effects on attention, motor function and response control were noted. For example DGB (0.5-5mg/kg) did not impair attention (% correct: Veh: 92 $\pm$ 2%, DGB(5): 90 $\pm$ 2%), or reaction time (Veh: 0.70 $\pm$ 0.01s, DGB(5): 0.70 $\pm$ 0.01s). In sum, the rat CER assay was able to demonstrate an anxiolytic-like profile of the α 2/ α 3- and α 3-GABA_AR subtype-selective compounds darigabat, TPA023B and SAN711, all of which showed an improved side effect profile relative to the non-selective GABA_AR PAM diazepam.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Topic: H.03. Motivation

Support: NIH R01 DA042820
Charles E. Kubly Mental Health Research Center

Title: The role of nucleus accumbens D2 medium spiny neurons in escape behavior

Authors: *B. E. COTE¹, E. M. GRAFELMAN¹, D. S. WHEELER¹, L. VLACH¹, J. R. MANTSCH², M. C. HEARING¹, R. A. WHEELER¹;

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Abstract: Previous work from our lab and others have 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-like 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 measure the activity pattern of MSN subtypes during the experience of an aversive stimulus, we used in vivo fiber photometry. Adora2 Cre⁺ (n=8) and D1 Cre⁺ (n=9) mice were injected with the Ca²⁺ sensor, GCaMP6f in the NAc and received a chronically implanted optic fiber. After recovery and viral expression, mice were then exposed to an aversive 90dB white noise, and a mild 72dB white noise (7dB above ambient noise) in different sessions. Two 2 (sex) X 2 (intensity) X 2 (epoch) ANOVAs revealed a significant intensity X epoch interaction where Ca²⁺ activity in both subtypes increased in response to intense, but not mild, noise (D1: F(1,8) =21.52; p<0.05, D2: F(1,6) =12.69; p<0.05). To test the causal role of this activity in D2 MSNs, we used a pharmacological approach. Male and Female Sprague-Dawley rats received chronically implanted cannulae into the NAc core for the delivery of the D2 receptor agonist, quinpirole, or saline. After recovery, rats began behavioral training in a negative reinforcement design. During training sessions, rats could terminate a 90db white noise with a nose poke response. After acquiring negative reinforcement (3 consecutive days of at least 50 noise terminations), rats then underwent four test days in which behavior was assessed following the intra-NAc core administration of either quinpirole (1.0 µg/60s per side), (2f,4m) or saline (2f,4m). Preliminary results revealed a significant main effect of drug in a 2(drug) X 2(day) ANOVA (F(1,8)=5.10, p<0.05), indicating that quinpirole administration reduced white noise terminations (relative to pre-infusion baseline), compared to saline controls. Since D2 receptor activation is thought to inhibit MSN activity, these data suggest that aversion-induced increases in D2 MSN activity may play an important role in the motivation to escape an aversive stimulus. Future work will explore the role of D1 MSN activity in aversion-mediated tasks, and how MSN subtype activity may influence hedonic processing.

Disclosures: B.E. Cote: None. E.M. Grafelman: None. D.S. Wheeler: None. L. Vlach: None. J.R. Mantsch: None. M.C. Hearing: None. R.A. Wheeler: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.11/HH2

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIGM Grant SC3GM130467

Title: Chlordiazepoxide reduces anxiety-like behavior in the adolescent mouse elevated plus maze

Authors: *J. REYES, M. RODRIGUEZ, S. D. INIGUEZ;
Univ. of Texas at El Paso, El Paso, TX

Abstract: This study evaluates the effects of chlordiazepoxide, a benzodiazepine generally prescribed to manage anxiety-related disorders in adolescent/pediatric populations, on elevated plus-maze performance in juvenile male mice. This method was taken because chlordiazepoxide induces anxiolytic-like effects in various models in adult rodents, however, there is a gap in knowledge regarding the behavioral effects of this benzodiazepine in juveniles. Thus, we administered a single intraperitoneal injection of chlordiazepoxide (0, 5, or 10 mg/kg) to postnatal day 35 male C57BL/6 mice. Thirty min later, mice were allowed to explore the elevated plus-maze for 5-min. The findings of our study indicate that chlordiazepoxide-treated mice (5 and 10 mg/kg) spent more time exploring the open arms of the maze, when compared to controls. No differences in velocity (cm/s) or distance traveled (cm) were observed between the experimental groups. Collectively, our results suggest that chlordiazepoxide induces anxiolytic-related behavior in juvenile male mice.

Disclosures: J. Reyes: None. M. Rodriguez: None. S.D. Iniguez: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.12/HH3

Topic: H.06. Anxiety Disorders

Title: Characterization of an Yohimbine-induced rat anxiety model

Authors: *M. DUDEK, L. JAUKE, A. FANTINA-WOBLISTIN, R. RABL, L. BREZNIK, M. DAURER, I. SCHILCHER, T. LÖFFLER, S. FLUNKERT, M. PROKESCH;
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Abstract: Anxiety disorders constitute the most prevalent form of mental disorders, with an estimated lifetime prevalence of 14%. They manifest with a variety of peripheral and central symptoms. Despite the subjective and complicated nature of the symptoms experienced by patients suffering from anxiety disorders, rats have proven to be an invaluable tool to mirror several symptoms and have been employed in drug development. In this study we are inducing an anxiety-like state in rats by application of the anxiogenic drug yohimbine. Afterwards, rats are tested in a behavior battery containing open field (OF), elevated plus maze (EPM), and pre-pulse inhibition (PPI) before being sacrificed. Blood, urine, cerebrospinal fluid (CSF), and brain are collected and analyzed for anxiety-related markers such as adrenocorticotrophic hormone (ACTH), corticosterone, and serotonin. Primary results reveal reduced activity in the OF and increased time spent in the closed arm of the EPM, both indicating an increased anxiety level. PPI inhibition further emphasized the elevated anxiety state by showing increased startle pulse responses compared to control animals. A first ex vivo analysis unveiled increased corticosterone

levels in the plasma after yohimbine injection compared to vehicle injected animals. Additional analyses and trials including a reference compound are currently underway but initial results provide strong evidence of the suitability of the yohimbine-induced rat model for anxiety disorder research and provides a promising platform to evaluate anxiolytic compounds.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.13/HH4

Topic: H.06. Anxiety Disorders

Support: grant 2023/01003-5 FAPESP
2024/08300-8 FAPESP
Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)
grant 302605/2021-5 CNPq

Title: Behavioral markers of anxiety and risk assessment in a predator threat model of depression in mice.

Authors: *W. C. COELHO-SILVA¹, N. C. COIMBRA²;

¹Neurol. and Behaviour Sci., Univ. of São Paulo, Ribeirão Preto Medical School, Brazil; ²Lab. De Neuroanatomia E Neuropsicolbiologia, Ribeirao Preto, SP 1, Brazil

Abstract: Background: Chronic stress is a major contributor to affective disorders, impacting both emotional and cognitive neural circuits. Despite advances in preclinical research, there remains a need for novel, ethologically grounded models to better understand the comorbidity between depression and anxiety. This study aimed to validate a behavioral paradigm that combines chronic stress with exposure to a real predator to assess depression- and anxiety-like behaviors in mice. **Methods:** Male C57BL/6 mice were exposed to 16 days of chronic stress (restraint stress + social defeat). On day 17, depression-like behavior was evaluated by Splash Test (ST) and Forced Swim Test (FST). On days 22-24, mice were submitted to a risk assessment (RA) paradigm using a real snake (*Bothrops jararaca*). Behavioral markers of anxiety and panic were measured over a 5-minute exposure. **Results:** Chronically stressed mice exhibited a reduced latency to grooming ($p = 0.0211$) and a paradoxical increase in the number of grooming bouts ($p = 0.0206$), suggesting altered behavioral regulation. Grooming duration did not differ significantly between groups ($p = 0.3660$). In the forced swim test (FST), both immobility frequency ($p = 0.0010$) and immobility time ($p = 0.0364$) were elevated in the stressed group, indicating a depressive-like state. During predator exposure, stressed mice exhibited an increased duration of stretch-attend posture (% of time, $p = 0.0473$), indicating

heightened risk assessment. There were no significant differences between groups in flat-back approach, defensive immobility, or escape responses. **Conclusion:** That psychobiological model of depression and anxiety comorbidity reproduces core features of depressive-like behavior and demonstrates that chronic stress enhances cognitive components of threat processing, evidenced by increased risk assessment behavior, without engaging typical panic-like motor responses such as escape or freezing. These results suggest a dissociation between hypervigilant risk assessment and the reactive defense limbic circuit, providing behavioral evidence that chronic stress selectively sensitizes evaluative, anxiety-related mechanisms in potentially dangerous environments.

Disclosures: W.C. Coelho-Silva: None. N.C. Coimbra: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.14/HH5

Topic: H.03. Motivation

Support: NIH Grant DA048280
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Title: Chronic variable stress enhances escape behavior and increases dopamine transient amplitude in male rats

Authors: E. M. GRAFELMAN¹, B. E. COTE¹, L. M. VLACH¹, N. PADULA¹, K. L. ZIMOLZAK¹, D. S. WHEELER¹, M. C. HEARING¹, J. R. MANTSCH², *R. A. WHEELER¹;
¹Marquette Univ., Milwaukee, WI; ²Pharmacol. and Toxicology, Med. Col. of Wisconsin, Milwaukee, WI

Abstract: We have previously shown that aversive stimuli reduce dopamine in the nucleus accumbens and that this reduction predicts both cocaine intake and escape behavior. However, adverse events are rarely experienced in isolation. Instead, they often occur within a context of chronic stress. We used a chronic variable stress paradigm to test how exposure to chronic aversive experiences would change the escape response and mesolimbic dopamine. Sprague Dawley rats (24 male, 22 female) underwent surgery to deliver dLight 1.3b to the nucleus accumbens and received a chronically implanted optic fiber to the same location. After 3 weeks of recovery and incubation, baseline measures of transient dopamine release were taken using fiber photometry. Then, rats were exposed 14 days of chronic variable stress, entailing twice-daily heterotypic stressors. Rats in the control condition were handled twice per day. Following the stress regimen, dopamine transients were measured again. Rats then learned an escape task over the course of 5 days. All rats learned to terminate a white noise by nosepoking ($F(4,120)=40.48, p<0.0001$), and males, but not females, in the stress group performed more escapes than those in the control groups (Males: ($F(1,30)=8.69, p<0.01$); Females:

($F(1,30)=0.25$, $p=0.62$)). Tethering rats for photometry recording was found to interfere with this stress effect ($F(1,33)=0.16$, $p=0.70$). Ongoing work is further scrutinizing the sex-differences seen in this experiment. Noise-aligned dopamine signaling in male rats was comparable to previous measures taken in our lab, and with no difference observed between groups ($t(11)=-0.22$, $p=0.83$). However, chronic stress was found to significantly increase dopamine release event amplitude, compared to the control condition ($F(1,20)=13.51$, $p<0.01$). The increased escape behavior observed in males following chronic stress may reflect an increased sensitivity to aversive stimuli, as we hypothesized. It could also, and non-exclusively, reflect an adaptive coping mechanism acquired through repeated exposure to stress. That is, because rats have experienced different types of stress, they are more equipped or motivated to seek an escape. Regardless of the motivating factor, the enhanced behavioral response is associated with a change in naturally occurring dopamine release events. Future experiments will examine if stress induced changes in transient amplitude or frequency cause increased escape.

Disclosures: E.M. Grafelman: None. B.E. Cote: None. L.M. Vlach: None. N. Padula: None. K.L. Zimolzak: None. D.S. Wheeler: None. M.C. Hearing: None. J.R. Mantsch: None. R.A. Wheeler: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.15/Web Only

Topic: H.06. Anxiety Disorders

Title: Differential reaction after kind of stress in male and female

Authors: *Y. B. VIDAL-DE LA O¹, P. TORRES-CARRILLO², K. B. VALENCIA³, D. B. PAZ-TREJO⁴, H. SANCHEZ-CASTILLO⁵;

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Abstract: Stress is considered the main predisposing factor for development of stress-related disorders (depression, anxiety, etc). The impact of stress depends of factors such as age, sex and the kind of the stress. However, there are few reports where the kind of stressor is considered as a major variable, nevertheless, it has been show that, distinct kinds of stressors have differential effects that were observed when they are compared among them. It is important to consider female subjects in stress studies because the majority of studies of stress effects are made with males. However, is important the comparisons between males and females, the evaluation of the estrous cycles, the effects over the gonads, etc. For the above, the main goal of this research was to analyze the effect of different stress types of animal models: chronic mild stress, social

isolation and predator scent stress in male and female Wistar rats. We used a chronic unpredictable stress battery (CUSB), social isolation model (PWSI) and predator scent stress (PSS). We evaluated the depression-like behaviors using the saccharin preference test (SPT) and free choice test (FCT) for the hedonic value, and anxiety-like behaviors with elevated zero maze test (EZM). We found that the CUSB and PSS induced an anhedonic effect only in females when there is not caloric value (saccharine consumption), but when there is caloric value (consumption of the milk), the anhedonic effect is observed only in males; On the other hand, the females didn't show differences in the milk consumption after the exposure of different kinds of the stress, but we observed preference for milk when the rats are in Diestro phase of the hormonal cycle. Additionally, we found that the chronic stress induced anxiety like behaviors in all subjects but, in the social isolation females (the females spent less time in open arms). In the physiological response, we found that the only PSS induced an Increase of corticosterone in both males and females. The leukocytes in males showed a tendency for an increase but is non-significative, however in females we found a significantly diminution in CUSB and PWSI subjects. Those results demonstrate that the type of stress and the sex modulate differentially the effects of the stress, therefore is important the characterization of the effect of stress in male and female and in the different kinds of the stress because.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.16/HH6

Topic: H.02. Reward and Appetitive Learning and Memory

Support: SC3GM130467
T34GM145529
R16GM145552

Title: Chronic social defeat stress induces an anxiety-like outcome in male prairie voles (*Microtus ochrogaster*)

Authors: *J. A. GARCIA, M. RODRIGUEZ, S. D. INIGUEZ;
Psychology, The Univ. of Texas at El Paso, El Paso, TX

Abstract: Anxiety-related illnesses constitute one of the leading causes of disability across the globe. Consequently, the need for validated preclinical models to uncover the etiology of anxiety phenotypes remains essential. Given the link between social stress experience and the manifestation of anxiogenic-like outcomes, we evaluated whether social defeat stress (SDS) reduces open-space exploratory behavior in prairie voles (*Microtus ochrogaster*). Thus, we exposed adult sexually naïve male voles to 10 consecutive days of SDS and evaluated responses

to the anxiogenic environment of the light/dark box test or the elevated plus-maze, 24 hours later. We found that, when compared to non-stressed controls, SDS-exposed voles displayed longer latency to enter the light compartment of the light/dark box. Similarly, on the elevated plus maze, SDS-exposed voles displayed decreases in the number of entries into the open arms, while spending more time in the closed arms of the maze. No differences in locomotor activity were noted between the experimental groups. Collectively, these data indicate that chronic SDS exposure induces anxiety-like responses in adult male prairie voles, thus, providing a preclinical model for the study of social stress-induced anxiogenic phenotypes.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.17/HH7

Topic: H.03. Motivation

Support: NIH Grant MH123495
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Title: Behavioral Strategies and Sex Differences During Motivational Conflict in Platform-Mediated Avoidance

Authors: *J. PEREZ-TORRES¹, C. E. MARÍA-RÍOS², A. DELGADO¹, P. D. PEREZ-VAZQUEZ¹, V. RIVERA¹, J. PADILLA¹, A. M. RIVERA HERNÁNDEZ¹, C. REGALADO¹, C. BRAVO-RIVERA²;

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Abstract: Although reward-approach and threat-avoidance are often studied in isolation, their interplay is central to many psychiatric disorders—for example, depression involves diminished reward approach and heightened avoidance, while addiction reflects compulsive reward pursuit despite threat. Addressing this requires a rodent model of active avoidance with adjustable conflict levels. We therefore expanded the platform-mediated avoidance (PMA) task (Bravo-Rivera et al., 2014) to support both low-conflict (LC) and high-conflict (HC) (Bravo-Rivera et al., 2021) contingencies in mice. In this task, a light cue in the nose-poke port signals reward availability (20% sucrose solution, 6 μ L), while an auditory warning cue (8 kHz tone, 75 dB, 20 s) co-terminates with a mild footshock (0.2 mA, 2 s). Mice were first trained in LC PMA for 10 days, during which reward was available throughout the session—including inter-trial intervals—and delivered on a variable interval 30 s schedule. Each daily session included 20 warning tones spaced ~2 minutes apart. This was followed by 10 days of HC PMA training, in

which reward (1:1 fixed ratio) was available only during the warning tone. In LC, animals acquired avoidance over time, reducing shocks received from 64% on day 1 to 35% by the end of training ($p = 0.0021$). Under HC, animals increased reward intake (104 to 176 rewards, $p = 0.0081$) while reducing shocks received from 63% to 39% ($p = 0.0430$). The contingencies elicited distinct strategies: in LC, animals avoided cues rapidly (mean latency to avoid = 6.95 s), whereas in HC, they increased latency to avoid (12.6 s) to obtain rewards ($p = 0.0004$). During extinction, avoidance declined from 59% to 4% by day 3 ($p < 0.0001$), while cue-driven reward approach increased from 25% to 67% nose-poking time ($p = 0.0022$). Re-exposure to a single shock reinstated avoidance, with platform time returning to 62% ($p = 0.0066$). Sex differences were evident across learning, conflict, and reinstatement. In LC, males showed more reward approach during intertrial intervals ($p = 0.0007$) and earned more rewards ($p = 0.0235$), while early tone-platform time in females predicted later avoidance ($p = 0.0101$). In HC, females initially spent more time on the platform during the tone but converged with males by mid-training ($p = 0.0008$), while males gradually increased avoidance ($p = 0.0009$). During reinstatement, females showed significantly higher avoidance ($p = 0.0469$). Taken together, these findings reveal distinct behavioral strategies across motivational contexts and highlight sex-specific differences in how animals integrate threat and reward during learning, conflict resolution, and extinction.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.18/HH8

Topic: H.06. Anxiety Disorders

Support: NIMH R01MH132795
Fulbright Foreign Student Program (to SA)

Title: A Temporal Window During Extinction Reduces Fear Re-emergence Through Oxytocin Modulation of Infralimbic Circuit

Authors: *S. ALBANNA¹, J. STANSIL², P. SHRESTHA¹;

¹Neurobio. & Behavior, Stony Brook Univ., Stony Brook, NY; ²Neurol., Renaissance Sch. of Med. at Stony Brook Univ., Stony Brook, NY

Abstract: Abstract: The return of fear following successful extinction remains a major barrier in the treatment of post-traumatic stress disorder (PTSD). To examine how extinction timing and underlying circuit dynamics influence fear relapse, we used a Pavlovian threat conditioning paradigm in mice, followed by extinction sessions spaced at intervals of 5, 60, or 360 minutes.

After extinction, all animals received an unsignaled reminder foot shock and were tested for cue induced freezing in a novel context. We observed that the 60-minute interval was associated with a significant reduction in freezing, suggesting the existence of a temporally sensitive window that supports extinction memory consolidation and suppresses the return of fear. To understand the neural mechanisms involved, we performed dual-channel fiber photometry in wild type mice co-expressing the oxytocin sensor GRAB-OT and the calcium indicator jRGECO1a in infralimbic cortex (IL) neurons projecting to the centrolateral amygdala (CeL). Retrogradely transported AAV expressing Synapsin-Cre was injected into the CeL to enable projection-specific expression. Recordings were collected across conditioning, extinction days 1 and 2, the reminder shock, and cue testing in a novel context. IL oxytocin signaling and IL-CeL neural activity were observed to increase during successful retrieval of extinction memory and appear attenuated in cases of poor fear regulation. To further test the causal role of oxytocin-expressing neurons in the infralimbic cortex, we selectively inhibited these cells using hM4Di DREADDs during novel context exposure. Silencing IL oxytocin neurons has been associated with disrupted extinction memory retrieval and increased freezing, suggesting their importance in regulating fear expression. These findings highlight a consolidation-sensitive window for extinction learning and support a role for oxytocin-modulated IL-CeL circuits in fear regulation. Understanding these processes may offer new strategies for improving PTSD treatment outcomes.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.19/HH9

Topic: H.06. Anxiety Disorders

Support: NIH R01MH132795
T32GM148331

Title: Tsc-mtorc1 signaling in prelimbic stress ensemble regulates maladaptive avoidance learning and memory

Authors: *S. LAWAL, O. TABAKA, M. MUJTABA, S. JHA, P. SHRESTHA;
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Abstract: Emotional regulation plays a key role in helping us respond to environmental stimuli, including recognizing danger cues and proactively coping with them, and is essential for survival. Protein synthesis is crucial for several cellular processes, including fear learning, memory, and emotional regulation. TSC proteins act as a molecular brake on mammalian target of rapamycin complex I (mTORC1) and integrated stress response (ISR), which are two opposing pathways regulating nascent protein synthesis. Loss-of-function mutations in TSC

genes (*Tsc1/Tsc2*), known to cause tuberous sclerosis complex, disrupt protein synthesis. However, the exact pathway and cell-type specific mechanisms of the role of perturbed protein synthesis in emotional dysregulation is unknown. Moreover, due to the fundamental need for social connection in social animals, prolonged involuntary isolation can act as a psychological stressor, inducing a sustained negative affective state that can precipitate maladaptive avoidance, a hallmark of pathological anxiety, in genetically susceptible individuals. The prefrontal cortex (PL) serves as a higher-order regulator of learned emotional responses through projections to subcortical limbic regions and is, therefore, a potential therapeutic target for disorders associated with dysregulated learned fear. We hypothesized that selectively inactivating *Tsc2* in adult PL neuronal ensembles activated during social isolation will precipitate maladaptive anxiety-like phenotypes via mTORC1 and/or ISR pathway. To test this, we used viral-mediated deletion of *Tsc2* in PL stress ensemble and examined the effect of prolonged social isolation on behavior in mice. We further examined the effects of drugs targeting downstream TSC effectors in rescuing the observed phenotypes. Our findings indicate that the lack of social buffering and perturbed protein synthesis precipitates maladaptive anxiety-like phenotypes, specifically in signaled active avoidance paradigm where mice learn to shuttle in response to the threat-predictive auditory cue for avoiding the footshock. We also showed that this phenotype is associated with stress ensemble-specific *Tsc2* deletion, and not random PL neurons. These ensembles have elevated mTORC1 signaling, with increased cellular hypertrophy. Finally, chronic rapamycin injection rescued maladaptive phenotypes. In conclusion, stress-associated dysregulation of protein synthesis in the PL via the mTORC1 pathway exaggerates learned fear by inducing maladaptive anxiety-like phenotypes, and not innate anxiety in mice, indicating the role of PL stress ensemble in context-specific emotional regulation.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.20/HH10

Topic: H.06. Anxiety Disorders

Support: NIMH RO1 MH132795

Title: Translational control of prefrontal neuron ensembles during systems consolidation of pavlovian threat memories

Authors: *J. IQBAL¹, S. KIM³, A. GALLAGHER¹, A. WILSON¹, P. SHRESTHA²;
¹Neurobio. and Behavior, ²Neurobio. & Behavior, Stony Brook Univ., Stony Brook, NY; ³Dept. of Neurobio. and Behavior, Stony Brook University, Neurobio. & Behavior, Stony Brook, NY

Abstract: Transformation of emotional memories from labile state to long-term form requires protein synthesis in a distributed network of cells in the limbic system, but the dynamics of this molecular process during systems-level consolidation is poorly understood. Here, we investigated the role of protein synthesis in memory consolidation, focusing on the prelimbic cortex, a brain area involved in associative memory formation and retrieval. We examined how protein synthesis, particularly through the translation checkpoints involving eIF4E and eIF2 α pathways, contributes to the remote consolidation of cued threat memories. We used molecular, behavioral and in vivo fiber photometry techniques to explore this process after threat conditioning and observed experience-dependent changes in calcium signaling in the prelimbic cortex which were coordinated with conditioned freezing responses over time. Our findings highlight that protein synthesis is crucial for remote long-term memory (LTM) consolidation in CamK2 α + excitatory neurons of the prelimbic cortex. Knocking down eIF4E in these neurons impaired remote LTM, whereas enhancing protein synthesis in these neurons improved memory strength for remote LTM, provided there were no intervening retrievals. However, overexpression of eIF4E disrupted memory updating during reconsolidation, impaired remote LTM, and interfered with the ability to shift from freezing to active avoidance behavior. Additionally, knockdown of eIF4E in recent memory ensemble enhanced remote LTM retrieval, suggesting that the representation of different stages of memory is dynamic and requires suppression of protein synthesis in recent engram cells for proper consolidation. In summary, we demonstrate that precise regulation of protein synthesis in the prelimbic cortex is critical for effective long-term memory consolidation, offering potential avenues for therapeutic intervention in post-traumatic stress disorder (PTSD).

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

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Program #/Poster #: PSTR183.21/HH11

Topic: H.03. Motivation

Support: R21DA058160
University of Memphis Faculty Research Grant

Title: The role of the ventral pallidum and kappa opioid receptors in decision-making with delayed punishment

Authors: E. RILEY¹, Z. MIKKELSON², S. LOWE², C. HARTLESS², N. PATTERSON², J. WHITEHEAD², G. MINNES², *N. W. SIMON²;

¹Rhodes Col., Memphis, TN; ²Univ. of Memphis, Memphis, TN

Abstract: Insensitivity to punishment is a hallmark of many psychiatric disorders, including substance use disorder and pathological gambling. The neurobiological processes underlying sensitivity to delayed punishment, which is frequently underestimated compared to immediate punishment, remain unclear. A brain region that may contribute to this decision-making is the ventral pallidum (VP), which is involved with both reward motivation and punishment avoidance. A subset of VP neurons express kappa opioid receptors, which play a key role in stress response and punishment sensitivity. We investigated VP/KOR involvement in sensitivity to immediate and delayed punishment in rats. Decision-making was assessed using the Delayed Punishment Decision-making Task (DPDT), which reveals that rats, like humans, discount delayed punishment. Reversible inactivation of the VP reduced choice of punishment in the DPDT across all punishment delays, indicating that the VP plays a critical role in decision-making involving punishment sensitivity. Systemic administration of a KOR agonist decreased the choice of punishment, but this effect was most notable at shorter rather than extended delays. Finally, infusion of a KOR antagonist into VP increased sensitivity to delayed punishment, suggesting that KORs in the VP may play a role in modulating sensitivity to delayed punishment. Collectively, these experiments suggest VP KORs as a potential therapeutic target to improve decision-making in substance use and other disorders.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.22/HH12

Topic: H.03. Motivation

Support: NIH Grant R21DA058160

Title: The role of the dorsocentral striatum in decision-making with immediate and delayed punishment

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Abstract: Cost/benefit decision-making requires the assessment of many potential outcomes to maximize reward and minimize punishment. However, punishments that occur later in time are often underestimated compared to those occurring immediately after choice, leading to harmful decision-making. This delay discounting of punishment can be measured using the Delayed Punishment Decision-making Task (DPDT), in which rats choose between a small, safe reward and a large reward accompanied by a mild shock which increases in delay throughout the task. In DPDT, rats avoid the large reward when it is accompanied by immediate punishment, and shift preference to the large reward as the punishment becomes delayed. Previous work has

demonstrated that sensitivity to delayed punishment is regulated by the lateral orbitofrontal cortex (LOFC), a region that engages in top-down communication with multiple areas involved with emotional processing and motivation. However, the specific LOFC circuits that contribute to its role in delay discounting of punishment during decision-making are unclear. The dorsocentral striatum (DCS) receives dense projections from the LOFC, with this circuit appearing to be implicated in sensitivity to punishment during decision-making. Here, we investigated the role of the DCS in the delay discounting of punishment via reversible inactivation via infusion of a baclofen/muscimol solution. DCS inactivation increased choice of large rewards with both immediate and delayed punishment without impacting flexibility, choice latency, or overall task engagement. Preliminary data suggest that chemogenetic inhibition of LOFC projections to DCS do not influence decision-making. These findings will help elucidate the biological mechanisms underlying the delay discounting of punishment, laying a foundation for potential biological treatments to improve decision-making in psychiatric disorders.

Disclosures: Z. Mikkelsen: None. S. Lowe: None. C. Hartless: None. N.W. Simon: None.

Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.23/HH13

Topic: H.03. Motivation

Support: The Templeton World Charity Foundation
NARSAD Young Investigator

Title: Orexins as anxiety modulators in instrumental safety-seeking

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Abstract: Understanding the neuromodulatory systems that regulate adaptive coping behaviors in response to threat is essential for advancing our knowledge of stress and anxiety in health and disease. A key system in this area is the hypothalamic orexin (hypocretin) system, which shapes arousal, stress, and reinforcement—behaviors vital for survival. Orexins project densely to the dopaminergic ventral tegmental area (VTA), where they reinforce instrumental behaviors that lead to rewarding outcomes, like food-seeking. However, their role in reinforcing threat-motivated, goal-directed behaviors remains unexplored. Active avoidance (AA) behaviors are instrumental actions that enable organisms to prevent or escape latent harm. A reliable laboratory model of this is signaled active avoidance (SigAA), where animals learn to perform a specific action, such as shuttling between chambers, during a fear-conditioned warning signal (WS) to

avoid foot shock. Building on prior work proving that SigAA is positively reinforced by safety signals, we hypothesized that ‘safety’ acts as an appetitive-like goal, and that the lateral hypothalamus (LH) orexin → VTA circuit is necessary for such safety-seeking action. To test this, we used inhibitory optogenetics in Sprague-Dawley rats. An orexin-specific inhibitory opsin (Arch; AAV1-Ple112-Arch3.0-eYFP) was injected into the LH, and bilateral optic fibers were implanted in the VTA. Rats were then trained in the SigAA task, where shuttling during a WS (white noise) prevented foot shocks and triggered explicit feedback (FB) cues (pure tones) signaling safety. Training continued at 15 daily trials until animals met a predefined avoidance criterion. In shock-free test sessions, optoinhibition of orexin terminals in the VTA during FB cue led to a gradual reduction in within-session avoidance behavior compared to laser-free controls. Inhibition during the inter-trial interval (ITI) also reduced avoidance, yet the effect was weaker. A similar attenuation of avoidance was seen when inhibition occurred closer to WS onset. These findings suggest that either: 1) tonic orexinergic input to the VTA is essential for sustaining instrumental avoidance, or 2) orexin activity signals a prolonged safety period encompassing most of the ITI. Overall, our results provide evidence that AA is positively reinforced by safety and implicate the orexin-VTA pathway as a key contributor to this process. Ongoing studies aim to further dissect the temporal dynamics of orexinergic modulation in SigAA. This work may ultimately inform the development of novel therapeutic strategies for maladaptive coping behaviors beyond conventional models of anxiety.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.24/HH14

Topic: H.06. Anxiety Disorders

Support: CAPES
CNPq
FAPERJ

Title: Effect of environmental enrichment on the excitatory/inhibitory balance and behavior of a rat model of generalized anxiety disorder

Authors: *G. V. R. M. MATTOS¹, J. LANDEIRA-FERNANDEZ³, P. CAMPELLO-COSTA²;
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Abstract: Anxiety disorders are among the most prevalent psychiatric conditions in the world today, affecting approximately 4% of the global population (Javaid et al., 2023). Despite their high incidence, the available therapeutic arsenal remains limited, and many patients do not

respond adequately to conventional treatments. Additionally, the medications commonly used often cause side effects. This scenario has driven a growing body of scientific research aimed at understanding the etiological mechanisms of anxiety and seeking new therapeutic approaches. In this context, the present study aims to evaluate the potential of environmental enrichment (EE) in modulating behavior, assessed through classical anxiety tests, and neurochemistry, in a male rat strain model of Generalized Anxiety Disorder (GAD), selected based on their response to contextual fear. For this purpose, after weaning, on postnatal day 21 (PND21), high-freezing animals (Carioca High-Freezing, CHF) and control animals (CTR) were subjected to an environmental enrichment protocol involving sensory, social, and cognitive stimuli for a period of two months. In parallel, another group of CTR and CHF animals was kept in standard cages for the same period. During the final week of the EE protocol, animals from all groups underwent a battery of behavioral tests, with 10 animals in each group. Two days after the completion of testing, brains were collected for analysis by Western blot and immunofluorescence. Our results showed increased expression of the GluN1 subunit of the NMDA receptor in the prefrontal cortex of the CHF strain compared to controls. Similarly, the expression of the GABA transporter (GAT1) was elevated in anxious animals. In both cases, exposure to environmental enrichment effectively reduced GluN1 and GAT1 levels, whereas EE did not produce significant changes in these molecular markers in control animals. Behaviorally, we observed that CHF animals housed in standard cages (61.5 ± 0.8) exhibited higher freezing rates compared to the control group (25.2 ± 2.8). Exposure to EE significantly reduced immobility in the CHF group (47.7 ± 6.2) compared to CHF animals kept in standard cages (61.5 ± 2.8). On the other hand, no significant differences were observed in other anxiety tests. We propose that environmental enrichment is capable of restoring the balance between excitatory and inhibitory systems in the anxious brain, possibly by reducing glutamatergic activity and strengthening GABAergic inhibition. These findings suggest that EE may represent a promising and non-invasive therapeutic approach for the treatment of anxiety disorders.

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Poster

PSTR183: Preclinical Models of Anxiety, Fear, and Stress

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR183.25/HH15

Topic: I.04. Executive Functions

Title: Unraveling the cognitive cost of anxiety: implications for behavioral flexibility.

Authors: A. G. SOTO-CONFER¹, M. AWAN¹, *S. B. LINLEY²;

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Abstract: Cognitive flexibility (CF)—the capacity to adapt behavior and thought in response to changing environmental demands—is critical for decision making and goal directed behavior. In

rodent models, CF is commonly assessed using the odor-texture attentional set-shifting task (AST), a multi-stage paradigm employing olfactory and tactile cues to evaluate stimulus-response contingencies. While the AST has strong ethological validity and reverse translational relevance, data analyzed from a sample of 56 naïve Long-Evans rats revealed marked individual differences in task performance - suggesting underlying variability in cognitive abilities. Anxiety is known to influence performance on cognitive and executive tasks in both human and animal models. High-anxiety rat strains and those subjected to stress paradigms frequently exhibit impairments in attention and memory. In this study, we examined whether anxiety phenotypes affect CF in an outbred strain of Long-Evans rats using the AST. Rats ($n = 33$) were first evaluated on the elevated plus maze (EPM), with time spent in the open arms serving as an index of anxiety-like behavior. Animals in the upper and lower quartiles were categorized as low- and high-anxiety, respectively, while those in the middle quartiles comprised an intermediate group. No significant sex differences were observed in open-arm time (mean difference = 3.71 s, $p > 0.05$), nor in the distribution of anxiety classifications. Following, subjects then will complete the 7-stage AST. Performance on reversal learning and extra-dimensional set-shifting—two key measures of CF—will be compared across anxiety groups. Consistent with existing literature linking anxiety to executive dysfunction, we hypothesize that high-anxiety rats will demonstrate impairments in reversal learning and set-shifting relative to low- and intermediate-anxiety groups. Finally, findings will be compared to concurrent human studies investigating the impact of trait anxiety on analogous cognitive processes. Understanding how behavioral traits and cognition are interleaved and defining the relationship between anxiety and cognitive flexibility can help to identify individuals at risk and reveal insights that can inform interventions aimed at improving adaptability through anxiety reduction and cognitive flexibility training.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.01/III1

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

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T32 MH119049-02
T32 DA050558-03
NSF GRFP DGE1845298
Canadian Institutes of Health Research: Project Grant 169203

Title: The role of high hippocampal estrogen levels, age, and sex-specific receptor signaling in memory disturbances induced by acute trauma

Authors: *R. E. HOKENSON¹, K. RODRIGUEZ⁴, Y. CHEN⁶, A. K. SHORT², S. SAMRARI³, B. DEVIREDDY³, B. DOCOLAS⁷, J. WINTER⁵, S. E. BOLOTSKY³, I. RAYNA³, C. M. GALL³, K. K. SOMA⁸, E. A. HELLER⁴, T. Z. BARAM³;

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Abstract: Background: With increasing incidence of mass shootings and natural disasters, it is evident that acute traumatic events can provoke enduring disturbances of memory. When persistent and associated with intrusive trauma memories, these traumatic stress aftermaths can evolve to posttraumatic stress disorder (PTSD). PTSD is twice as common in women than men, even when controlling for trauma type. Why do these sex differences exist? What are the implications for aging? Trauma vastly elevates risk for Alzheimer disease and related dementias, which are more common in women. While many studies focus on the low estrogen (17 β -estradiol, E2) levels during menopause, the potential role of high E2 levels during the transition to menopause (the perimenopause) in the onset of aging-related cognitive problems has not been examined. These studies probe the roles of sex, age, and sex-hormones on memory disruptions following acute trauma. **Methods:** To probe the sex differences underlying memory vulnerability to trauma, we modeled acute traumatic stress (ATS) in mice by imposing simultaneous physical, social, and emotional stresses for two hours. Studies were conducted in male, proestrous female (high E2), and estrous female (low E2) adult mice. We focused on the role of hippocampal E2 levels, which were higher in male and proestrous female than estrous female hippocampus. We probed estrogen receptor (ER) contribution by treating mice with selective ER blockers or employing mice with selective deletion of ER α or ER β . Impacts of stress on memory were assessed through several memory tests. To identify the mechanisms by which ATS enduringly disrupts memory, we tested differential gene expression and enrichment of permissive/repressive histone modifications across male, proestrous, and estrous female hippocampus. To study the impact of high, “perimenopausal” E2 levels and ATS on cognitive decline, middle aged (10 months) female mice were given subcutaneous E2 pellets or placebo. **Results:** ATS enduringly disrupted memory in males and in females stressed during proestrus, while females stressed during estrus were protected. Pharmacological and transgenic approaches indicated signaling in ER α in males and, in contrast, ER β in females, as mechanisms for these memory problems. ATS-vulnerable male and proestrous females had a higher prevalence of hippocampal permissive chromatin compared to estrous females at baseline. Ongoing experiments are probing differential gene expression and enrichment of permissive and repressive histone modifications following ATS. Studies examining the role of high E2 levels and ATS on cognitive decline in aging are underway.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.02/II2

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIMH
Hope for Depression Research Foundation

Title: Role of astrocytes in the prefrontal cortex in regulating stress-related behaviors

Authors: *V. KONDEV¹, L. HOLT⁵, B. T. KIPP¹, C. BLASCHKE¹, G. ROJAS², R. FUTAMURA³, A. M. MINIER-TORIBIO⁴, A. LABANCA⁶, E. J. NESTLER⁷;

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Abstract: Stress exposure confers risk for many psychiatric disorders, ranging from major depression to PTSD. However, the factors that make certain individuals more susceptible to developing these pathologies remain incompletely understood. This is an especially critical gap in knowledge given that most people exposed to stress do not develop a psychiatric disorder and are considered resilient. The prefrontal cortex (PFC) has been identified as a critical locus mediating stress susceptibility vs. resilience, yet most research to date has focused on neuronal cell-types and circuitry, despite recent evidence that glial cells, such as astrocytes, regulate synaptic plasticity, neurotransmission, and cortical activity. Here, we explore the contribution of PFC astrocytes in modulating fast neurotransmission under baseline conditions and after chronic stress, and in controlling behavioral susceptibility vs. resilience, using a combination of *in vivo* fiber photometry, chemogenetics, and RNA-sequencing. Our data shed new light on how astrocytes coordinate cortical activity to modulate stress-related behavioral outcomes.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.03/II3

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: T32-NS082145
VA #BX004693
VA #BX004646

Title: Targeting the Orexin System to Alleviate Stress-Induced Dopamine Dysregulation

Authors: *O. YANG¹, S. M. PEREZ², D. J. LODGE³;

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Abstract: Stress is a major risk factor for psychiatric disorders, including post-traumatic stress disorder (PTSD) and psychosis. Numerous studies have shown that stress profoundly disrupts dopamine system function, notably increasing dopamine neuron population activity—defined as the number of spontaneously active dopamine neurons in the ventral tegmental area (VTA). These stress-induced increases have been linked to psychosis-like symptoms, such as hallucinations, delusions, and disorganized thinking, and are believed to contribute to comorbid psychosis in PTSD. However, the neural circuits and molecular mechanisms driving this dopamine dysregulation remain poorly understood, and effective treatments are lacking. Preliminary data from our lab have identified a multisynaptic circuit involving the insular cortex (IC) and orbitofrontal cortex (OFC) as critical for regulating stress-induced dopamine system dysfunction. This circuit may represent a promising target for restoring normal dopamine function following stress. One potential target is the orexin system, and we have previously shown that systemic administration of the dual orexin receptor antagonist suvorexant normalizes dopamine activity after stress. However, the specific circuit mechanisms through which orexin signaling contributes to dopamine dysregulation remain unclear. Given the dense orexinergic innervation of the OFC and its expression of orexin receptors, we hypothesized that suvorexant elicits its effects by acting in OFC. Here, we demonstrate that intra-OFC infusion of suvorexant reverses stress-induced increases in dopamine neuron population activity, implicating orexinergic modulation of the IC-OFC circuit in this process. Additionally, we utilized in vivo electrophysiology and fiber photometry to demonstrate that suvorexant attenuates IC-evoked glutamatergic activity in the OFC. Finally, we examined how stress alters orexin release in the OFC. By identifying the circuit and molecular mechanisms through which stress alters dopamine system function, and by evaluating orexin receptor antagonism as a potential therapeutic strategy, this work aims to advance our understanding of stress-related neuropsychiatric disorders and inform novel treatments for PTSD, psychosis, and related conditions.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

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Program #/Poster #: PSTR184.04/II4

Topic: H.05. Mood Disorders

Support: STI2030-Major Projects (2021ZD0203000 and 2021ZD0203002)
the National Science Foundation of China (32171016)
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Title: Orbital Circuits Transform Stress into Reactive Aggression

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Abstract: Emotional stress often triggers maladaptive aggression, a core symptom across many psychiatric disorders, yet its underlying neural mechanisms remain elusive. Here, we develop a vicarious social defeat stress (VSDES) paradigm that models anxiety-associated reactive aggression, revealing individual differences in stress vulnerability. We identify the lateral orbitofrontal cortex (ORBl) as a key integrator that transforms internal emotional states into aggressive action. In susceptible individuals, ORBl neurons encode both anxiety and attack behavior through shared population dynamics, linking emotional arousal directly to maladaptive output. Stress selectively amplifies ORBl activity, with anxiety-related inputs from the ventromedial thalamus enabling ORBl outputs to the dorsal striatum to drive aggression. Bidirectional manipulations targeting ORBl or its ventromedial thalamic afferents modulate both anxiety and aggression, establishing a direct causal mechanism for stress-driven social pathology. Importantly, anxiolytic intervention normalizes ORBl hyperactivity and prevents the emergence of maladaptive aggression. These findings redefine the classic view of prefrontal cortex function in aggression—not as a passive brake on attack circuits, but as an active translator of emotional stress into maladaptive actions via striatal pathways. Our work establishes a mechanistic framework linking internal affective states to external behavioral pathology and identifies ORBl circuitry as a promising therapeutic target for stress-related neuropsychiatric disorders.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

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Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: NIH Grant 1R21MH136446
NIH Grant R15HD110925
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Title: Cortical-amygdala dysfunction in traumatic stress-induced aggression

Authors: *M. AHOLT¹, J. C. NORDMAN¹, N. MOJAHED¹, J. T. JACOBS², M. ADJEI¹;
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Abstract: The orbitofrontal cortex (OFC) is a critical region involved in decision-making, emotional regulation, and the modulation of aggression. Traditionally conceptualized as exerting inhibitory control over impulsive behaviors, emerging evidence indicates a more nuanced role for the OFC in aggression regulation. Moreover, neuroimaging studies have revealed that traumatic stress disrupts OFC functionality and its connectivity with aggression-related brain regions such as the amygdala, suggesting the OFC plays a pivotal role in stress-induced aggression. However, the precise neural circuitry through which the OFC modulates aggression following traumatic stress remains unclear. To clarify the role of the OFC in traumatic stress-induced aggression, we employed a multidisciplinary approach combining viral tracing, fiber photometry recordings, and chemogenetic manipulations. Our results demonstrate that excitatory neurons in the OFC densely project to the medial amygdala (MeA), a key region implicated in aggression triggered by traumatic stress. Fiber photometry recordings confirmed that traumatic stress selectively activates these excitatory OFC neurons that project to the MeA (OFC^{MeA}), as well as the corresponding MeA neurons receiving this OFC input. Critically, chemogenetic inhibition of these excitatory OFC^{MeA} neurons during traumatic stress exposure significantly attenuated the subsequent increase in aggressive behavior. These findings provide compelling evidence that traumatic stress drives hyperactivity in the excitatory OFC^{MeA} circuitry, resulting in dysregulated aggression via enhanced MeA activation. This work identifies the OFC-MeA pathway as a promising target for therapeutic intervention in stress-related aggression disorders.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

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Program #/Poster #: PSTR184.06/II6

Topic: H.05. Mood Disorders

Support: NIH Grant T32DA007027-49

Title: Effects of Acute Ketamine and Chronic Desipramine on Brain Structure and Neurochemistry in a model of chronic stress in adolescent rats

Authors: *F. ZHANG¹, M. NEWMAN², M. HOLLIDAY¹, F. CORWIN², K. NICHOLSON¹;
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Abstract: Depression is the most common psychiatric condition in the United States, affecting nearly 10% of adults and up to 20% of adolescents. Antidepressant medications remain a

cornerstone of treatment; however, traditional monoamine-based antidepressants are limited by their delayed onset of action, typically requiring four to eight weeks to achieve therapeutic effects. In contrast, ketamine has emerged as a rapid-acting antidepressant effective in treatment-resistant depression. Despite its promise, the mechanisms by which ketamine and conventional antidepressants exert their effects—especially on the developing brain—remain poorly understood. This study used a longitudinal preclinical model to compare the effects of acute ketamine and chronic desipramine on brain structure and neurochemistry in adolescent rats exposed to chronic dexamethasone. At postnatal day (PND) 35, female Long-Evans rats underwent baseline magnetic resonance imaging (MRI) scanning, including T2-weighted imaging and diffusion tensor imaging (DTI) for assessing structural integrity, and magnetic resonance spectroscopy (MRS) for evaluating neurochemical profiles. Animals were then administered daily dexamethasone injections (1 mg/kg) for 21 consecutive days, modeling the impact of glucocorticoid-induced stress during adolescence. After the “stress-exposure” period, a second MRI session was conducted, followed by behavioral assessment using the sucrose preference test (SPT) to evaluate anhedonia. The dexamethasone-treated rats were then divided into three groups: one group received six weeks of daily desipramine (1 mg/kg), a second received a single acute dose of ketamine (10 mg/kg) 24 hours before the final MRI session, and a third group received saline for six weeks. After the treatment phase, all rats underwent a third MRI session, followed by additional behavioral testing using the SPT and the novelty-suppressed feeding test (NSF) to assess depressive-like behaviors. Results demonstrated that chronic dexamethasone exposure during adolescence led to lasting neurobiological and behavioral impairments, including reduced sucrose preference and increased latency to feed in a novel environment—markers of depression-like behavior. Both repeated desipramine and acute ketamine reversed these behavioral effects. MRS revealed that both treatments similarly elevated glutamate concentrations in the medial prefrontal cortex. However, T2-weighted imaging showed that only desipramine treatment significantly increased the volume of the left anterior cingulate cortex, suggesting distinct structural effects between the two antidepressants.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

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Program #/Poster #: PSTR184.07/II7

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Effect of Acute R-S Ketamine and Chronic Fluoxetine Treatment on Behaviors of Anxiety and Stress in Female Mice.

Authors: *E. M. IRWIN¹, L. MEDINA², A. L. LACROSSE³;

¹Dept. of Psychological Sci., ²Northern Michigan Univ., Marquette, MI; ³Psychological Sci., Northern Michigan Univ. Departments of Psychology, Marquette, MI

Abstract: Post-traumatic stress disorder (PTSD) occurs due to exposure to a traumatic event. Symptoms associated with this disorder include persistent intrusive re-experiencing of stressful memories and fear generalization. Current pharmacological treatments for PTSD are inadequate, with less than thirty percent of patients reporting symptom remission. Previous research in our lab found that the combination of acute (R, S) Ketamine and chronic Fluoxetine (FLX) effectively reduced fear responses induced by contextual cues succeeding fear conditioning (FC) in male C57 mice. However, females are twice as likely to develop PTSD, and previous literature has demonstrated sex differences in response to treatment, with females exhibiting greater sensitivity to the effects of ketamine compared to males. It is important to examine these compounds in both sexes to further the translational potential of this treatment from mice to humans. This study aims to determine the efficacy of acute (R, S) Ketamine and chronic FLX in reducing fear memory and fear generalization in female C57 mice. Fear conditioning (FC) is commonly used in the literature to induce behaviors related to symptoms of PTSD in rodents. In this study, FC consists of a white noise cue stimulus paired with four inescapable foot shocks. Treatment administration is 4 hours after FC. Treatments are tested through re-exposure to analyze context-based fear, and an open field test (OFT) allows us to assess cue-based fear and generalized anxiety during exploration of a novel environment. Fear behaviors are recorded during re-exposure to the FC context and cue at 24 hours, 2 weeks, and 4 weeks following FC. The OFT is conducted 2 weeks and 4 weeks after FC. We hypothesize that fear responses will decrease when mice are administered a combination of acute (R, S) Ketamine and chronic FLX compared to control groups and the current standard treatment options. This study contributes to the existing literature on pharmacological treatment for fear responses relating to fear memory and fear generalization. Continued research is necessary to replicate results, optimize treatment protocols, and investigate the molecular adaptations to trauma and treatment.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

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Program #/Poster #: PSTR184.08/II8

Topic: H.05. Mood Disorders

Support: RS-2022-NR072375

Title: Stress responsiveness shapes neuronal dynamics in the lateral habenula

Authors: *H. PARK, C. CHUNG;
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Abstract: Acute stress activates the lateral habenula (LHb), an epithalamic brain region. Excessive or prolonged negative stimuli induce abnormal hyperactivity in the LHb, which is strongly linked to mood disorders. Understanding how LHb activity changes after stress

exposure is essential for uncovering the mechanisms of depression. However, because the LHB is highly heterogeneous, studying these changes has been challenging. This heterogeneity suggests that distinct neuronal subpopulations may respond differently to stress. We therefore hypothesized that a specific subset of stress-activated neurons undergoes distinct physiological changes that may underlie depressive behavior. We labeled stress-responsive neurons (SRs) in both male and female mice using two independent activity-dependent tagging methods, including a viral vector approach and a transgenic mouse line based on c-fos expression. Neuronal activation was induced using the acute learned helplessness (aLH) paradigm, involving one hour of inescapable and unpredictable foot shocks. Both methods successfully labeled neurons activated under this condition, enabling targeted electrophysiological recordings. SRs predominantly exhibited burst firing, while non-responsive neurons (NRs) showed tonic or silent activity. SRs also displayed enhanced excitatory synaptic transmission, likely due to increased presynaptic vesicle release probability. To examine how stress intensity affects these responses, we labeled neurons activated by mild stress (20 minutes of foot shocks). These neurons initially lacked SR-like properties. However, after aLH exposure, they showed burst firing and enhanced presynaptic release, suggesting that excessive stress induces lasting physiological changes in stress-responsive neurons. We confirmed these changes in vivo using fiber photometry, which revealed dynamic LHB activity patterns consistent with ex vivo findings. Ongoing studies are investigating the behavioral significance of these changes, including optogenetic manipulation of SRs during stress-related tasks. These findings provide insight into how excessive stress alters specific neural circuits and may contribute to the development of depressive behavior.

Disclosures: H. Park: None. C. Chung: None.

Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.09/II9

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

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P30DA033934
R01DA058958
R01DA058089
Blick Scholars Fund
V30 Training Award
F31MH133309

Title: Transposable element stability in the prefrontal cortex is implicated in social behavior changes

Authors: *C. SMITH¹, R. K. KIM¹, N. L. TRUBY¹, G. SILVA¹, R. L. NEVE², P. J. HAMILTON¹;

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Abstract: Engaging in social behavior is essential for group-based organisms, but chronic stress experience can lead to changes in social functioning that constitute a serious quality of life issue. Transposable elements (TEs) are mobile DNA segments that are implicated in the evolution of transcriptional networks via *cis* regulatory activity and have been demonstrated to be dysregulated in a multitude of human neurological and neuropsychiatric disorders. TE transcription is largely controlled by the KZFP family of transcription factors along with the repressive cofactor, TRIM28. Our lab has developed three synthetic TRIM28 constructs—TRIM28^{WT} (wild-type), TRIM28^{NFD} (no functional domain), and TRIM28^{VPR} (synthetic activator domain VP64-p65-Rta)—which we deliver stereotactically via HSV viral vector to the medial prefrontal cortex (mPFC) of female and male C57BL/6J mice. These tools were validated in a luciferase assay to exert divergent control over KZFP-regulated gene transcription. In stress-naïve mice, inverting TRIM28's natural repression with the synthetic activator HSV-TRIM28^{VPR} or introducing the transcriptionally inert HSV-TRIM28^{NFD} causes nuanced deficits in social behavior in the Three-Chamber Social Recognition Test, Five-Trial Social Memory Test, and Tube Test for Social Dominance, while overexpressing the endogenous mimic HSV-TRIM28^{WT} does not impact behavior. In mPFC, HSV-TRIM28^{VPR} and HSV-TRIM28^{NFD} induced a significant upregulation of TE transcripts and a significant downregulation of interferon-related gene expression compared to the HSV-GFP control, in proportion to their behavioral effects. Thus, we hypothesize that in stress-naïve mice, TE repression enables normal social behavior by allowing normal *cis* regulation of immune genes. Building upon these findings, we are seeking to understand whether stress-induced social deficits manifest via the same mechanism. By introducing the synthetic TRIM28 constructs either before or after a period of chronic social stress and performing the Social Interaction Test and Three-Chamber Social Recognition Test, we aim to determine if stabilizing TEs in mPFC with TRIM28^{WT} is able to rescue or prevent the development of stress-induced social deficits.

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Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

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Program #/Poster #: PSTR184.10/II10

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: U.S. Department of Defense Grant- HT9425-24-1-0638

Title: An ephrinA4 mimetic peptide targeting the EphA binding site impairs the formation and reconsolidation of fear memory and demonstrates therapeutic potential for PTSD

Authors: *M. DINES¹, B. POPIK¹, F. SHHADE¹, R. LAMPRECHT²;

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Abstract: Fear memory allows individuals to recall situations, environments, and cues that might pose potential danger. However, following a traumatic event, this adaptive mechanism can become dysregulated, leading to post-traumatic stress disorder (PTSD), in which fear responses are exaggerated or triggered inappropriately. Treatments for PTSD center on continued medication, addressing symptoms rather than the source of the problem, which is the traumatic experience. We, therefore, sought to develop a drug capable of effectively treating the underlying causes of PTSD. We previously designed an inhibitory ephrinA4 mimetic peptide (pep-ephrinA4) that targets the ligand binding site of EphA tyrosine kinase receptor. We found that an acute subcutaneous injection of pep-ephrinA4 in rats, administered 1 hour after fear conditioning, impaired long-term fear memory when tested 24 hours later. Additionally, acute subcutaneous injection of pep-ephrinA4 30 minutes before a memory retrieval session on the day following conditioning also significantly impaired memory when tested 24 hours after that session. These findings highlight the efficacy of the peptide in mitigating fear memory development and in reducing fear symptoms even when treatment is delayed, demonstrating its potential as a therapeutic tool for PTSD. We are performing a rigorous evaluation of pep-ephrinA4 to achieve the most effective and safe dosing regimen. We are exploring several dosing strategies, levels, and routes (i.e., subcutaneous, nasal, and intravenous) that may further enhance pep-ephrinA4 efficacy in rats. We will describe the outcome of these studies in detail. Our novel peptide drug thus represents a potentially invaluable tool that may help alleviate the burden of PTSD.

Disclosures: **M. Dines:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **B. Popik:** None. **F. Shhade:** None. **R. Lamprecht:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.11/II11

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Footshock stress induces post-traumatic stress disorder-like symptoms in behavior and neural mechanisms in mice: Assessments of c-Fos and oxytocin expression in the medial prefrontal cortex, amygdala, and hippocampus

Authors: *P.-J. HUNG¹, W. MA^{2,1}, A. C.-W. HUANG¹;

¹Fo Guang Univ., Yilan County, Taiwan; ²Natl. Def. Med. Ctr., Taipei, Taiwan

Abstract: Post-traumatic stress disorder (PTSD) is a chronic psychiatric disease that severely impairs daily functions. Social support has been increasingly recognized as a key factor in mitigating PTSD symptoms. However, in animal models, the mechanisms through which oxytocin modulates stress-related disorders—such as PTSD or fear conditioning—remain poorly understood. This study aimed to investigate the role of oxytocin in this context. In this study, male C57BL/6 mice were used. The experimental group was placed in a footshock box for two minutes, followed by the administration of an electric shock (3 mA, 10 seconds). For the subsequent three days, mice were re-exposed to the same context for two minutes without receiving additional shocks, during which freezing behavior was recorded to assess conditioned fear. Following the behavioral recording, animals were subjected to either the Open Field Test (OFT) or the Forced Swim Test (FST) to evaluate anxiety- and depression-like behaviors. The results indicated that footshock exposure significantly increased fear-related behaviors and induced anxiety-like behavior in the OFT and depression-like behavior in the FST. Additionally, footshock stress enhanced corticosterone levels in serum and increased c-Fos expression in the cingulate cortex area 1 (Cg1) of the medial prefrontal cortex (mPFC). Notably, oxytocin expression in the Cg1 was reduced following footshock exposure. It is hypothesized that reduced oxytocin signaling in the Cg1 may lead to hyperactivity of this region, thereby contributing to PTSD-like symptoms. These findings offer preliminary evidence supporting the therapeutic potential of oxytocin in PTSD, warranting further investigation.

Disclosures: P. Hung: None. W. Ma: None. A.C. Huang: None.

Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.12/II12

Topic: H.05. Mood Disorders

Title: Role of MCH+ Neuron-mediated Sleep Homeostatic Regulation in Social Isolation-Resulted Anxiety.

Authors: *B. LIU¹, Z. WANG²;

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Abstract: Objective: Sleep, comprising rapid-eye-movement sleep (REM) and non-rapid-eye-movement sleep (NREM), plays a pivotal role in modulating emotions and recovering from negative affective states. As a common stressor that can disrupt these sleep patterns, social isolation can also induce anxiety-like behaviors. However, the neural mechanisms underlying these sleep alterations and their potential role in inciting anxiety from social isolation remain obscure. We aim to elucidate their roles further through a series of experiments manipulating dopamine receptor neurons and melanin-concentrating hormone (MCH) neurons. Methods: Our investigative method involve stereotactic injections of viruses for chemogenetic and receptor-

genetic manipulations of neuronal activity. We use a patch-clamp technique to record neuron excitability and employed behaviors including elevated plus maze, open field test, light-dark box, forced swimming test, and three-chamber test to monitor the animals. The alterations in the sleep architecture of the subjects were gauged using the ECoG sleep recording system. Results: (1) By examining the sleep states of the post weaning social isolation (PWSI) model rats, we found that male rats experienced more REM sleep after PWSI. (2) We manipulated D2 receptor neurons in the dorsal BNST, and found that the inhibition of dBNST Drd2⁺ neurons reduces sleep in a long-term way while the activation of dBNST Drd2⁺ neurons reduces sleep in a short-term way. (3) PWSI stress affects the neuronal excitability of MCH⁺ neurons in lateral hypothalamus (LH). Conclusion: Our findings imply that social isolation-induced anxiety may result in distinct changes in sleep patterns, with dBNST Drd2⁺ neurons potentially mediating these changes. The role of the MCH system during social isolation may be pivotal in regulating emotions and sleep, highlighting potential avenues for the study of the neurobiology of sleep, pandemics, and mental health.

Disclosures: B. liu: None. Z. Wang: None.

Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.13/II13

Topic: H.05. Mood Disorders

Support: John Brown University Startup Grant
Arkansas INBRE Faculty Recruitment Grant

Title: Correlation between quantity changes of parvalbumin-positive interneurons and perineuronal nets in the ventral hippocampus and stress-modulated antidepressant effect of ketamine in mice

Authors: O. KIM¹, B. WILLIAMS², *Q. WANG³;

¹The Stowers Inst. for Med. Res., Kansas City, MO; ²Neurosci., Univ. of Texas at Dallas, Richardson, TX; ³Biol., John Brown Univ., Siloam Springs, AR

Abstract: As part of the preparation for ketamine treatment, patients are instructed to relax, as the time before treatment is a crucial part of the process. Animal studies provided evidence for such practice. For example, Fitzgerald *et. al.* showed that stress before ketamine treatment diminished its antidepressant effect. In this study, we investigated the quantitative changes of PV interneurons and perineuronal nets in the ventral hippocampus during the forced swim test (FST) after two kinds of stress treatment, namely mild stress (MS) and unpredictable chronic stress UCS, in male CD-1 mice with or without ketamine treatment. MS mimics social isolation, which was created by individual housing and a human handling session once a day for seven days. UCS was created by alternating mild stressors for four weeks. As predicted, in FST, ketamine-treated

mice showed no significantly different immobility time compared to untreated mice. Brains were extracted two hours after the onset of FST. PV interneurons and perineuronal nets (labeled with vicia villosa agglutinin, VVA) in the ventral hippocampus were quantified using immunohistochemistry and fluorescent imaging. After MS exposure, FST with ketamine treatment did not significantly alter the number of PV interneurons in the ventral hippocampus. However, after UCS exposure, in mice not treated with ketamine, FST alone reduced the number of PV interneurons. Interestingly, in mice that were treated with ketamine and underwent FST, the number of PV interneurons was restored. In addition, in ketamine-treated mice, FST reduced the number of VVA puncta. Moreover, in mice with no ketamine treatment or FST, more VVA puncta were present in mice that were exposed to the UCS condition compared to the MS condition. Similarly, in mice that were treated with ketamine and underwent FST, UCS exposure increases the number of VVA compared to MS. The percentage of neurons labeled with both PV and VVA among PV interneurons was calculated. After MS exposure, without FST, ketamine treatment alone increases the percentage compared to the control. In conclusion, under the two stress conditions, quantities of PV interneurons and perineuronal nets changed during treatments such as ketamine injection and FST, or a combination of both. Stress conditions may also influence the amount of perineuronal nets. As the future direction, it is necessary to determine whether there is a cause-and-effect relationship between the change of quantities and different treatments. Furthermore, it is important to explore the molecular mechanisms of such quantitative changes.

Disclosures: O. Kim: None. B. Williams: None. Q. Wang: None.

Poster

PSTR184: Stress, Anxiety, and Related Disorders

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR184.14/II14

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Effects of early life trauma on prefrontal innervation of downstream targets in adulthood.

Authors: *M. R. MAYEAUX¹, E. E. HISEY²;

¹Boston Univ., Boston, MA; ²Psychiatry, Boston University/VA Boston, Concord, MA

Abstract: The lasting impacts of ongoing trauma exposure during adolescence is a rising public health concern linked to increased risk for developing psychiatric disorders later in life. Despite its prevalence, the mechanisms driving these lasting impacts are not well understood, leading to significant obstacles in the development of effective psychiatric treatment options. To bridge this gap in knowledge, we have conducted extensive analysis on the behavioral and anatomical changes observed in mice post chronic adolescent social defeat compared to non-defeated control mice. Male and female C57 mice were exposed to 5 days of chronic social defeat by a CFW mouse of the same sex in early adolescence (P29-33). Social behavior was measured at multiple time points after defeat using traditional open field social interaction paradigms as well as home

cage social interaction with mice of the same strain as the aggressor (CFW) and with mice of the same strain as the defeated (C57). Upon reaching early adulthood (P60), mice underwent unilateral stereotaxic viral injections of green fluorescent protein-tagged adeno-associated virus (AAV-GFP) into the pre-limbic (PL) brain region for axon tracing between the PL, nucleus accumbens (NAc), basolateral amygdala (BLA), and ventral tegmental area (VTA); these brain regions are closely associated with key symptoms of complex trauma including the top-down control of fear learning and fear extinction as well as social behavior. Behaviorally, defeated male mice showed consistent avoidance and defensive related behaviors in all social interaction paradigms used, resulting in a decreased social interaction ratio in the open field social interaction task. Alternatively, female mice showed no effect in the open field social interaction task and showed marked increases in contact with both CFW and C57 stimulus females during the home cage social interaction task. Analysis of fluorescence microscopy images confirmed significant decreases in axon density in the BLA and VTA of defeated mice as compared to control mice. Without proper innervation between these identified brain regions, successful emotion regulation and fear extinction processes are impeded. This circuit-level finding suggests a potential explanation for the driving factor behind hallmark PTSD symptoms such as hyper-arousal, fear generalization, and unsuccessful fear-extinction post-exposure to triggers. Interestingly, we found no significant changes in PL innervation of NAc between control and defeated animals. Future research will be aimed at functionally confirming the connection between behavioral symptomatology and loss of axon density within the VTA.

Disclosures: M.R. Mayeaux: None. E.E. Hisey: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.01/JJ1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant R01DA002812
NIGMS Grant T32GM07019
NCATS Grant KL2TR002387

Title: Psychostimulant-driven network changes: methamphetamine enhances attention and arousal signatures

Authors: *Y. LYU;
UCLA, Los Angeles, CA

Abstract: Previous studies using between-subjects measurements have found that psychostimulants can shift whole-brain connectivity toward patterns that suggest increased sustained attention. Here, we investigated how a single oral dose of methamphetamine (MA; 20 mg) alters sustained attention and the associated functional network organization in healthy

adults. We conducted a within-subject study in which 104 healthy volunteers completed two fMRI sessions, one after taking MA and one after taking placebo. We examined whether MA selectively modulates behavioral and whole brain functional connectivity patterns linked to attention and arousal. Relative to placebo, participants under MA showed improved attention task performance and connectivity signatures associated with high sustained attention and elevated arousal ($p < .001$). These changes appeared consistently during resting-state and task-based fMRI, suggesting that MA influences attention-related networks across cognitive context. Moreover, a support-vector classifier reliably distinguished MA from placebo sessions using functional connectivity data, with the most informative edges overlapping previously defined arousal networks. Consistent with work on other psychostimulants (e.g., methylphenidate), MA modulates large-scale brain networks that relate to attention and arousal. These results highlight the value of psychostimulants as causal tools for probing the robustness, generalizability, and interpretability of brain-based biomarkers of behavior.

Disclosures: Y. Lyu: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.02/JJ2

Topic: H.08. Drugs of Abuse and Addiction

Title: Molecular mechanisms underlying Methamphetamine-related hypofrontality and cognitive deficits

Authors: C. PERRETTA¹, *A. LAVIN²;

¹Neurosci., MUSC, Charleston, SC; ²Neurosci., Med. Univ. of South Carolina (MU Neurosci. Inst. - Grad., Charleston, SC

Abstract: Neuronal PAS Domain Protein 4 (Npas4) is an activity-dependent Immediate Early Gene (IEG), and transcription factor that plays a critical role in regulating the excitation/inhibition (E/I) balance in cortical circuits. NPAS4 promotes the formation of inhibitory synapses onto excitatory neurons and excitatory synapses onto inhibitory neurons, thereby acting as a homeostatic regulator to stabilize neural network activity and prevent circuit hyperexcitability. Recent evidence implicates NPAS4 in neuropsychiatric disorders marked by hypofrontality. In particular, Npas4 expression is elevated in mPFC pyramidal neurons following chronic social defeat stress and cocaine exposure, coinciding with reductions in dendritic spine density and excitatory synaptic transmission—two cellular correlates of hypofrontal states. Additionally, NPAS4 expression is upregulated in the nucleus accumbens following chronic amphetamine administration and has been linked to cocaine self-administration behaviors in mice. Methamphetamine (METH), a widely abused drug with high potency, elicits hypofrontality and cognitive deficits that persist even after 11 months of abstinence, however, the molecular and cellular mechanisms mediating the METH related hypofrontality and

cognitive dysfunction are unknown. Using young adult male Long Evans rats and C57 mice, combined with immunohistochemistry, electrophysiology and a battery of behavioral tests, focusing in the medial prefrontal cortex (mPFC) we investigate the role of NPAS4 on METH-related cognitive deficits and hypofrontality. We found that acute (5.0 mg/Kg in mice, 10 mg/Kg in rats) significantly increases expression of NPAS4 in the mPFC, with higher expression in the prelimbic cortex (PRL) than in the infralimbic cortex (IL). Furthermore, acute METH injections (2.0 to 5.0 mg/Kg) significantly increase expression of NPAS4 in a dose-dependent manner, with higher increases in the PRL-compared to the IL-mPFC. Additionally, we found that acute METH administration elicits a significant increase in expression of NPAS4 in mPFC that peaks between half an hour to an hour and last that last for at least 2 hours. These preliminary results show that METH increases NPAS4 expression in mPFC. Forthcoming experiments will investigate the changes in NPAS4 expression in the mPFC after repeated exposure to METH and will explore the role of NPAS4 in the METH-related cognitive deficits.

Disclosures: C. Perretta: None. A. Lavin: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.03/JJ3

Topic: H.08. Drugs of Abuse and Addiction

Support: NINDS 1R35NS1168

Title: Brain-wide screening of neurotransmitter plasticity: effects of methamphetamine or acute stress

Authors: *M. PRATELLI^{1,2}, K. SHOJAEI^{1,2}, E. LARRONDO^{1,2}, A. ASTHANA^{1,2}, D. KHARIDIA^{1,2}, C. FREDMAN^{1,2}, D. ALVAREZ^{1,2}, M. WITHEE^{1,2}, L. WU^{1,2}, N. C. SPITZER^{1,2},
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Abstract: Neurotransmitter switching is the ability of neurons in the developing or adult nervous system to begin expressing a new neurotransmitter, lose one they previously expressed, or both. It often involves changes from excitatory to inhibitory transmitters—or vice versa—and affects behavior. For example, repeated exposure to methamphetamine (METH) induces glutamatergic neurons in the prefrontal cortex to gain GABA, generating cognitive deficits. Similarly, experiencing acute inescapable foot-shock stress (FS) causes serotonergic neurons in the dorsal raphe to switch their co-transmitter from glutamate to GABA, resulting in generalized fear. However, whether METH and FS also induce transmitter switching in other brain regions was unknown. To address this question, we developed a largely automated pipeline to map transmitter switching throughout the brain, focusing on changes involving glutamate and GABA—the brain's most common excitatory and inhibitory neurotransmitters. We used VGAT-Flp::VGLUT2-Cre::Con/FonTdTomato mice, in which neurons that currently express or have

ever expressed both transmitters—even at different time points—are permanently marked with TdTomato fluorescence. We exposed these mice to either METH or FS, reasoning that if these stimuli caused glutamatergic neurons to gain GABA (or vice versa), the affected neurons would become labeled with TdTomato, increasing the total number of TdTomato+ cells. Using two-photon array tomography, registration to the Allen Brain Atlas, and automated cell counting, we found that both repeated METH and acute FS increased the number of TdTomato+ neurons in 34 and 27 brain regions, respectively. But are these glutamatergic neurons that gained GABA, or GABAergic neurons switching to glutamate? And is the transmitter change stable over time? Transmitter switching can be transient or stable, and only stable changes are likely to influence behavior. To answer these questions, we focused on three brain regions with METH-induced increases of over 10,000 TdTomato+ neurons. After METH exposure, switched neurons co-expressed glutamatergic and GABAergic markers or expressed the glutamatergic marker alone. Preliminary data indicate these neurons were either GABAergic or glutamatergic prior to treatment. We are now examining whether the induced phenotype is retained one month later. These findings show that environmental stimuli can trigger transmitter switching in multiple brain regions, enabling broader investigation into how such changes impact behavior.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.04/JJ4

Topic: H.08. Drugs of Abuse and Addiction

Support: DA051450

Title: Glutamate release probability from the orbitofrontal cortex to direct pathway spiny projection neurons in the dorsomedial striatum is decreased during protracted abstinence from ten but not five days of methamphetamine self-administration

Authors: *H. METHIWALA, S. M. GRAVES;
Pharmacol., Univ. of Minnesota, Minneapolis, MN

Abstract: Methamphetamine (meth) is an addictive psychostimulant. The dorsomedial striatum (DMS) is primarily comprised of direct pathway spiny projection neurons (dSPNs) and indirect (iSPNs) pathway spiny projection neurons and is implicated in substance use disorders (Gremel et al., *Genes Brain Behav.*, pp. 71, '17). The orbitofrontal cortex (OFC) preferentially innervates the DMS and is involved in goal-directed behaviors (Hintiryan et al., *Nat. Neurosci.*, pp. 1100, '16; Gremel et al., *Nat Commun.*, pp. 2264, '13). Both alcohol and cocaine have been shown to disrupt the OFC-DMS circuit function (Cheng et al., *Neuropharmacol.*, pp. 108560, '21; Bariselli

et al., *Nat Commun.*, pp. 3996, '20). However, potential meth-induced neuronal dysfunction in this circuit is unclear. To determine the impact of meth on OFC-DMS circuit function, male and female D1-TdTomato/D2-GFP transgenic mice were implanted with jugular vein catheters and underwent meth self-administration (MSA; 2 hr/day, 0.1 mg/kg/infusion) for 5 or 10 days (d) using a fixed ratio 1 reinforcement schedule with a cue-light paired with each meth infusion; saline-yoked control mice were run in parallel. AAV9-CamKII-chronos-eBFP was bilaterally injected into the OFC 1-4 days after the last operant session and *ex vivo* brain slices were prepared after 21-24 days of abstinence. Presynaptic glutamate release was assessed by paired-pulse ratio (PPR) measurement using whole-cell patch clamp and optogenetic stimulation techniques. After abstinence from 5d MSA, PPR was unchanged in male DMS dSPNs (meth: n=18 cells/6 mice, saline: n=8 cells/3 mice; unpaired t-test, p=0.696) and iSPNs (meth: n=7 cells/3 mice, saline: n=13 cells/4 mice; unpaired t-test, p=0.1963). In contrast, after abstinence from 10d MSA, PPR was increased in male DMS dSPNs (meth: n=15 cells/6 mice, saline: n=20 cells/7 mice; unpaired t-test, ***p=0.0002) indicating decreased glutamate release probability with no change observed in iSPNs (meth: n=10 cells/4 mice, saline: n=12 cells/5 mice; unpaired t-test, p=0.1427). To determine whether the OFC-DMS dSPN change was sex-specific, female mice underwent 10d of MSA, and PPR was assessed. Consistent with male findings, after abstinence from 10d MSA, PPR was increased in DMS dSPNs (meth: n=19 cells/7 mice, saline: n=19 cells/7 mice; unpaired t-test, *p=0.0324) and unchanged in iSPNs (meth: n=16 cells/6 mice, saline: n=9 cells/4 mice; unpaired t-test, p=0.3444). These findings suggest the emergence of OFC-DMS circuit dysfunction during abstinence from 10d but not 5d MSA. This effect appears to be cell-type specific and is marked by a reduced probability of glutamate release from OFC inputs onto DMS dSPNs.

Disclosures: H. Methiwala: None. S.M. Graves: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.05/JJ5

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA053328

Title: Investigating the biochemical correlates of incubated methamphetamine craving in the prefrontal cortex

Authors: *F. J. CANO¹, S. DAVANTES^{1,2}, K. STUEMKE¹, C. IBARRA¹, A. DELMONICO¹, C. LIEN¹, C. TEMPORAO¹, J. GELFOND¹, S. GONZALEZ¹, P. BHATTARAI¹, M. RUDOLPH SNYDER¹, C. JOO¹, L. L. HUERTA SANCHEZ¹, C. J. E. DENNING¹, K. K. SZUMLINSKI¹;

¹Univ. of California Santa Barbara, Santa Barbara, CA; ²Univ. of California-Santa Barbara, Riverside, CA

Abstract: The similar temporal profile observed for the incubation of craving across different psychostimulants (i.e., cocaine vs methamphetamine) has led to the hypothesis that these behavioral phenomena may involve common, time-dependent, biochemical adaptations within neural circuits governing motivated behavior. Previously, we reported that the mTOR inhibitor Everolimus dose-dependently blocks incubated cocaine-seeking and reverses incubation-related changes in protein expression in the prelimbic (PL) subregion of the prefrontal cortex (PFC). To elucidate whether mTOR signaling also drives incubation of other psychostimulants, we examined the biocorrelates of incubated methamphetamine craving in the PL, infralimbic (IL), anterior cingulate cortex (ACC), orbital frontal cortex (OFC) and Insula. Female and male rats were trained to self-administer methamphetamine (0.1 mg/kg/infusion), paired with a 20-s light + tone compound stimulus, during daily 6-h sessions over 10 consecutive days. One or 30 days following the last operant-conditioning session, rats were pretreated with vehicle or Everolimus (1.0 and 10.0 mg/kg) per os and tested for cue-elicited responding. All female and male rats expressed incubated methamphetamine-craving despite mTOR inhibition and female estrous phase did not affect intake or incubated craving of methamphetamine. Lastly, molecular studies detected no incubation-specific changes in mTOR signaling in methamphetamine-experience rats relative to methamphetamine-naïve rats. Taken together, our behavioral pharmacological and immunoblotting data to date argue that different biomolecular mechanisms drive incubated cocaine- versus methamphetamine-craving.

Disclosures: F.J. Cano: None. S. Davantes: None. K. Stuemke: None. C. Ibarra: None. A. Delmonico: None. C. Lien: None. C. Temporao: None. J. Gelfond: None. S. Gonzalez: None. P. Bhattarai: None. M. Rudolph Snyder: None. C. Joo: None. L.L. Huerta Sanchez: None. C.J.E. Denning: None. K.K. Szumlinski: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.06/JJ6

Topic: H.08. Drugs of Abuse and Addiction

Title: Comparing polysubstance and single substance use: effects on locomotion, social behavior, and the potential of psychedelic interventions

Authors: *K. C. DIAZ¹, L. M. SALINSKY¹, J. L. FOX¹, A. F. GARCIA², S. M. FERGUSON²; ²Psychiatry and Behavioral Sci., ¹Univ. of Washington, Seattle, WA

Abstract: As rates of opioid use disorder (OUD) have surged to an astonishing 2.5 million individuals, trends of concurrent psychostimulant use have also risen at an alarming rate. Despite this, current research has primarily focused on the behavioral effects of single-substance drug exposure--creating a gap in our understanding of the behavioral and neurobiological impacts of polysubstance use. We thus aimed to investigate the effects of repeated methamphetamine (METH) and fentanyl (FENT) polysubstance versus single substance administration on

locomotor activity and social interaction. Additionally, we examined whether administration of the psychedelic compound R-(-)-2,5-dimethoxy-4-iodoamphetamine (DOI) would ameliorate drug-induced social deficits, following research implicating its prosocial and therapeutic effects on substance use disorders. Male and female Sprague Dawley rats (n=80) were injected daily with either saline (1 mg/mL), METH (1 mg/kg), FENT (20 ug/kg), or both drugs given 5 hours apart for 14 days. Drug-induced locomotion was measured on days 1, 7, and 14. After treatment, all subjects underwent 10 days of withdrawal. A three-chambered social interaction test was given prior to the start of drug treatment and on day 11 of withdrawal. On day 12, all subjects received DOI (0.3 mg/kg; 30 min) and were reassessed for sociability. We observed that while polysubstance treatment did not exacerbate drug-induced locomotor sensitization, it generated distinct social deficits compared to single-substance treatment in a sex-dependent manner that was reversed by the treatment of DOI. Following these results, we are currently studying the potential role of the nucleus accumbens and prefrontal cortex in driving these drug-induced social deficits using in-vivo fiber photometry.

Disclosures: K.C. Diaz: None. L.M. Salinsky: None. J.L. Fox: None. A.F. Garcia: None. S.M. Ferguson: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.07/JJ7

Topic: H.08. Drugs of Abuse and Addiction

Title: Mapping neuronal ensembles associated with intoxication and withdrawal from fentanyl exposure using a dual-labeling strategy in TRAP2::Ai14 mice

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Abstract: Background: Opioid use disorder involves alternating phases of intoxication and withdrawal, each with distinct motivational and affective states. Understanding how overlapping or distinct neuronal ensembles are recruited across these states is critical for understanding neural patterns of addiction. While previous studies have mapped neural activity during isolated phases of addiction, it remains unclear whether intoxication and withdrawal recruit segregated or overlapping sets of neurons. To address this, we used a dual TRAP2::c-Fos labeling approach in mice to compare neuronal activation patterns across fentanyl-induced intoxication and withdrawal. **Methods:** Male and female TRAP2::Ai14 mice (8 weeks old, n=5/group) were implanted with osmotic minipumps delivering fentanyl (0.4 mg/kg/day) or saline as a control. In the intoxication-labeled group, 4-hydroxytamoxifen (4-OHT) (50 mg/kg) was injected on day 6 of fentanyl exposure to permanently label active neurons with tdTomato. On day 13, withdrawal was induced via naloxone injection (5 mg/kg) and brains were collected 90 min later to examine

endogenous Fos protein expression compared with the intoxication activity labeled by tdTomato. Control groups included a sham ensemble group (4-OHT given before fentanyl exposure) and a saline group. Brain sections were immunostained for Fos protein and imaged using Keyence BZ-X810. Neurons positive for tdTomato and Fos were quantified in selected brain regions using ImageJ. **Results:** Across most regions, tdTomato+ (intoxication) and cFos+ (withdrawal) neuronal counts, and their spatial overlap, showed no significant differences across groups, indicating largely distinct sets of neurons engaged during intoxication and withdrawal. However, two regions, the nucleus accumbens (NAc) and paraventricular hypothalamic nucleus (PVH), exhibited significantly increased Fos+ neurons in the fentanyl-withdrawal group compared to saline controls. These two regions are known to regulate negative affect, stress, and homeostatic drives, and their selective activation may reflect their roles in mediating withdrawal-driven behavior and negative reinforcement. **Conclusion:** Our study shows the utility of dual mapping for dissecting dynamic neural engagement across phases of addiction. Despite minimal intoxication-withdrawal overlap, the elevated withdrawal-associated activity in NAc and PVH highlights these regions as key nodes in opioid withdrawal processing. Ongoing iDISCO+ clearing and light-sheet imaging will validate and extend these findings across distributed networks with greater spatial resolution and anatomical context.

Disclosures: Y. Cao: None. Y. Chen: None. A.J. Kimbrough: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.08/JJ8

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA 056331-03

Title: Effect of Systemic and Domain-Specific Inhibition of Angiotensin-Converting Enzyme on Fentanyl Conditioned Place Preference

Authors: *L. CUNITZ, F. HANAK, C. WHINDLETON, P. E. ROTHWELL;
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Abstract: Opioid use disorders are a major public health crisis in the US. However, the options for medication remain limited. Novel therapeutic targets for opioid use disorders are essential to combating this epidemic. Our previous studies showed that systemic administration of captopril (30mg/kg, i.p.), an angiotensin-converting enzyme (ACE) inhibitor for treating high blood pressure, decreases opioid reward by regulating endogenous opioid signaling in the nucleus accumbens (Trieu et al., Science, 2022). This mechanism appears to involve the N-terminal catalytic domain of ACE which degrades Met-enkephalin-Arg-Phe, an endogenous opioid peptide. In this study, we used conditioned place preference (CPP) to investigate the behavioral impacts of inactivating each catalytic domain of ACE. We hypothesized that inactivating the N-

terminal catalytic domain in mice would attenuate fentanyl CPP. We used male and female mice with mutations in the active site of either the N-terminal catalytic domain (NKO) or the C-terminal catalytic domain (CKO). We assessed opioid preference in these mice during CPP, where preference for a specific floor type was calculated before and after six conditioning sessions in which saline and fentanyl were each paired with a different floor texture/color. Surprisingly, we found no difference in fentanyl CPP for either knockout strain. This could be due to a compensatory mechanism that is regulating endogenous opioid signaling in the absence of ACE enzymatic activity. Ongoing studies will use microinfusions in the nucleus accumbens of compounds designed to acutely inhibit the N and C catalytic domains during CPP. We also plan to administer an ACE inhibitor to the NKO and CKO mice, to explore the role of each catalytic domain in regulation of opioid preference. Together, these data highlight layers of complexity in regulation of endogenous opioid signaling by ACE, which may present an opportunity for therapeutic development to create more effective medications for opioid use disorder.

Disclosures: L. Cunitz: None. F. Hanak: None. C. Whindleton: None. P.E. Rothwell: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.09/JJ9

Topic: H.08. Drugs of Abuse and Addiction

Support: University of Minnesota Medical Discovery Team on Addiction

Title: Microglia synaptic engulfment and morphology following abstinence from repeated fentanyl exposure

Authors: *D. W. HART, M. ESGUERRA, A. D. UMPIERRE, M. THOMAS;
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Abstract: Over the past decade and a half, non-inflammatory roles of microglia have come to the forefront of glial research. Alongside direct modulation of neuronal activity, reports have described microglia-mediated mechanisms of synaptic and structural plasticity. One such mechanism is synaptic engulfment. Synaptic material such as the post-synaptic scaffolding protein PSD95 can be internalized in microglia, indicative of synapse removal. Separately, studies over the past 25 years have repeatedly demonstrated abstinence-dependent synaptic and structural plasticity following exposure to opioids. Previous work has documented cell type and circuit-specific increases in synaptic strength within the nucleus accumbens shell (NAcSh) following morphine abstinence. Additionally, a reduction in the number of dendritic spines on medium spiny neurons in the accumbens has been described under similar conditions. Recent reports have also detailed internalization of PSD95 within microglia following repeated exposure to ethanol. Our study evaluates whether microglia structural plasticity via synaptic engulfment occurs following exposure to fentanyl and whether this might underlie abstinence-dependent

changes in synaptic strength previously seen in the NAcSh. Following ten days of fentanyl administration (0.3 mg/kg, i.p.) or saline (10 mL/kg, i.p.), two separate cohorts of 12 C57BL/6/J mice (6 male and 6 female per cohort, split evenly between treatment conditions) underwent one day or 14 days of forced home cage abstinence before tissue collection. Cell body counts using the microglial marker Iba1 in the NAcSh revealed no differences in microglial density between fentanyl- and saline-treated controls at either time point. Ongoing experiments of sections stained with Iba1, the lysosomal/endosome marker CD68, and PSD95 will explore microglia morphology and whether synaptic engulfment is occurring following repeated exposure to fentanyl. Should changes in engulfment be observed, future studies will mechanistically investigate the process and determine the functional and behavioral consequences of abstinence-dependent microglial synaptic engulfment on drug seeking.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.10/JJ10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA047413

Title: Changes in perineuronal nets and parvalbumin-expressing GABAergic interneurons in the orbitofrontal cortex during acquisition and escalation of intravenous fentanyl self-administration in male Wistar rats

Authors: *M. I. DEJEUX¹, C. WERNETTE³, F. BRESSLER¹, J. D. NGUYEN²;
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Abstract: The opioid epidemic has quickly become a major public health crisis in the US within the past several years. Recently, synthetic opioids such as fentanyl have drastically increased opioid related deaths. Understanding the neurobiology behind acquisition and escalation of fentanyl intake could give us insight into potential treatments for substance use disorders. Perineuronal nets (PNNs) are mesh-like extracellular matrix structures that surround neurons. Recent research has focused on exploring how PNNs may mediate the formation and maintenance of memories. PNNs also have recently been linked to drug related memory formation and several drug taking behaviors. Parvalbumin (PV⁺)-expressing GABAergic interneurons, which are critical for maintaining inhibitory control over the brain, are often encased in PNNs. The aim of this study was to assess PNN and PV⁺ expression in the OFC, a region associated with several drug taking behaviors, during intravenous fentanyl self-administration (IVSA). In order to accomplish this, male Wistar rats (~10-11 weeks) underwent up to 21 daily self-administration sessions (1 hr or 8 hrs), excluding weekends. During these

sessions a single lever press (FR-1) administered saline or fentanyl (0.625, 2.5, 10 µg/kg/inf). In addition to this we used progressive ratio schedule of reinforcement to assess motivation to lever press for drug after fentanyl exposure. OFC slices were stained with Wisteria Floribunda Agglutinin (WFA) and parvalbumin using immunohistochemistry and analyzed using ImageJ/Polygon.AI. Rats significantly increased lever responding for fentanyl infusions over 21 sessions in a dose-dependent manner. Ongoing analysis suggest that intravenous fentanyl self-administration may alter WFA and PV⁺ expression in the OFC during different stages of acquisition or escalation.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Program #/Poster #: PSTR185.11/JJ11

Topic: H.08. Drugs of Abuse and Addiction

Support: Michael C. Gibson Addiction Research Program
Moore's Professorship Program

Title: Sex and estrous stage alter affective and sensory responding to pain

Authors: *K. M. LITTLE, C. A. LOPEZ ARTEAGA, B. E. FRANKLIN, M. HUSAINAT, C. N. HAILE, T. A. KOSTEN;
Psychology, Univ. of Houston, HOUSTON, TX

Abstract: Fentanyl (FEN) is a highly potent synthetic opioid exerting its effects through mu-opioid receptors and is a major contributor to the growing rates of OUD (Opioid Use Disorder) and opioid-related overdoses and deaths. Sex differences in response to various psychoactive drugs including opioids have been reported previously. Circulating sex hormones such as estradiol impacts the development of addictive disorders in females. Preclinical studies report that pain elicits affective (emotional) responses that can be measured with ultrasonic vocalizations (USVs) and are altered by opioids. However, few studies focus on opioid effects on affective responses and even fewer address whether sex or circulating sex hormones differentially alter these responses. We examined whether sex, estrous stage, or FEN has differential effects on affective or sensory responses to a pain stimulus as well as neural activation in pain-associated neural regions. Sensory regions included the periaqueductal gray (PAG) and thalamus, while affective regions included the amygdala and insula. Adult male and female Sprague-Dawley rats were tested for: 1) sensory and affective responses to a pain stimulus; 2) appetitive responses to stroking and FEN; and 3) neural activation to a pain stimulus in regions associated with affective or sensory responses through c-Fos expression. Preliminary findings suggest sex- and estrous-related differences in affective and sensory responses to FEN. Tail flick latencies were significantly lower in females compared to males at 0.05 mg/kg FEN

that was associated with the non-estrous phase in females (p 's < 0.05). FEN reduced USVs during tail flick tests in males relative to baseline ($p < 0.05$), with no effect seen in females ($p > 0.05$). In the open field test, males emitted more USVs at 0.1 mg/kg FEN relative to 0.05 mg/kg FEN and saline ($p < 0.01$), while females showed minimal vocalizations. No sex or estrous effects were observed during stroking (p 's > 0.05). Neural activity in pain-related regions is currently being assessed using c-Fos, and ongoing behavioral analyses will further clarify these patterns. Outcomes elucidate mechanisms of sex and estrous stage effects on behavioral responses to FEN-induced analgesia. Findings highlight sex differences in affective responding and enhance our understanding of sex-related differences as they relate to FEN-induced OUD and analgesia.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.12/JJ12

Topic: H.08. Drugs of Abuse and Addiction

Support: Michael C. Gibson Addiction Research Program
Moore's Professor Program

Title: Alcohol consumption and immune response in a model of PTSD

Authors: *B. FRANKLIN¹, C. HAILE², J. MATHEW¹, K. LITTLE¹, C. LOPEZ ARTEAGA¹, T. A. KOSTEN²;

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Abstract: In humans, alcohol use disorder (AUD) and post-traumatic stress disorder (PTSD) are highly comorbid, especially in females. However, the relationship between stress effects and alcohol consumption is multifaceted and poorly understood. This study investigates whether predator odor stress, a rodent model of PTSD, alters alcohol self-administration in female rats on days 3, 8, 11, and 15 following stress exposure. Collected data demonstrate that alcohol self-administration significantly increased on days 8, 11, and 15 following exposure to predator odor stress. However, when studying alcohol consumption in rodents, it is important to consider the potential occurrence of the alcohol deprivation effect, which consists of enhanced responding for alcohol when access is reinstated following a period of deprivation. Thus, a group exposed to a sham predator odor is included. If the group exposed to a sham predator odor does not show enhanced alcohol self-administration, it would demonstrate that predator odor exposure increases alcohol consumption and provide a translational model of how PTSD enhances AUD. Moreover, our data shows increased alcohol self-administration is persistent and seen several days after predator odor exposure, but not immediately after. Understanding the mechanisms that underlie

this delayed and persistent effect is important to elucidating the pathophysiology of co-occurring PTSD and AUD. Additionally, PTSD has been linked to a persistent proinflammatory state and long-term altered immune responses. Specifically, it is reliably associated with elevated levels of circulating peripheral proinflammatory cytokines, including IL-6. The second aim of this study is to assess serum levels of peripheral cytokine, IL-6 using ELISA on days 3, 8, 11, and 15 following predator odor exposure. If this cytokine is elevated from baseline on days corresponding to enhanced alcohol drinking, this study could provide a potential mechanism underlying how AUD is enhanced by PTSD.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 1R21DA058746-01A1

Title: The role of hyperphosphorylated tau proteins in alcohol and opioid co-consumption

Authors: *M. LORTIE¹, Y. WANG², S. HAUX², D. WEST², B. K. ATWOOD³;

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Abstract: The opioid epidemic presents a serious public health crisis, with efforts to manage its prevalence often failing to curb use. Individuals with opioid use disorder (OUD) often co-use with other substances such as alcohol, resulting in dangerous synergistic effects on the central nervous system that may lead to overdose and death. Recent clinical and preclinical studies have found an accumulation of hyperphosphorylated tau protein in the brain following independent alcohol and opioid exposure, including work from our lab that suggests region-specific differences in tau phosphorylation occur following drug exposure. Hyperphosphorylation of tau leads to aggregates that are a central hallmark of neurodegenerative disorders such as Alzheimer's disease and contribute to synaptic dysfunction and altered neurotransmission. While those with OUD are not at higher risk of developing tauopathy-related neurodegenerative diseases, these findings beg the question of whether these tau maladaptations play a role in drug-induced neurobehavioral changes. Here, we aimed to investigate whether the presence of tau would increase voluntary co-use of alcohol and oxycodone. We utilized PS19 transgenic mice expressing the human P301S mutant tau protein and tau knockout mice to assess the impact of tau presence and absence on consumption levels. Mice were given 4 weeks of limited daily access to a solution of 1 mg/mL oxycodone + 20% alcohol in 2% sucrose water, according to well-established drinking in the dark procedures. Compared to wild-type mice, we found that

PS19 mice displayed increased consumption of both alcohol and oxycodone, while tau knockout mice showed decreased consumption of both substances. These data confirm a link between tau presence and increases in alcohol and oxycodone drinking, and when combined with current literature, suggest the possibility of a bidirectional relationship between opioid and alcohol use and tau maladaptations. Future studies will further probe this effect through molecular assays, in addition to parsing apart the neurobehavioral differences between PS19 and tau knockout mice participating in both independent and polysubstance consumption.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Program #/Poster #: PSTR185.14/JJ14

Topic: H.08. Drugs of Abuse and Addiction

Support: P30DA046345-05W1

Title: Effects of opioid use disorder and non-fatal opioid overdose on hippocampal volume and brain tau pathology

Authors: *D. MCKINSTRY¹, Z. SHI³, A. P. RAMOS-ROLÓN², N. HAGER¹, S. DAS¹, D. D. LANGLEBEN¹, J. G. DUBROFF⁴, H. KRANZLER¹, C. E. WIERS⁵, I. NASRALLAH¹; ²Neurosci., ¹Univ. of Pennsylvania, Philadelphia, PA; ³Dept. of Psychiatry, Univ. of Pennsylvania Department of Psychiatry, Philadelphia, PA; ⁴Radiology, Hosp. of the Univ. of Pennsylvania, Philadelphia, PA; ⁵Psychiatry, Univ. of Pennsylvania, Philadelphia, PA

Abstract: Opioid use disorder (OUD) is a public health emergency associated with high rates of opioid overdose (OD)-related morbidity and mortality. OD can result in severe respiratory depression and hypoxic ischemia, which can damage brain areas sensitive to reduced oxygenation (e.g., the hippocampus) and thereby impair neurocognitive functioning. There is ample evidence of Alzheimer's disease-like pathology, i.e., hyperphosphorylated tau and amyloid precursor protein, in the post-mortem brain tissues of individuals with OUD. The neurocognitive impairments present in individuals with OUD and those who suffer a non-fatal OD may reflect incipient dementia and contribute to poor clinical outcomes, including OUD treatment resistance. Alternatively, OUD and non-fatal OD could be independent risk factors for Alzheimer's disease. To date, no studies have evaluated the effects of non-fatal ODs or chronic opioid exposure on tau deposition in humans in vivo. Here we investigate the effects of non-fatal OD and chronic opioid exposure on Alzheimer's disease-like pathology: brain morphology, brain tau deposition, and visual episodic memory task performance. First, we examined hippocampal volumes in OUD individuals (n = 61) and healthy controls (HC, n = 30) using T1-weighted 3D magnetization-prepared gradient-echo (MPRAGE) structural scans. Hippocampal volumes were

segmented using the Automatic Segmentation of Hippocampal Subfields (ASHS) toolbox. We found lower hippocampal volumes in OUD patients (6148mm^3 ($+ 757\text{ mm}^3$) than HC (6695mm^3) ($+ 545\text{mm}^3$) ($F_{2,81}=7.86$, $p<0.001$), but no group differences in hippocampal volumes between OUD individuals who reported a history of an OD ($n = 22$) and those without (NOD, $n = 30$); corrected age, sex, and intracranial volume. In a subset of these patients, we studied the effects of non-fatal OD on brain tau deposition using Positron Emission Tomography (PET) with $[18\text{F}]\text{PI-2620}$ in $n=6$ OUD/OD, $n=4$ OUD/NOD, and $n=4$ HC. We found no evidence of greater brain tau in the OUD groups than HC, nor in OUD/OD compared to OUD/NOD. Performance on the episodic memory task was impaired in the OUD/OD group compared to HC with a medium effect size (Cohen's $d=0.5$). In summary, we confirm evidence for lower hippocampal volumes in patients with OUD compared to HC. However, our findings do not support the hypothesis that non-fatal OD leads to brain tau deposition in individuals with OUD. Future studies with larger sample sizes are needed to confirm these findings.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.15/JJ15

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH NIDA DA056922

Title: The effects of oxycodone self-administration on cognitive flexibility and associated cortical activity in male and female rats

Authors: *S. DICK¹, A. HEATON², A. CLAYPOOL², K. DRIVER², V. GALBAVA², M. SCHWENDT³, E. COLLEY⁴, L. A. KNACKSTEDT³;

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Abstract: Individuals who use opioids often display cognitive deficits in the domain of cognitive flexibility/set-shifting. Here we used a rat model of oxycodone intravenous self-administration (IVSA) followed by cognitive testing to test the hypothesis that the same deficits would be observed in male and female rats following opioid exposure. Male and female Sprague-Dawley rats were trained to self-administer either oxycodone or food pellets. Two conditions were employed for oxycodone IVSA training: short-access (ShA) and long-access (LgA). Both conditions first underwent three days of 3 hr/day access to oxycodone IVSA. For the subsequent 9 days, the ShA rats continued to experience 3 hr/day IVSA sessions, while the LgA rats experienced 6 hr/day IVSA sessions. Control rats underwent 3 hr/day food self-administration.

Next, all rats underwent economic demand analyses wherein the number of lever presses required to obtain the reinforcer (oxycodone or food) was increased every second day until 0 reinforcers were attained. After 14 days of abstinence, rats were tested for cue-primed reinstatement of oxycodone (or food) seeking. Next, rats were tested for cognitive flexibility using the probabilistic reversal learning task for 15 days and were perfused immediately following the task on Day 15 for assessment of cortical activity via c-fos immunohistochemistry. Rats that underwent LgA oxycodone IVSA displayed greater oxycodone intake relative to ShA rats, an effect driven by male rats. Cue-primed reinstatement was similar between LgA and ShA groups, and was correlated with several measures of economic demand. During the 15 days of the probabilistic reversal learning task, LgA rats completed more reversals than ShA and food self-administration groups, likely due to a greater number of trials completed. Despite equivalent behavior shown by all three groups during the probabilistic reversal task on Day 15, the ShA group displayed increased c-fos expression throughout the orbitofrontal cortex and the prelimbic cortex, indicating that more activity was necessary to maintain the same level of performance in these rats. C-fos expression in the cingulate cortex positively correlated with task performance. These results indicate that the length of access to oxycodone self-administration influences cortical responsiveness during a reversal learning task.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R33 DA045150

Title: The effects of ceftriaxone on cue induced cocaine seeking in a simultaneous model of cocaine and alcohol polysubstance use

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Abstract: Polysubstance use (PSU) refers to the use of multiple drugs over a specific timeframe and is commonly observed among cocaine users. Ceftriaxone, a beta-lactam antibiotic, effectively reduces cue/cocaine primed reinstatement in preclinical studies by restoring balance in glutamate levels after cocaine self-administration. However, it does not achieve this effect when rats use both cocaine and alcohol together in a sequential model. Here we used a simultaneous model of cocaine and alcohol PSU, where rats self-administered an intravenous cocaine+alcohol solution to determine whether ceftriaxone could attenuate cued seeking after

abstinence. Rats underwent intravenous self-administration (IVSA) of either cocaine alone or cocaine+alcohol for five consecutive two-hour sessions followed by 10 six-hour sessions either on consecutive days (Daily group) or with 1-2 days off between each session, a drug schedule that is commonly found in human cocaine users (Intermittent group). Rats underwent a cue test on the first day of abstinence, followed by 20 days of forced abstinence and a second cue-primed test on Day 21. On the last six days of abstinence, rats received either ceftriaxone (200 mg/kg IP) or vehicle. Rats in the PSU condition displayed greater cocaine-intake than rats in the cocaine-only condition, as well as increased cued-seeking on Day 1 of abstinence. Ceftriaxone attenuated active lever presses during the Day 21 cue test for cocaine-only rats but not for cocaine+alcohol rats. While rats in the Daily cocaine-only IVSA group showed incubated cocaine-seeking, an intermittent schedule of IVSA did not produce incubation of drug seeking in both the cocaine-only and PSU conditions. Both Daily and Intermittent cocaine-only rats displayed reduced GLT-1 expression in the nucleus accumbens that was restored by ceftriaxone; these effects were not observed in the PSU condition. Finally, cocaethylene was detected in the blood of PSU rats. These results support the idea that there are novel and unique neuroadaptations produced by cocaine-alcohol PSU compared to cocaine alone. Furthermore, the schedule at which the drugs are taken affects the incubation of drug craving/seeking.

Disclosures: A. Sanchez: None. M. Schwendt: None. B. Setlow: None. L.A. Knackstedt: None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.17/JJ17

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH grant R03DA059681

Title: Investigating the Effects of Oxytocin on Incubated Oxycodone-Seeking in Male and Female Rats

Authors: *E. COLLEY¹, H. L. BLOUNT², L. A. KNACKSTEDT², M. SCHWENDT²;
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Abstract: High relapse rates persist even after extended periods of abstinence from opioid use, posing a significant public health challenge and contributing to the chronic nature of opioid use disorder (OUD). This highlights the critical need for translational preclinical models to investigate potential pharmacological interventions that target relapse mechanisms. Oxytocin, a neuropeptide recognized for its prosocial and stress-reducing properties, has demonstrated emerging promise in reducing cue-induced relapse in preclinical models of heroin seeking. While oxytocin has been found to reduce heroin and cocaine seeking, there remains a critical

lack of studies specifically addressing the effects of oxytocin on the seeking of the commonly used prescription opioid, oxycodone. We have previously found that oxytocin reduces the motivation to seek intravenous oxytocin during economic demand assessments in male but not female rats. The present study aimed to investigate whether the same effect would be seen for incubated oxycodone seeking and whether this effect varies by sex. Adult male and female SpragueDawley rats were trained to self-administer intravenous oxycodone under a fixed ratio (FR)-1 schedule for 2 hours/day across 7 days, followed by 6 hours/day for 10 days. Rats underwent a cued seeking test on Day 1 of abstinence, followed by a 15-day home cage abstinence period, after which a second cue-induced relapse test occurred on Day 15. On Day 1, all rats received only vehicle. On Day 15, rats were pretreated with intraperitoneal oxytocin (0, 0.3, 1, or 3 mg/kg) 30 minutes prior to the relapse test. A separate cohort of rats underwent fiber photometry using GRAB DA sensors to assess the effects of oxytocin on the nucleus accumbens dopamine response to intravenous oxycodone. Preliminary findings indicate that oxytocin did not reduce the incubation of oxycodone seeking in male or female rats, despite producing increases in dopamine levels in the nucleus accumbens core. These results indicate that while oxytocin might be effective at reducing ongoing drug use, it is not effective after a period of oxycodone abstinence. Future studies need to explore the mechanisms of oxytocin action on drug-taking.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA056595
T32 DA053558

Title: Sex and cell-type specific transcriptomic responses during heroin abstinence and relapse in medial prefrontal cortex

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Abstract: Opioid use disorder impacts millions of Americans, resulting in tens of thousands of deaths annually. Relapse, often driven by heightened craving during abstinence, is linked to

altered neuroplasticity. The medial prefrontal cortex (mPFC), a region responsible for executive function, plays a key role in drug-seeking behavior and relapse. To better understand how opioids impact neural plasticity in the mPFC, it is critical to understand how specific cell-types are affected. Here, we collected single-nuclei (sn) multiome data (snRNA-seq/snATAC-seq) from the mPFC of male and female rats across three conditions: (1) 10-days of heroin self-administration on a fixed ratio schedule of reinforcement followed by 14 days of forced abstinence; (2) heroin self-administration followed by drug re-exposure on abstinence day 14 using a progressive ratio model of relapse; and (3) saline non-reinforcement controls. Following robust quality control assessments and stringent bioinformatics analyses, we found that only excitatory neurons of mPFC, particularly the Layer 2/3 intratelencephalic (IT) neurons, displayed substantially induced gene expression and chromatin accessibility changes. These alterations were almost exclusively observed in female rats, with limited changes identified in males. Interestingly, following progressive ratio mediated heroin relapse, many of these same genes and open chromatin regions were found to be downregulated or rendered inaccessible, indicating a reversal of transcriptional changes by drug relapse. Thus, we are currently in the process of utilizing cell-specific enhancers identified in our multiome dataset to bidirectionally manipulate genes dysregulated by heroin abstinence/relapse to assess drug-induced behavioral changes and other aspects of heroin-mediated neural plasticity. Ultimately, we seek to gain valuable insights into the mechanisms regulating drug craving and relapse.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA006214
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Title: Chronic oxycodone leads to increased numbers of anteriorly located orexin cells which scale with withdrawal severity.

Authors: *K. NEWMAN¹, G. S. ASTON-JONES²;

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Abstract: The orexin neuropeptide system is a promising pharmacological target for substance use disorders, including opioid use disorder. Numbers of orexin-immunoreactive neurons in the hypothalamus are increased following chronic exposure to multiple drugs of abuse, indicating that a reserve of orexin neurons may be recruited to drive addiction behaviors, including negative

affect and withdrawal symptoms. Here, we sought to characterize changes in the orexin neuronal population following chronic prescription opioid exposure. Male and female Sprague Dawley rats were given 3wk of twice-daily saline (n=7 and 6, respectively) or 3mg/kg i.p. oxycodone (oxy; n=6 and 6, respectively) and tested for signs of withdrawal and negative affect during acute abstinence with body weight, Von Frey paw withdrawal thresholds, saccharin preference, time spent in the open arms of the elevated plus maze, and time immobile in the forced swim test. Composite withdrawal/negative affect severity scores for each rat were generated by summing the normalized measures from these 5 behavioral tests. Tissue was processed for immunohistochemistry 24h following treatment and hypothalamic brain slices were labeled for orexin. Withdrawal/negative affect severity was significantly greater in oxy compared to saline rats ($p<0.05$). In males, we found an overall increase in numbers of orexin-ir neurons in oxy compared to saline rats ($p<0.05$). We observed increases in orexin cell numbers across the rostral-caudal and medial-lateral extents of the orexin cell field; however, the most marked increase was found in the rostral and medial portions of the orexin cell field ($p<0.05$). Interestingly, we found a correlation between individual total orexin neuron number and composite severity score, such that rats experiencing more severe withdrawal/negative affect had greater numbers of orexin neurons ($p=0.060$). We observed a similar correlation between number of rostromedial orexin neurons and withdrawal/negative affect severity score ($p=0.055$). Together, these results show an increase in numbers of orexin neurons following chronic prescription opioid exposure and identify a subpopulation of orexin neurons which may regulate addiction-related behaviors. Current studies are evaluating orexin cell numbers in females following chronic oxy exposure. Future studies will seek to map the inputs to and outputs of rostromedial orexin neurons which might reveal a circuit mediating drug-relevant behaviors. Ongoing studies are currently investigating potential upstream targets leading to increased recruitment of orexin cells following chronic oxy exposure.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Support: NIDA 2U01DA043098-06
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Title: Selective activation of dopamine receptor-expressing subtype neurons in the nucleus accumbens after initial morphine exposure and during the expression of morphine sensitization

Authors: *Q. WEI, V. KUMAR, H. KHALIL, M. FOLTZ, L. ZHANG, S. J. WATSON, H. AKIL;
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Abstract: Repeated, intermittent morphine exposure produces behavioral sensitization that is thought to contribute to drug craving, compulsive use, and relapse. To investigate neural dynamics underlying morphine sensitization, we employed Fos-TRAP to label neurons activated during initial morphine exposure (Day 1) using tdTomato reporter gene expression. These mice then underwent a full sensitization protocol, allowing us to compare acute and sensitized responses within the same animal by detecting cFos expression on Day 14. Brain-wide analyses in this model revealed both quantitative and qualitative shifts in neural network activity during sensitization, indicating the dynamic circuit reorganization that occurs during morphine sensitization. Prominent among the altered regions were mesolimbic structures, including the nucleus accumbens (NAcc). We therefore focused on the NAcc and asked whether distinct subpopulations of activated neurons are recruited across the initial morphine exposure and during the expression of morphine sensitization using HCR-FISH. Morphine exposure induces selective activation of D1-expressing neurons in the NAcc with distinct subsets of D1 engaged during initial exposure versus sensitization. In contrast, a saline challenge following repeated morphine administration recruits a different pattern of neural activity, which includes D2-positive neurons, with limited overlap with previously activated cells. These findings suggest experience-dependent shifts in NAcc circuitry, reflecting dynamic neuroadaptations across phases of drug exposure.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.21/JJ21

Topic: H.08. Drugs of Abuse and Addiction

Support: DA00069

Title: The Missing Zinc: Silencing zincergic neurons in the prefrontal cortex

Authors: *I. SCHOENBORN¹, W. DUNNE², O. SOLÍS CASTREJÓN², M. MICHAELIDES²;
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Abstract: Synaptic zinc (Zn²⁺) is essential for modulating neurotransmission and has been linked to neuropsychiatric disorders, including cocaine use disorder. Our lab previously showed that many glutamatergic neurons in the prefrontal cortex (PFC) express zinc transporter 3 (ZnT3) and co-release Zn²⁺ with glutamate. These zincergic neurons are highly interconnected and project to subcortical areas such as the striatum and amygdala. However, their specific roles in brain

function remain unclear. To map these neurons and assess their behavioral impact, we used inhibitory chemogenetic tools (hM4Di DREADDs). ZnT3-Cre and wild-type (WT) littermates were bilaterally injected in either the prelimbic (PrL) or anterior cingulate cortex (Cg) to temporarily inhibit ZnT3-expressing neurons. Mice received JHU37160 to activate these inhibitory DREADDs prior to PET imaging with [^{18}F]FDG to examine changes in brain metabolism. The inhibition of PrL zingergic neurons resulted in widespread increases in brain activity, suggesting strong network connectivity. Similar studies in Cg-injected mice are planned. Following imaging, mice underwent behavioral testing to assess PFC-related functions, including anxiety, nociception, and cocaine-conditioned place preference. Our preliminary results showed inhibition of PrL zingergic neurons altered social behavior and showed a trend toward reduced anxiety in the elevated plus maze compared to WT mice. Behavioral studies will be repeated in Cg-injected mice to determine whether zingergic neurons in this region also contribute to PFC-mediated behaviors. Future studies will use retrograde DREADDs in PET-identified brain regions to further map the zingergic network.

Disclosures: **I. Schoenborn:** None. **W. Dunne:** None. **O. Solís Castrejón:** None. **M. Michaelides:** None.

Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.22/JJ22

Topic: H.08. Drugs of Abuse and Addiction

Title: The role of synaptic Zn^{2+} in dopamine transmission and dynamics in the striatum

Authors: ***W. DUNNE**, A. E. TISCHER, I. SCHOENBORN, O. SOLÍS CASTREJÓN, M. MICHAELIDES;
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Abstract: The striatum integrates dopaminergic inputs from the ventral tegmental area (VTA) and substantia nigra (SN). It also receives glutamatergic inputs from the cortex, a subset of which co-release Zn^{2+} from synaptic vesicles, which our lab has shown modulates cocaine induced behavior and dopamine (DA) transmission. Here we investigate Zn^{2+} dynamics at these synapses and examine how Zn^{2+} modulates DA *in vivo*. We use fiber photometry to image DA and synaptic Zn^{2+} dynamics. Two cohorts of mice ($n = 5$) received injections of DA sensor AAV-hSyn-GRABDA m1 and Zn^{2+} sensor AAV-hSyn-GRISZ, respectively, in the dorsal striatum (DS). Mice were recorded while freely behaving after a single challenge of saline or cocaine (10 mg/kg; i.p.). Between minutes 10-30 post injection, cocaine significantly increased ($p < 0.05$) area under the curve (AUC) compared to saline in both DA and Zn^{2+} , suggesting that synaptic zinc might be involved in the striatal response to cocaine. This cocaine-induced increase in striatal DA and synaptic Zn^{2+} led us to measure the effects of the presence of Zn^{2+} and chronic cocaine on its target, the dopamine transporter (DAT). C57BL/6 mice were injected for 14 days

with cocaine (15 mg/kg; i.p.; n = 10) or saline (n = 10). Following treatment, coronal sections of the striatum were taken. Sections were incubated with dopamine transporter (DAT) antagonist [³H]WIN-35428 in the presence or absence of ZnCl₂ to assess the effect of Zn²⁺ to binding to DAT. While chronic cocaine did not change binding of [³H]WIN-35428 to DAT compared to saline, the presence of Zn²⁺ strongly increased [³H]WIN binding (~465%-508% of saline group) regardless of treatment group. This finding suggests an allosteric effect of Zn²⁺ on DAT that is independent of prior cocaine exposure. To study DAT-expressing dopaminergic axons in the striatum, TH-Cre mice are being injected in the VTA with AAV-hSyn1-FLEX-axon-GCaMP6, and fibers are implanted in the DS or nucleus accumbens (NA). These mice will undergo the same behavioral conditions, with an additional injection of the Zn²⁺ chelator TPEN (100 nL; i.c.). These ongoing studies will assess if zinc modulates calcium dynamics in dopaminergic terminals. Our data show that cocaine increases the presence of DA and Zn²⁺ in striatal synapses, and that Zn²⁺ greatly affects binding activity of the DAT, but chronic cocaine exposure does not. Photometry experiments aim to demonstrate how DA cells are affected in real time by the effects of Zn²⁺ on the DAT, during native behavior and cocaine use. These findings will shed light on the role of Zn²⁺ as a neuromodulator in the striatum, and its role in cocaine pharmacology.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR185.23/KK1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant ZIADA000069

Title: Longitudinal PET Imaging of Synaptic Density and Brain Metabolism Following Cocaine Self-Administration and Withdrawal in Rats

Authors: *O. SOLÍS CASTREJÓN¹, I. SCHOENBORN², W. DUNNE², M. MICHAELIDES³;

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Abstract: Chronic cocaine exposure produces neurobiological changes that may persist well beyond the period of drug intake. These adaptations are thought to play a role in the long-term impact of drug use on brain function. Most of what we know about these changes comes from post-mortem studies, which limit our ability to track them over time. To examine these adaptations over time, we used longitudinal PET imaging with [¹⁸F]SynVesT-1, a radiotracer that enables non-invasive measurement of synaptic density, and [¹⁸F]FDG to assess brain metabolic activity. Rats were trained to self-administer cocaine (0.5 mg/kg/infusion; n=8) or food pellets (n=7) in daily 3-hour sessions for two weeks. PET scans were performed immediately after the

self-administration phase (Day 15) and again following 30 days of withdrawal (Day 45). On Day 15, [¹⁸F]SynVesT-1 imaging revealed an overall reduction in synaptic density across the brain in the cocaine group ($p < 0.01$). ROI analyses showed significant [¹⁸F]SynVesT-1 uptake reductions in the nucleus accumbens, dorsal striatum, parietal cortex, retrosplenial cortex, and visual cortex ($p < 0.05$), consistent with cocaine-induced synaptic remodeling. [¹⁸F]FDG scans revealed decreased metabolic activity in regions associated with reward compared to the food self-administration control group. A second set of PET scans is underway following a 30-day withdrawal period to assess the persistence or recovery of these changes. These ongoing experiments will help determine the long-term trajectory of cocaine-induced synaptic and metabolic alterations, providing insight into circuit-level adaptations that may underlie cocaine-use disorders. These results will highlight the value of longitudinal PET for tracking circuit-level changes after chronic cocaine exposure and identifying neuroadaptations that may underlie vulnerability to cocaine consumption.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant 5R01DA04681805

Title: Medial Septum Modulates Cocaine-Seeking Behavior During Abstinence

Authors: *D. R. FEDERICO¹, L. M. STRAND², A. L. GARCIA LOPEZ³, X. LI⁴, K. HIGDON¹, S. YUE⁵, J. B. WILLIAMS⁶, Z. WANG⁷, D. M. DIETZ⁸;

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Abstract: Septal nuclei have long been implicated in the regulation of reinforcing behaviors, yet the Medial Septum (MSep), a key component of the septohippocampal (SH) circuit, remains understudied in the context of substance use disorder (SUD). We have previously reported that the HPC contributes to cocaine-seeking after forced prolonged abstinence (abstinence day 30; AD30) following cocaine self-administration (SA). In the current study, chemogenetic inhibition of the MSep in male Sprague Dawley rats attenuated cue-seeking behaviors at early abstinence day (AD1), but not at AD30 following long-access to cocaine (0.5 mg/kg/inf). In contrast, selective inhibition of the SH circuit enhanced cue-seeking at AD1, demonstrating the dynamic integration within the septum which drives cocaine craving. To further understand the molecular

mechanisms, we then performed bulk RNA-seq of the MSeP at AD1 in cocaine and saline-exposed animals, revealing distinct transcriptional profiles between rats that self-administered cocaine compared to those in the saline self-administration group. Additionally, we included further comparisons within each treatment condition (i.e., cocaine v. saline) which included rats that were re-exposed to drug-associated cues. Our analysis uncovered both drug and cue-specific gene expression changes, indicating MSeP transcriptional activity is responsive to both drug history and cue exposure, but in transcriptionally diverse ways. Ongoing analyses combining cell-type-specific immunolabeling and in vivo fiber photometry aim to elucidate the neuronal populations and temporal dynamics of these effects.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

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Emory National Primate Research Center (ENPRC) Base Grant OD
P51OD011132

Title: Long-term Effects Of Early Life Stress On Brain Dopamine and Serotonin Receptor Systems Involved In Cocaine Reinforcement In Adult Macaques

Authors: *J. H. ACEVEDO-POLO¹, E. R. SIEBERT¹, J. KHAN¹, M. ALLEN², N. BRING¹, A. LANDSTEIN¹, R. J. VOLL¹, L. N. CHAVAN¹, M. M. GOODMAN¹, J. A. NYE^{3,1}, M. A. NADER², M. SANCHEZ¹;

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Abstract: Early life stress such as child maltreatment (MALT) is associated with substance use disorder (SUD), but the neurobiological mechanisms remain unclear. This study examined long-term effects of infant MALT on adult brain serotonin (5HT) and dopamine (DA) receptors in corticolimbic regions involved in reward and emotional control, using PET imaging. Monkeys had a history of cocaine (COC) self-administration (SA) but had been abstinent for ~ 3 years prior to this study. We assessed whether 5HT and DA receptors availability following time-off from COC was associated with reacquisition of COC SA under a fixed-ratio (FR) and progressive-ratio (PR) schedule of reinforcement and the dynamic changes in 5HT and DA

receptors following chronic COC SA. PET receptor binding potential (BP) measured in brain regions of adult MALT (n=13, 7M, 6F) and Control animals (n=9, 5M, 4F) prior to COC SA re-exposure showed long-term effects of MALT on brain 5HT, but not DA, receptors in corticolimbic circuits. MALT animals had lower 5HT_{1A} BP in the anterior cingulate cortex [ACC] (F(1,18)=5.16, p=.036), medial prefrontal cortex [mPFC] (F(1,18)=6.13, p=.023), and hippocampus [HIP] (F(1,18)=4.65, p=.045) compared with Controls. A MALT X Sex interaction was detected in 5HT_{2A} BP in the orbitofrontal cortex [OFC] (F(1,18)=5.01, p=.038), with lower levels in MALT than Control males, but not in females. Following chronic COC SA an upregulation of 5HT_{1A} and 5HT_{2A} receptors was detected in most PFC subregions, HIP, and nucleus accumbens [NAcc], driven by Control animals (e.g. 5HT_{1A}: OFC (F(1,7)=33.02, p=.001), dlPFC (F(1,7)=85.75, p<.001); 5HT_{2A}: dlPFC (F(1,7)=21.81, p=.002)), with some regions showing no change in the MALT group. We did not detect the expected downregulation in D₂/D₃ receptors in NAcc, caudate or putamen. These findings suggest long-term effects of infant MALT on adult 5HT, but not DA, receptors. We also found associations between PET baseline BP and COC SA measures; caudate 5HT_{1A} receptors predicted response rates (RR) under a FR schedule (β =2.51, p=0.043), while amygdala 5HT_{1A} receptors levels were positively correlated with PR peak breakpoints (ρ =0.61, p=0.046), and a negative correlation was found between D₂/D₃ receptors and FR RR (ρ =-0.63, p=0.021). Our findings suggest (1) broad long-term effects of MALT on adult corticolimbic 5HT, but not DA, receptors, (2) an important role of 5HT PFC receptors in early COC-related changes in reward circuitry and (3) a role of amygdala DA and 5HT receptors on motivated behaviors. Our findings also suggest the potential of targeting dynamic responses of 5HT receptors as biomarkers for risk of CUD and inform future pharmacotherapies.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Program #/Poster #: PSTR185.26/KK4

Topic: H.08. Drugs of Abuse and Addiction

Support: DA33641
DA58168

Title: Accumbens Mef2c is a mechanistic link between sensation seeking and motivation for cocaine in rats

Authors: *S. DE GUZMAN, R. SOLIS LAYBON, S. O'CONNOR, T. SACKO, M. H. JAMES, S. E. SWINFORD-JACKSON, C. PIERCE;

Dept. of Psychiatry and Rutgers Addiction Res. Ctr. at the Brain Hlth. Institute, Robert Wood Johnson Med. School, Rutgers Univ. and Rutgers Hlth., Piscataway, NJ

Abstract: Externalizing disorders include various problematic behaviors related to poor impulse control. Children diagnosed with an externalizing disorder are significantly more likely to develop a substance use disorder (SUD) in adulthood. Recent human GWAS studies indicate that externalizing disorders have shared genetic liability. Moreover, externalizing traits were strongly positively correlated with SUDs and with impulsivity, including sensation seeking. A commonly used model of an externalizing behavior is sensation seeking in rodents, which can be assessed by measuring differences in rodent locomotor activity when exposed to a novel, inescapable environment. Rats displaying higher activity in the novel environment (high responders, HR) self-administer higher amounts of psychostimulants after learning cocaine self-administration, compared to low responders (LR). Screening potential candidates from the GWAS in a sensation seeking rodent model revealed lower expression of mRNA for myocyte enhancer factor 2C (*Mef2c*), a neurodevelopmental transcription factor, in HRs relative to LRs. We manipulated accumbens *Mef2c* expression to reverse sensation seeking phenotypes and augment cocaine intake and motivation, thus recapitulating human gene x environment interactions.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: Da52993

Title: Corticosterone Levels as Predictor of Future Cocaine Consumption Following Fear Conditioning in Male Rats

Authors: *R. T. GOGA¹, J. YAZIGI², H. ROHILLA⁵, T. SACKO³, O. TAYLOR⁴, A. SHARMA⁷, M. T. RICH⁸, C. PIERCE⁶;

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Abstract: Pathological fear resulting from exposure to stressful, aversive experiences can contribute to the development of maladaptive disorders including post-traumatic stress disorder (PTSD) and substance use disorders (SUDs). Individuals with PTSD have higher instances of

SUDs than the general population, with comorbidity rates ranging from 50-75%. Previous work from our group showed that cued fear conditioning, an animal model of PTSD, enhanced subsequent cocaine intake only in male rats. The current experiments assessed the potential role of stress and/or gonadal hormones on the differential effects of cued fear conditioning on subsequent cocaine self-administration in male and female rats. Here, we assessed the effect of tone-paired or unpaired footshocks (2-second, 1 mA foot shock) on plasma corticosterone, testosterone, estrogens (i.e. estradiol) and progesterone levels. Blood samples were collected from the saphenous vein to measure plasma hormone levels with commercially available ELISA kits. Samples were collected before and 30 minutes after fear conditioning. Results indicated that only male rats exposed to 10 cue-footshock pairings had increased corticosterone levels at 30 minutes, which persisted for at least 24 hours ($p < 0.001$). Furthermore, a significant correlation was found between corticosterone levels and subsequent cocaine intake; rats with elevated corticosterone levels tended to consume more total cocaine over the two weeks of self-administration. The results indicate that increased levels of plasma corticosterone following robust fear conditioning are associated with a greater future intake of cocaine in male rats. This effect appears to be primarily related to learned fear cues rather than simply the exposure to footshocks, as rats that were unpaired showed similar levels of cocaine use as those in the control group. These findings suggest that heightened activity of stress hormones may increase the likelihood of cocaine self-administration after robust fear conditioning. Current experiments are further investigating the role of gonadal hormones in this context.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Title: Paternal methamphetamine intake and lower accumbens fibroblast growth factor 14 expression increase methamphetamine susceptibility in male rats

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Abstract: Exposure to drugs of abuse has been increasingly linked to changes in offspring physiology and behavior. For example, we previously demonstrated delayed acquisition of cocaine self-administration in male, but not female, progeny of cocaine-experienced sires. Here, we sought to determine whether this phenotype extended to another psychostimulant, methamphetamine. In contrast to cocaine, male methamphetamine-sired offspring acquired methamphetamine self-administration more rapidly than controls; there was no difference in methamphetamine taking between female methamphetamine- and saline-sired rats. Single nuclei RNA-sequencing of the nucleus accumbens was used to identify differences in gene expression between naïve methamphetamine- and saline-sired offspring. Interestingly, expression of fibroblast growth factor 14 (Fgf14), a regulator of voltage-gated sodium and potassium channels, was decreased in the nucleus accumbens core of methamphetamine-sired male offspring compared to their saline-sired counterparts. Specifically, the decrease of Fgf14 expression was seen in cells containing dopamine D1 and/or D2 receptors, which was confirmed by qPCR and RNAscope. To evaluate functional relevance of this decrease in Fgf14 expression, naïve rats received intra-accumbens core delivery of a lentiviral vector containing either Fgf14 shRNA or a scrambled shRNA control. Methamphetamine intake was increased in rats with intra-accumbens Fgf14 knockdown relative to scrambled controls. Taken together, these results indicated that sire methamphetamine exposure enhanced methamphetamine reinforcement in male offspring, which is due in part to lower Fgf14 expression in the nucleus accumbens. This work suggests that Fgf14 is a putative target for the treatment of methamphetamine use disorder.

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Poster

PSTR185: Addictive Drugs: Plasticity, Behavior, Neurotransmitters

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Title: Heroin preference over social interaction: the role of GABAergic transmission in the medial amygdala

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Abstract: Background: Although millions of individuals use opioids each year, only a subset develop opioid use disorder, highlighting significant interindividual variability in vulnerability to addiction. We developed a mutually exclusive operant discrete-choice procedure that let us to identify a subset of “vulnerable” rats that consistently prefers heroin over rewarding social interaction. **Aim:** In this study, we explored the molecular mechanisms underlying this maladaptive choice, with a focus on the medial amygdala - a key region in the regulation of social homeostasis - where GABAergic transmission plays a central role in processing social rewards. **Methods:** We trained male rats to lever-press (FR1) for social self-administration (2h-d/6days), followed by heroin self-administration (FR1) under a continuous-access, no-timeout schedule (6h-d/15days). We then tested the rats for drug-seeking (30 min) at early and late abstinence day. In between, we employed a discrete-choice procedure (FR5) where rats faced a choice between heroin and social interaction (6-h/11days) based on their heroin preference during choice. **Following the behavioral procedures, we sacrificed the animals and collected** medial amygdala tissue for Western blot analysis. We assessed markers of glutamatergic (GluN2A, GluN2B) and GABAergic (GAT-1, GAT-3, GAD67, GABA_A α 1, GABA_A α 2, GABA_B R1, Neuroligin-2, Gephyrin) transmission. **Results:** Rats referred to as “vulnerable” exhibited a marked preference for heroin and a significant reduction in GAT3 expression in the medial amygdala, as revealed by Western Blot analysis. No differences were observed in glutamatergic markers between the two groups. **Conclusions:** These findings provide the first molecular evidence linking heroin preference to altered GABAergic signaling in the medial amygdala. GAT-3 expression may represent a novel target for interventions aimed at restoring social function in opioid use disorder.

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Poster

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Title: Drn's vglut3+tpH2+ neurons projecting to cea play a critical role in relapse after food-based voluntary abstinence from methamphetamine

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Abstract: Summary:

Contingency management is one of the few effective treatments for psychostimulant addiction, yet relapse is common after its discontinuation. To investigate the neural mechanisms underlying relapse after voluntary abstinence, we used a rat model where palatable solution suppresses methamphetamine (METH) self-administration. This study focuses on the involvement of the dorsal raphe nucleus (DRN) to central amygdala (CeA) pathway. We identified the DRN->CeA projection as a novel addiction- and motivation-related pathway and a potential target for relapse prevention. Our data showed that this pathway is positive for Vesicular Glutamate Transporter 3 (VGLUT3) and Tryptophan Hydroxylase 2 (TPH2). Inhibition of DRN's metabotropic glutamate receptor 5 (mGluR5) positive neurons through photopharmacological manipulation with negative allosteric modulators (NAM) of mGluR5 and terminal inhibition of the DRN->CeA pathway with inhibitory DREADD reduced METH seeking behavior.

Methods:

We trained rats (males, Sprague Dawley, total n=39) to self-administer palatable solution (6 sessions) and then METH (0.1 mg/kg/0.1 mL) for 12 sessions (2 hours/day). Cue-induced METH seeking was assessed in extinction tests after 21 days of abstinence. During abstinence, rats underwent voluntary abstinence using a discrete choice procedure between METH and palatable solution (20 trials/day). Neuronal activation in brain areas projecting to CeA was determined by co-labeling the retrograde tracer cholera toxin subunit B injected in CeA with Fos, TPH2, and VGLUT3 during cue-induced METH seeking. The effect of DRN reversible inactivation was tested by NAM of mGluR5 via JF-NP-26, which releases raseglurant under 405 nm light delivered through an optical fiber implanted in the DRN. The role of the DRN->CeA pathway in relapse was tested using an inhibitory DREADD (AAV8-CamKIIa-hM4Di-Gi) injected in DRN and activated with CNO delivered through cannulas in the CeA. After the experiments, we verified the phenotype of DREADD-infected neurons using immunofluorescence labeling for VGLUT3, TPH2, and mCherry.

Results:

Cue-induced METH seeking in extinction tests was high after 21 abstinence days. CTb + Fos analysis showed that METH seeking was associated with selective activation of DRN VGLUT3+/TPH2+ neurons projecting to CeA. JF-NP-26 in the DRN reduced cue-induced METH seeking. Terminal inhibition of DRN->CeA neurons with DREADD reduced METH seeking behavior.

Conclusions:

Our results suggest that the VGLUT3+/TPH2+ output from the DRN to the CeA is critical to the incubation of METH craving after voluntary abstinence.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Structural underpinnings of addiction-like behavior in the 0/3crit model of cocaine use disorder

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Abstract: Cocaine use disorder (CUD) is a mental health condition that affects around 20% of regular consumers and is associated with significant physiological and behavioral dysfunction. Assessing biological drivers of vulnerability and resilience to CUD is challenging due to inter-individual variability in psychological traits and early-life conditions. The 0/3Crit model is a highly translational rodent model that mimics clinical diagnostic criteria by capturing different behavioral dimensions, such as motivation for cocaine, persistence of drug seeking, and compulsivity. Based on their scores in these domains, animals can be classified as addicted (3Crit) and non-addicted (0Crit). Gray matter abnormalities in CUD patients are well established. Thus, using the 0/3Crit model in combination with longitudinal structural MRI, we explored the neurobiological underpinnings of resilience and vulnerability to addiction-like behavior in 48 male Wistar rats. Voxel-based morphometry on T2-weighted MR images was utilized to characterize resilient (0Crit) and vulnerable (3Crit) rats before cocaine exposure, after 15 days of self-administration, and after 50 days of self-administration. No significant differences in gray matter volume (GMV) were observed at baseline. However, addiction-prone rats exhibited earlier onset and more widespread GMV increases within the frontostriatal network, particularly the caudate putamen, the insula, and prefrontal areas. In several of the affected regions, GMV increases correlated with addiction-like behavior, suggesting a functional relevance of gray matter abnormalities in this model. While the observed effects showed substantial anatomical overlap in both phenotypes, onset and magnitude of cocaine-induced GMV growth differed. These findings imply that individual variability in frontostriatal plasticity may underlie differences in CUD vulnerability. Similar effects have been observed in other preclinical and, in part, clinical studies. Molecular and histological experiments informed by these results could help elucidate the mechanisms underlying these differences and identify potential targets for intervention.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

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Title: The brain in time and space: dynamics of chronic cocaine use

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Abstract: Intrinsic neural timescales (INTs) are hierarchically organized across the brain, ranging from fast in sensory areas to slow in association areas. INTs reflect temporal dynamics of input integration within specific brain regions. Multiple studies report altered INTs in individuals with substance use disorder (SUD), suggesting a role in SUD pathophysiology. However, the dynamics of change throughout drug use and specific cocaine-induced alterations remain unclear. Nonhuman primate models are vital for characterizing these shifts from baseline, exhibiting comparable brain organization, drug biodistribution, and pharmacokinetic profiles to humans. Using a longitudinal cocaine self-administration design in 4 naive macaques, we collected resting-state fMRI data at 5 time points: 2 pre-drug baselines; days 5/45/95 of cocaine use. We first examined changes in INTs across the whole brain during stages of cocaine use. Next, given that functional connectivity (FC) influences INTs and is affected by cocaine, investigating their relationship in this context offers valuable insight into spatiotemporal brain dynamics. After initial exposure, INTs decreased globally except for localized increases in the caudate and putamen. After 45 days, INT changes became more heterogeneous: increases emerged in reward and central executive areas, while decreases persisted in somatosensory, self-referential, and attention related areas. After 95 days, INT patterns resembled initial exposure. Changes in INT and FC relative to baseline showed a linear relationship across the brain but diverged progressively throughout cocaine use. After 5 days, both measures increased in reward areas, with reductions in sensory, self-referential, and attention-related areas. At 45 days, we observed the same pattern with additional increases in striatal regions. Notably, after 95 days, this relationship diminished: INT alterations persisted, while FC showed no significant change. This decoupling suggests prolonged cocaine use alters how local connectivity influences spatiotemporal dynamics. We next examined percent change from baseline as a potential driver of this divergence. Initially, area-specific increases in both FC and INT were linearly related. However, with prolonged use, this relationship diverged: INTs maintained area-specific changes, while FC exhibited an attenuated, more global effect. Overall, this shift helps explain why

cocaine-induced spatiotemporal changes diverge with extended use. We show that INTs play a critical role in cocaine-related neuroadaptations, underscoring the need to study how spatiotemporal dynamics evolve during chronic drug use.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

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Topic: H.08. Drugs of Abuse and Addiction

Title: Abstinence from repeated cocaine exposure strengthens prefrontal cortex regulation of striatal dopamine in mice

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Abstract: Cocaine is a stimulant drug of abuse known for its highly reinforcing properties and its ability to impair cognitive control. It is well established that cocaine works as a monoamine transporter blocker, elevating dopamine (DA) levels in the striatum and mediating its rewarding effects. However, the involvement of the prefrontal cortex (PFC), a major cortical area implicated in cognitive control, is less understood and it might prove critical for understanding how cocaine promotes compulsive seeking and relapse vulnerability as observed in individuals who suffer from substance use disorder. In this study, we examine the strength of inputs to the striatum from the PFC and how repeated cocaine exposure and subsequent abstinence affect this cortico-striatal circuitry. Mice received daily injections of cocaine (15 mg/kg, i.p.) or saline for 5 days, with recordings conducted the day after or following 14 days of abstinence. DA signals in the dorsomedial striatum (DMS) were measured via fast-scan cyclic voltammetry (FSCV) in ex vivo brain slices and in vivo fiber photometry using dLight in a head-fixed configuration. Both ex vivo and in vivo recordings reveal that cocaine acutely depresses striatal DA signals evoked by PFC stimulation. This suppression may serve to potentiate midbrain DA signaling and contribute to rewarding effects. Cocaine-exposed mice do not show changes in PFC regulation over DA release when assessed the day after the last cocaine exposure. However, after 14 days of abstinence, cocaine-exposed mice exhibited enhanced regulation over DA release by PFC inputs compared to saline controls. In vivo fiber photometry of dLight signals in the striatum shows similar results. Mice in abstinence from repeated cocaine exposure showed larger DA signals evoked by PFC stimulation, indicating a potentiation in this circuit's strength to regulate striatal dopamine during abstinence. Further, we observed an increased frequency of spontaneous, non-evoked DA transients in cocaine-exposed mice, indicative of a hyperdopaminergic state. These findings suggest that cocaine induces lasting changes in PFC-striatal connectivity, with enhanced control over DA signaling during abstinence which may contribute to heightened relapse

vulnerability. Future directions include intravenous self-administration (IVSA) paradigms combined with behavioral assays to directly assess how altered cortico-striatal signaling impacts drug-seeking and addiction-like behaviors.

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Title: Characterizing the impact of cocaine on spatial patterns of striatal dopamine release

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Abstract: A key feature of cocaine use disorder (CUD) is deficits in dopamine release in the nucleus accumbens core (NAc). These deficits in dopamine release are concomitant with disruptions in the ability to process non-drug stimuli and the severity of these deficits correlates with negative treatment outcomes in patients. Understanding how drug use leads to impaired stimulus processing is critical for both understanding and treating individuals suffering from CUD. Dopamine is often discussed as a reward or valence signal; however, recent work has demonstrated that in the NAc both appetitive and aversive stimuli increase dopamine release. While both aversive and appetitive stimuli induce dopamine release in the same brain region as measured with techniques like voltammetry and fiber photometry with optical dopamine sensors, these techniques suffer from poor spatial resolution. Thus, it is possible that different stimuli cause dopamine release from different pools that are in the same region, but spatially distinct. We sought to examine spatial patterns of dopamine transmission in the striatum in response to appetitive and aversive stimuli, before and after repeated exposure to cocaine. Here, we utilized in vivo two-photon imaging of the dopamine sensor, dLight, to visualize spatial dopamine release, within the nucleus accumbens core, in awake and behaving mice. We aimed to test the following hypotheses: that patterns of dopamine release are spatially distinct in response to appetitive and aversive stimuli and that repeated exposure to cocaine disrupts patterns of dopamine transmission. Baseline recordings consisted of random, unsignaled presentations of sucrose or quinine, via an intraoral catheter. Following baseline recordings, animals received cocaine injections (10 mg/kg, i.p.) for 10 consecutive days or saline, as a control, before they were once again exposed to random presentations of appetitive or aversive stimuli. We find that

patterns of dopamine dynamics in response to quinine are visually distinct from dopamine responses to sucrose at baseline. Additionally, patterns of dopamine release vary in their intensity and duration in response to sucrose and quinine at baseline. As expected, repeated exposure to cocaine disrupts dopamine transmission in response to salient stimuli. Given the critical role of dopamine to control learning outside of the drug context, it is imperative we examine dopamine dynamics in response to non-drug stimuli. Collectively, these studies aim to uncover differences in dopamine release patterns in response to appetitive and aversive stimuli and how these patterns of release are affected by repeated exposure to cocaine.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

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Title: Orexin and glutamate in a hypothalamus-habenula circuit synergically inhibits cocaine-induced psychomotor responses

Authors: *D. AHN^{1,2}, E. JO¹, H. KIM¹, N. KANG¹, G. NAN¹, Y. OH¹, H. KIM¹;
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Abstract: Cocaine exposure drives addictive behaviors by diminishing GABAergic input to dopaminergic neurons in the ventral tegmental area (VTA) and concurrently elevating dopamine release in the nucleus accumbens (NAc). Complementary to this, a distinct circuit involving the lateral hypothalamus (LH) and lateral habenula (LHb) has been implicated in mediating aversion behaviors by influencing the mesolimbic dopaminergic system. Given this interconnectedness, we investigated whether the LH-LHb circuit could modulate cocaine-induced locomotor activity and sought to identify the specific neuropeptides responsible for this modulation. Optogenetic activation of the LH-LHb pathway strongly inhibited cocaine-enhanced locomotion. This effect was abolished by injecting local glutamate or orexin receptor antagonist into the LHb. *in vivo* extracellular recordings revealed that LH-LHb activation significantly increased LHb neuronal firing, which was also prevented by these antagonists. Crucially, co-administration of glutamate and orexin receptor agonists into the LHb led to a significantly greater reduction of cocaine-induced locomotion than either agonist alone. Our findings demonstrate that a synergistic

interaction between LH-derived glutamate and orexin, acting within the LHb, critically mediates the LH-LHb circuit's inhibitory effect on cocaine-induced behaviors.

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Topic: H.08. Drugs of Abuse and Addiction

Title: Predictive Genomic Modeling and Electrophysiological Analysis of Cocaine Addiction Vulnerability in Rats

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Abstract: *Background:* Cocaine Use Disorder (CUD) is characterized by compulsive cocaine consumption, precipitating significant psychosocial impairment. Preclinical investigations utilizing rodent models aim to delineate underlying neurobiological mechanisms; however, forecasting addiction propensity in naive subjects poses a formidable challenge. *Methods:* The RATTACA methodology harnesses genome-wide association study (GWAS) data (~7.3M SNPs) from rat pups to predict polygenic susceptibility to cocaine addiction-like behaviors (heritability ~0.14). Employing an 80% training and 20% testing paradigm within a 556-rat cohort, RATTACA delineates the top and bottom 5% as high- and low-addiction cohorts. *Results:* Whole-cell patch-clamp recordings from central amygdala (CeA) slices of predicted high- and low-addiction rats disclosed elevated baseline spontaneous inhibitory postsynaptic current (sIPSC) frequencies in high-addiction subjects, indicative of augmented GABAergic release. Ex vivo administration of 1 μ M cocaine selectively diminished sIPSC frequency in high-addiction rats, suggesting differential GABAergic modulation. No alterations in sIPSC amplitude or kinetics were detected, and glutamatergic transmission remained invariant across cohorts. Conversely, nucleus accumbens core (NaCC) recordings revealed no baseline or cocaine-induced GABAergic disparities, with both groups exhibiting uniform sIPSC reduction post-cocaine exposure, underscoring region-specific neuroadaptations. *Conclusions:* These findings illuminate

pre-existing CeA GABAergic dysregulations as a pivotal determinant of cocaine addiction vulnerability. By integrating RATTACA, this study elucidates neurobiological predispositions to CUD, paving the way for precision therapeutics and deeper inquiries into neurotransmitter dynamics underlying addiction susceptibility.

Disclosures: M. Kallupi: None.

Poster

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Title: Transposable elements are dynamically regulated in medium spiny neurons and contribute to the molecular and behavioral adaptations to cocaine

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Abstract: A more complete understanding of the molecular mechanisms by which substance use is encoded in the brain could inform novel strategies to treat substance use disorders, including cocaine use disorder (CUD). We previously identified that *Zfp189*, encoding a Krüppel-associated box zinc finger protein (KZFP) transcription factor (TF), differentially accumulates in nucleus accumbens (NAc) *Drd1*+ and *Drd2*+ medium spiny neurons (MSNs) during cocaine exposure and is causal in mediating MSN functional and behavioral responses to cocaine. Here, we investigated the brain cell type-specific molecular mechanisms through which this KZFP TF contributes to CUD-related changes, focusing on transposable elements (TEs), as KZFPs are known TE regulators. We annotated TEs in existing single-nucleus RNA sequencing (snRNAseq) datasets from rodents exposed to acute or repeated cocaine. Cocaine experience markedly altered NAc TE expression, particularly in MSNs. TEs in *Drd1*+ MSNs were more dynamically regulated than in *Drd2*+ MSNs over time. To test whether ZFP189 regulates TEs, we performed RNA-sequencing on virally manipulated NAc tissue from acutely cocaine-exposed mice. Our synthetic ZFP189 activator, ZFP189^{VPR}, altered TE expression and downregulated

immune-related transcripts, unlike our synthetic repressor, ZFP189^{WT}. We next conducted snRNAseq on NAc after viral ZFP189 TF manipulation at a later cocaine exposure stage. Compared to ZFP189^{WT}, ZFP189^{VPR} impaired cocaine-induced gene expression across all NAc cell types, including both MSN subtypes. ZFP189^{WT} enhanced immune gene expression, which was oppositely suppressed by ZFP189^{VPR}. To test causality, we delivered conditional synthetic ZFP189 TFs to *Drd1*+ or *Drd2*+ MSNs. Activating TEs via ZFP189^{VPR} in *Drd1*+ MSNs or stabilizing TEs via ZFP189^{WT} in *Drd2*+ MSNs produced behavioral and morphological adaptations to cocaine, revealing a persistent opponent process across MSN subtypes governed by TE stability. These findings demonstrate that KZFP-mediated TE repression in NAc MSNs enables cocaine-responsive gene expression and adaptations, and show that synthetic ZFP189 TFs offer cell-type specific strategies to block cocaine adaptations.

Disclosures: G. Silva: None. J. Picone: None. N.L. Truby: None. R.K. Kim: None. P.J. Hamilton: None.

Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR186.08/KK16

Topic: H.08. Drugs of Abuse and Addiction

Support: Fairfield Meditz College of Arts and Sciences - CAS Guarantee

Title: Cocaines impact on novelty suppressed feeding in male and female rats: anxiogenesis or hypophagia?

Authors: P. MENGOTTI ESTRADA, S. NELSON, S. DAS, S. SHAFFER, *K. T. SCHMIDT; Fairfield Univ., Fairfield, CT

Abstract: The effects of cocaine extend beyond the primary euphoria and psychomotor stimulation to include increases in anxiety-like responses and suppression of feeding behaviors. We first tested these effects of cocaine administration via the novelty suppressed feeding (NSF) assay in male and female Long Evans rats. We found that administration of 10 mg/kg cocaine increased latency to consume and reduced consumption of sucrose in a novel environment compared to saline controls. In this assay, rats also displayed anxiety-like behaviors including thigmotaxis following cocaine. To determine whether these NSF results reflected cocaine-induced anxiogenesis or could be attributed to cocaine-induced anorexia, we trained the same subjects to respond in operant conditioning chambers maintained by sucrose under a progressive ratio schedule of reinforcement. Across doses of cocaine (0-10 mg/kg), we did not observe changes in breakpoints, suggesting that these doses do not impact the reinforcing efficacy of sucrose. Therefore, we conclude that cocaine's impact on NSF behavior can be attributed to cocaine's anxiogenic effects.

Disclosures: P. Mengotti Estrada: None. S. Nelson: None. S. Das: None. S. Shaffer: None. K.T. Schmidt: None.

Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR186.09/KK17

Topic: H.08. Drugs of Abuse and Addiction

Support: Nu Rho Psi UG Grant

Title: Dose-dependent attenuation of oxytocin on the cocaine-seeking and cocaine-induced Fos expression of differentially reared rats

Authors: *T. MURRAY, M. J. GILL;
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Abstract: Differing socioeconomic statuses, accompanied by various environmental and behavioral factors during childhood, have been shown to impact an individual's susceptibility to drug dependence later in life. Differential rearing is an animal model that alters exposure to environmental enrichment, peers, and handling post-weaning. Rearing rats in an enriched (EC) versus impoverished (IC) or social (SC) conditions results in neurobiological and behavioral changes that protect EC rats against drug-seeking behavior later in life compared to IC and SC rats. Previous work has suggested oxytocin may mediate this protective effect, as oxytocin attenuates psychostimulant-seeking in standard housed rats, and environmentally enriched rats exhibit increased levels of oxytocin releasing factor compared to socially isolated counterparts. Based on this work, we hypothesize that systemic oxytocin will attenuate cocaine-seeking more drastically in EC compared to IC and SC rats. Additionally, oxytocin and Fos expression is impacted by stimulants, as oxytocin pretreatment during cue-induced reinstatement of standard reared rats increases oxytocin in the prefrontal cortex, subthalamic nucleus, and nucleus accumbens, decreases oxytocin in the central amygdala, and increases both oxytocin and Fos expression in the paraventricular nucleus. Based on previous work in our lab demonstrating attenuated Fos expression in the accumbal-pallidal glutamatergic circuit of EC rats compared to IC rats, we hypothesize that systemic oxytocin will attenuate rearing-induced differences in Fos + oxytocin expression following reinstatement. Male Sprague Dawley rats arrived at 21 days of age and were reared in EC, IC, or SC environments, for 30 days. Following rearing, rodents underwent cocaine self-administration, extinction, and cue-induced reinstatement paired with oxytocin (0.3 mg/kg or 1.0 mg/kg, i.p) or saline injections (i.p). Immunohistochemical analysis was conducted to measure Fos and oxytocin expression following the final reinstatement session. A dose-dependent effect of rearing was observed during cue-induced reinstatement, in which oxytocin attenuated cocaine-seeking in SC rats at low (0.3 mg/kg) doses, and IC rats at moderate (1.0 mg/kg) doses. These findings suggest that oxytocin could serve as a pharmacological therapy to alleviate socioeconomic-induced vulnerabilities to drug dependence.

Disclosures: T. Murray: None. M.J. Gill: None.

Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR186.10/KK18

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH DA031900
NSF GRFP No. 2041772

Title: The effects of hypocretin/orexin neuron modulation on incubation of cocaine seeking and dopamine terminal adaptations

Authors: *S. B. SAMELS¹, R. A. ESPAÑA²;

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Abstract: A major challenge for treating cocaine use disorder is the intensification or “incubation” of drug craving/seeking that occurs during cocaine abstinence. Recent studies suggest that mesolimbic dopamine adaptations that occur during cocaine abstinence may be a critical driver in the development of incubation of cocaine seeking. For example, abstinence from intermittent access to cocaine produces changes in dopamine transporter efficiency, sensitivity to cocaine, and promotes robust incubation whereas, short access is not associated with changes in dopamine transmission and does not promote incubation. These observations suggest the possibility that normalizing dopamine transmission after periods of abstinence may prevent incubation of cocaine seeking. The hypocretin/orexin system has been shown repeatedly to impact dopamine and behavioral responses to cocaine. Hypocretin receptor antagonism attenuates the effects of cocaine on dopamine transmission and decreases motivation for cocaine. To date, however, it remains unclear whether the activity of hypocretin neurons influences incubation of cocaine seeking and dopamine transmission. To determine to what degree hypocretin neuron activity is necessary and sufficient to drive cocaine seeking we utilized chemogenetic inhibition or activation of hypocretin neurons before cocaine seeking tests on abstinence day 28 in rats exposed to either intermittent access short access to cocaine. We hypothesize that inhibition of hypocretin neurons following intermittent access to cocaine will reduce incubation of cocaine seeking and normalize dopamine transmission, whereas excitation of hypocretin neurons following short access to cocaine will promote incubation of cocaine seeking and dopamine terminal adaptations.

Disclosures: S.B. Samels: None. R.A. España: None.

Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR186.11/KK19

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA K25VA047458

Title: A longitudinal assessment of impulsivity and functional connectivity in rats following active or passive cocaine exposure

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Abstract: Impulsivity is a hallmark behavioral symptom associated with the transition from voluntary drug use to compulsive drug-seeking behavior in cocaine use disorder (CUD). It has been proposed that functional connections in brain areas implicated in addiction are behind this behavioral shift. In this study, we used a delay discounting (DD) task to longitudinally assess impulsive choice and resting state (rs) functional connectivity in rats before and after drug administration. We compared passive intraperitoneal (IP) injections of cocaine, to voluntary intravenous self-administration (IVSA), as well as assessed functional connectivity at three time points using BOLD rs-fMRI. Rats were initially trained on the DD task to establish baseline impulsivity, defined by the preference for smaller immediate over larger delayed rewards. Rats received daily IP injections of cocaine (5mg/kg) for one week—resulting in a significant increase in impulsive choice compared to saline and naïve controls. Similarly, rats undergoing 10 days of short access (2hr/day) IVSA of cocaine (1mg/kg/infusion) showed a significant increase in impulsive choice following the drug administration period, consistent with results seen in the IP administration cohort. For both groups (IP and IVSA), rs-fMRI scans will provide connectivity results for various regions: infralimbic, prelimbic, orbitofrontal cortex, hippocampus, amygdala, and insula. Our results demonstrate both passive and active exposure to cocaine increases impulsive choice behavior in rats. These findings align with clinical observations of CUD patients exhibiting impaired decision-making in the face of drugs. Moreover, the similarities in behavioral outcomes following two different models of cocaine administration bolsters evidence of impulsive choice as a behavioral feature of cocaine use. Neuroimaging data analysis is ongoing; we aim to identify network-level correlates of the drug-induced behavioral changes seen.

Disclosures: J. Keitzer: None. L.M. Colon-Perez: None.

Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

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Program #/Poster #: PSTR186.12/KK20

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH 5R21DA058205

Title: Selective knockdown of oxytocin receptors or CB1 receptors in the ventral tegmental area disrupts the attenuating effect of oxytocin on cocaine conditioned place preference

Authors: *G. T. LE¹, I. MOOSA¹, K. DIXON¹, M. KANEKO¹, J. T. STALL¹, J. A. GRIFFIN¹, K.-C. LEONG²;

²Dept. of Psychology, ¹Trinity Univ., San Antonio, TX

Abstract: Cocaine use disorder (CUD) is a chronic relapsing condition with limited treatment options. We have demonstrated that oxytocin (OXT) is capable of attenuating cocaine conditioned place preference (CPP) behavior, but the neural mechanisms underlying this effect remain unclear. Prior evidence suggests that OXT receptor (OXTR) activation on dopamine (DA) neurons in the ventral tegmental area (VTA) modulates excitatory glutamatergic input onto DA neurons via presynaptic cannabinoid type 1 receptors (CB1Rs). Here, we examine whether (1) selective OXTR knockdown on VTA DA neurons or (2) selective CB1R knockdown on VTA glutamatergic synapses is sufficient to attenuate OXT's attenuating effect on cocaine CPP in male Long-Evans rats ($n = 84$). To dissect this two-fold mechanism, we employed a novel approach combining transgenic *Cre* animal models and viral-mediated short hairpin RNA (shRNA) to selectively silence OXTRs on DA neurons or CB1Rs on glutamatergic terminals in the VTA. In the first aim, Cre-dependent shRNA knockdown of OXTRs in VTA DA neurons of DAT^{Cre} male Long-Evans rats were used to evaluate the necessity of these receptors for OXT-mediated effects on cocaine conditioned place preference (CPP). Rats were conditioned with cocaine (10 mg/kg) and received either vehicle (VEH) or OXT (3 mg/kg) at test. Cocaine CPP was assessed by the percent of time spent in the drug-paired chamber and analyzed using a two-way ANOVA. While we consistently show that OXT attenuates cocaine place preference at test, this effect of OXT was no longer present in animals with selective knockdown on OXTRs on VTA DA neurons. In the second aim, CB1Rs were silenced in VTA glutamatergic afferents using a Cre-Off CB1 shRNA viral vector in GAD^{Cre} male Long-Evans rats to assess the role of retrograde eCB signaling in OXT-induced attenuation in cocaine CPP. The effect of CB1R knockdown on oxytocin-mediated attenuation of cocaine-associated reward was assessed. Together, our findings provide mechanistic insight into how OXT may attenuate cocaine reward behavior through the OXTR binding on DA neurons and interactions with CB1 receptors on glutamatergic inputs in the VTA.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

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Topic: I.05. Working Memory

Support: NIH DA057712
NIH NS031373
NIH MH119673

Title: Metabotropic mGlu1 Receptor Regulation of Cortical Inhibition and Cognitive Function: Implications in Adolescent Cocaine Exposure

Authors: *D. J. LUESSEN¹, I. GALLINGER², B. WOLFE³, M. MEADOWS¹, P. CONN⁴;
¹Emory Univ. Sch. of Med., Atlanta, GA; ²Wake Forest Univ. Sch. of Med., Winston-Salem, NC; ³Vanderbilt Univ., Franklin, TN; ⁴Vanderbilt Univ. Med. Ctr., Nashville, TN.

Abstract: Exposure to cocaine during adolescence produces persistent changes in the prefrontal cortex (PFC) which parallel cognitive deficits seen in adulthood. Further, adolescent exposure to psychostimulants impairs inhibitory transmission in the PFC in adulthood, suggesting that enhancing PFC inhibitory transmission may be a promising strategy to reverse drug-induced cognitive deficits. Activation of the mGlu1 subtype of metabotropic glutamate receptor increases inhibitory transmission in the PFC and working memory by selective excitation of somatostatin-expressing GABA interneurons (SST-INs). Therefore, we hypothesize that repeated exposure to cocaine during a critical developmental period in adolescence disrupts PFC inhibition via SST-INs and drives working memory impairments in adulthood which can be mitigated by activation of mGlu1.

As such, tdTomato mice were injected once daily with cocaine (20 mg/kg, i.p.) for 7 days (postnatal day 35-42). Whole-cell patch-clamp electrophysiological recordings from SST and PV interneurons within the PFC were conducted between 10-12 weeks of age. Additionally, touchscreen-based automated cognition testing was used to determine working memory performance in adult mice. Novel mGlu1 positive allosteric modulators (PAMs) were leveraged in behavioral and electrophysiology studies to determine their procognitive efficacy and mechanism of action within the PFC.

We found that repeated administration of cocaine during a critical adolescent period impaired PFC SST-IN, but not parvalbumin-expressing interneuron (PV-IN), firing compared to saline-treated mice. Adolescent cocaine exposure significantly decreased the frequency of spontaneous excitatory postsynaptic currents onto SST-INs but not PV-INs. These findings were paralleled by adolescent cocaine-induced impairments in spatial working memory in adulthood. Importantly, these physiological and behavioral effects of adolescent cocaine exposure were reversed by selective mGlu1 activation. Lastly, repeated amphetamine administration during the same adolescent critical period did not result in impaired SST-IN function or spatial working memory in adulthood. Together, these studies provide insight to the cell type- and brain region-specific consequences of adolescent drug exposure and lasting effects on cognitive performance in adulthood while highlighting a potential therapeutic avenue to treat these deficits.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA046457

Title: Reinforcement schedules reveal a dissociation between habitual cocaine seeking and punishment resistance in male and female rats

Authors: *J. K. TREADWAY¹, S. N. HANDEL¹, R. J. SMITH²;

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Abstract: Reinforcement schedules have been shown to influence behavioral processes. Random ratio (RR) schedules typically promote goal-directed responding, whereas random interval (RI) schedules bias behavior toward habit. Further, our lab recently showed that RI schedules produce greater resistance to punishment than RR schedules. Here, we wanted to investigate how fixed schedules—fixed ratio (FR) and fixed interval (FI)—compare, and to evaluate sex as a biological variable. We trained male and female Sprague Dawley rats to self-administer intravenous cocaine (0.5 mg/kg/infusion) via a seeking-taking chained schedule of reinforcement, with the seeking lever under one of four schedules (FR20, FI60, RR20, or RI60) and the taking lever reinforced under a fixed-ratio 1 schedule. During punishment testing (4 days), rats received footshock (0.4 mA, 0.3 s) on one-third of trials after completion of seeking. To determine whether rats were goal-directed or habitual, outcome devaluation via cocaine satiety was conducted several days before and after punishment testing. Surprisingly, we found that male and female rats trained on interval schedules (FI, RI) were generally sensitive to devaluation (i.e., goal-directed), whereas rats trained on ratio schedules (FR, RR) were insensitive (i.e., habitual). During punishment, interval-trained rats showed greater punishment resistance as compared to ratio-trained rats, with no significant differences between males and females. When assessing outcome devaluation after punishment testing, we observed an overall shift toward greater sensitivity to devaluation across all schedules, except RI60-trained females that became insensitive to devaluation, indicating habitual responding. These findings indicate that schedules may have a different influence on habitual responding for cocaine as compared to food. Further, these results indicate that reinforcement schedules influence habitual responding and punishment resistance via distinct mechanisms, based on our finding that habitual responding is not necessary for punishment-resistant cocaine seeking. This dissociation provides insight into the motivational processes driving compulsive drug use.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR186.15/LL1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH-NIDA-IRP-Z1A DA000611
NIH-NIDA-IRP-Z1A DA000389

Title: Vilazodone and its structural analogs. New clues for atypical dopamine transporter inhibitors?

Authors: *G. TANDA, C. D. VOGT, Z. FRANGOS, M. HERSEY, M. K. BARTOLE, J. G. MELTON, M. MICHAELIDES, A. H. NEWMAN;
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Abstract: Psychostimulant use disorder (PSUD) affects the lives of millions in the US and around the world. PSUD is often comorbid with neuropsychiatric disorders that are treated with a variety of pharmacotherapies, but there are still no FDA approved medications for the treatment of PSUD. Vilazodone (VLZ), a Serotonin Partial Agonist/Reuptake Inhibitor, is approved for the treatment of depression. VLZ has very high affinity ($K_i=0.101$ nM) for the serotonin transporter (SERT), and the 5HT1A receptor ($K_i=0.20$ nM), but also for the dopamine (DA) transporter (DAT; $K_i=11.1$ nM), which plays a role in the addictive liability of psychostimulants, like cocaine or methamphetamine. There are no reports of VLZ misuse, suggesting its affinity for DAT is not associated with rewarding effects, at least in the population of patients to which it is prescribed. This could be the result of its ~100-fold higher affinity for SERT over DAT. However, another explanation could be that it is an atypical DAT inhibitor, predicting reduced reinforcing effects that might lead to addiction. To better understand the pharmacological, behavioral and neurochemical properties of VLZ as they relate to DAT affinity, a series of its structural analogs have been synthesized with varying affinity ratios between SERT and DAT. In radioligand binding studies in hDAT or hSERT transfected HEK293 cell membranes, the VLZ analog, CDV-2-32, shows similar binding affinities to hDAT and hSERT ($K_i=231$ and 147 nM, respectively). We also tested VLZ and its analog(s) in behavioral open field activity tests and on DA neurochemistry in rodents. In the open field tests, administration of VLZ and CDV-2-32 (1, 3, 10, 30 mg/kg i.p.) in Swiss-Webster male mice did not elicit ambulatory activity significantly different from that produced by vehicle. In voltammetry tests in C57 male and female mice, administration of VLZ did not significantly modify DA dynamics in the nucleus accumbens shell showing no significant changes in evoked DA-max and DA clearance. We are currently studying the effects of VLZ, CDV-2-32, and additional novel analogs on DA levels measured by microdialysis in the nucleus accumbens shell in Sprague-Dawley rats. In summary, novel VLZ analogs have been synthesized and show different affinity ratios for SERT/DAT. VLZ and CDV-2-32 did not elicit significant changes in ambulatory activity and DA dynamics in mice. We are currently testing these compounds to assess their effects on DA levels in the rat NAC shell. In conclusion, the mechanism of action of these compounds may provide information that facilitates discovery of pharmacotherapies for the treatment of PSUD and potentially comorbid neuropsychiatric disorders.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant RO1DA047785

Title: Beclin2-mediated autophagy regulation of dopaminergic mechanisms in cocaine-taking behaviors

Authors: *A. SALAZAR^{1,2}, D. YANG³, Q. KONG², C. HE⁴, M. XU²;

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Abstract: Autophagy maintains cellular homeostasis via lysosomal degradation and recycling, yet its contribution to substance-use disorders remains incompletely defined. This study examines how the autophagy-related protein Beclin 2 (Becn2) modulates dopamine D2-receptor (D2R) dynamics and cocaine-reinforced behavior. Cocaine use disorder presents a major public health challenge, marked by high relapse rates, increasing overdose deaths, and a complete lack of FDA-approved pharmacotherapies. Previous work identified Becn2 as a presynaptic regulator of D2R turnover in ventral tegmental area dopaminergic neurons, with Becn2 mutations altering cocaine-reward behaviors. However, the function of Becn2 in postsynaptic neuronal populations has not been examined. Given that most D2Rs are localized postsynaptically, understanding how Becn2 regulates D2Rs in D2R-expressing medium spiny neurons (D2-MSNs) of the nucleus accumbens is of particular relevance. To address this, a cell-type-specific Becn2 knockout was generated in D2-MSNs using a cre⁺/loxP approach. Behavioral consequences were assessed using an intravenous self-administration paradigm. Mice lacking Becn2 in D2-MSNs exhibited significantly reduced cocaine intake during acquisition, suggesting that postsynaptic D2Rs mediate Becn2's role in modulating cocaine reward. These findings reveal a previously unrecognized postsynaptic function of Becn2 in regulating cocaine-related behavior, potentially through modulation of D2R stability. Ongoing studies aim to quantify D2R levels in D2-MSNs of knockout mice and to determine how these changes contribute to cocaine intake. Additional behavioral testing, including dose-response and reinstatement paradigms, will further evaluate Becn2's role and may reveal novel therapeutic targets for cocaine use disorder.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA051551
NIDA Grant DA056592

Title: Acetate as a mediator of cocaine-related behaviors and gene expression

Authors: *M. KOPERSKA;
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Abstract: Cocaine use disorder is a chronic neuropsychiatric condition characterized by compulsive drug use and altered reward neurobiology, yet no FDA-approved treatments currently exist. While most therapeutic research has targeted the central nervous system, limited success in clinical translation underscores the need to explore how peripheral systems contribute to addiction-like phenotypes in pre-clinical and clinical research. The gut microbiome and its metabolic byproducts are emerging as powerful modulators of brain function and behavior, with increasing evidence supporting their involvement in substance use disorders. Short-chain fatty acids (SCFA), including acetate, butyrate, and propionate are key microbial metabolites produced through fermentation of dietary fiber. These molecules have known neuroactive properties, influencing neurotransmission, epigenetic regulation of gene expression and behavioral effects in substance use disorders. Our lab previously demonstrated that a cocktail of all three SCFA reversed microbiome depletion-induced increases in cocaine conditioned place preference (CPP) and altered transcriptional activity in the nucleus accumbens (NAc), a key brain region in reward circuitry. To isolate the effects of individual SCFA in mice with intact microbiomes, male and female C57BL/6J mice were pretreated via drinking water with acetate for 10 days prior to CPP conditioning. Cocaine CPP was tested at two doses of cocaine (5mg/kg and 10mg/kg). Additionally, NAc tissue was collected from animals exposed to acute and sub-chronic high dose cocaine (10mg/kg) with qPCR analyses conducted to quantify expression of genes related to synaptic plasticity, immediate early gene activation and histone modification. We found that acetate modulated cocaine CPP in a dose-dependent manner, with behavioral changes accompanied by corresponding shifts in NAc gene expression, even in the absence of microbiome disruption. Notably, these findings demonstrate that individual SCFAs can directly influence cocaine-related behaviors and gene regulation, independent of global microbiome changes. This work supports the role of microbial metabolites as novel modulators of reward-related behavior and lays the foundation for future mechanistic and motivation-based studies of gut-brain interactions in cocaine use disorder.

Disclosures: M. Koperska: None.

Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR186.18/LL4

Topic: H.08. Drugs of Abuse and Addiction

Support: SuRE E grant

Title: Elucidating the Genomic Modulation of the H-current in VTA DA Neurons following Cocaine Sensitization

Authors: *A. I. ORTIZ CORREA¹, K. Y. BOSQUE CORDERO², D. CONSUEGRA GARCIA³, M. S. BRODIE⁴, R. VAZQUEZ-TORRES⁵, C. A. JIMENEZ-RIVERA⁶, C. CALO⁷; ¹Biol., Univ. of Puerto Rico Rio Piedras, San Juan, PR; ²Dept. of Psychiatry, Ctr. for Alcohol Res. in Epigenetics, Chicago, IL; ³Physiol., Univ. Of Puerto Rico Med. Sci. Campus, San Juan, PR; ⁴Physiol. and Biophysics, Univ. of Illinois Chicago, Chicago, IL; ⁵Temple Univ., Philadelphia, PA; ⁶Physiol., Univ. of Puerto Rico, San Juan, Puerto Rico; ⁷Physiol., Univ. of Puerto Rico, Canovanas, Puerto Rico

Abstract: Substance Use Disorder (SUD) is considered one of the leading causes of premature death worldwide, with cocaine ranking as the second most commonly used illicit substance in the United States. Despite its widespread use and serious health consequences, effective treatments for cocaine dependence remain absent. Drugs of abuse, such as cocaine, induce long-lasting plastic changes in the mesolimbic dopamine (DA) system, which plays a central role in reward processing. Epigenetic alterations may mediate these modifications in brain function. Previous studies have shown that cocaine sensitization alters the intrinsic properties of DA neurons in the ventral tegmental area (VTA), ultimately affecting dopamine transmission within the mesolimbic DA network. One intrinsic property affected by drug exposure is the hyperpolarization-activated cation current (I_h), mediated by HCN channels. Our laboratory has previously demonstrated a reduction in I_h in VTA DA neurons from cocaine-sensitized rats. However, little is known about the epigenetic regulation of HCN channels following drug exposure, and to date, no studies have addressed the epigenetic regulation of I_h. Using whole-cell patch-clamp recordings, we investigated the effects of the HDAC inhibitor SAHA on cocaine-induced changes in I_h. Additionally, we assessed SAHA's effect on evoked excitability in brain slices from cocaine-sensitized rats. Evoked action potentials were recorded in current-clamp mode and quantified as the number of spikes elicited by thirteen consecutive depolarizing current steps (50 pA increments, 1-second pulses). In vitro incubation of midbrain slices with SAHA (3 μM for two hours) restored I_h amplitude to baseline levels, reversing the cocaine-induced reduction. Current-clamp traces further demonstrated that cocaine exposure enhances DA neuron responsivity to depolarizing current injections, whereas SAHA-treated tissue exhibited baseline levels of evoked excitability. These results support the hypothesis that the cocaine-induced reduction in I_h amplitude in VTA DA neurons is epigenetically regulated. Moreover, the evoked excitability findings suggest that HDAC inhibitors may reverse cocaine-induced neuroadaptations in the mesolimbic DA system.

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Poster

PSTR186: Cocaine: Cell Signaling, Circuitry, Neurophysiology, and Behavior

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Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH U19NS123717
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Title: Substance abuse reshapes the hemodynamic response to brain activation

Authors: *B. RAUSCHER¹, N. FOMIN-THUNEMANN¹, N. CHAI¹, K. KILIÇ¹, J. JIANG¹, M. THUNEMANN¹, D. A. BOAS¹, A. DEVOR^{1,2};

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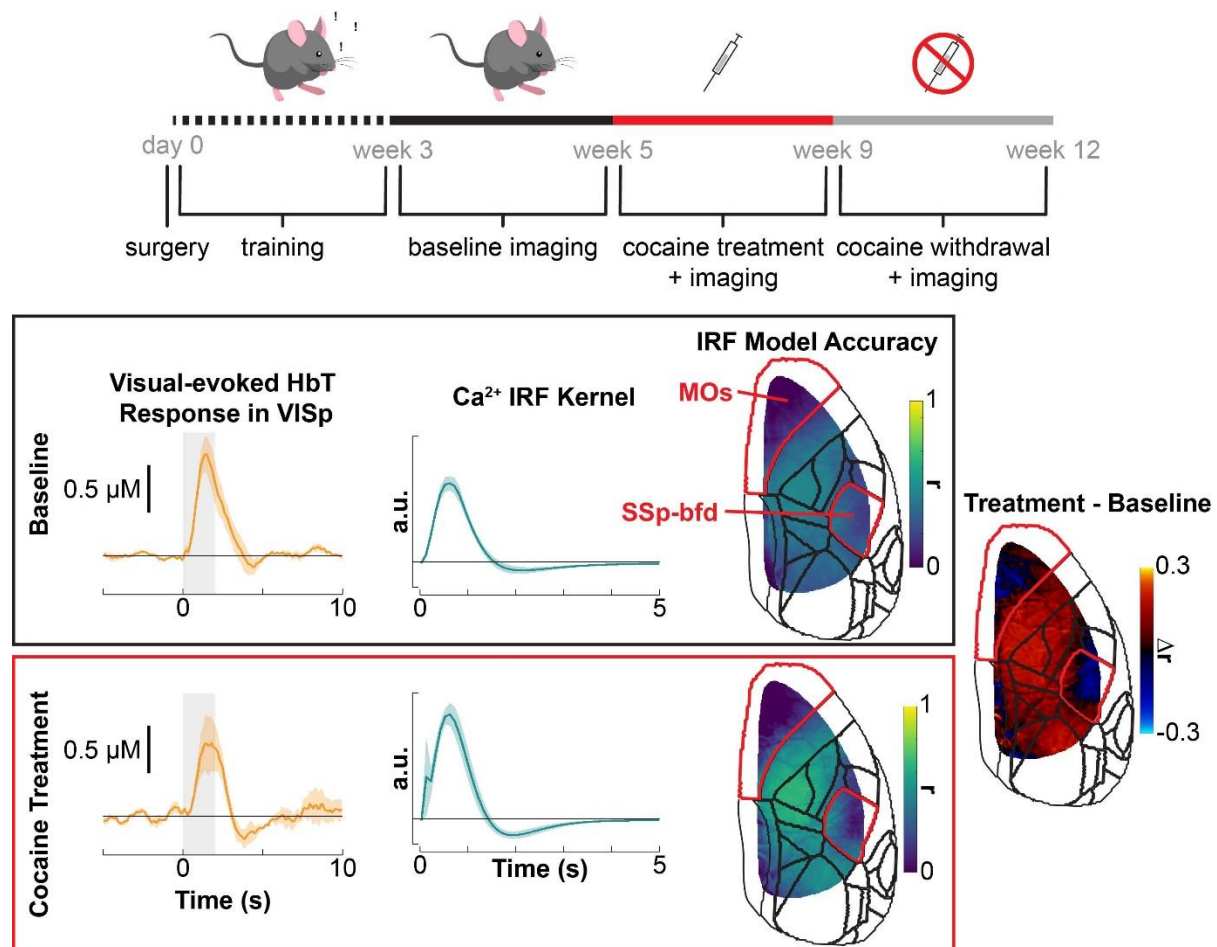
Abstract: Cocaine use is widespread, and individuals with a history of abuse may ultimately undergo clinical functional MRI (fMRI). However, interpreting fMRI signals relies on the assumption of a standard neurovascular relationship, which may be disrupted in those with prior cocaine use—potentially complicating the inference of neural activity from hemodynamic signals.

We previously showed that cortical hemodynamics can be accurately predicted using an impulse response function (IRF) model incorporating separate convolution kernels for local neural Ca^{2+} activity and norepinephrine (NE) release. The relative contributions of these components vary by region, with NE exerting the greatest influence in the barrel and motor cortices. Given the elevated noradrenergic tone in individuals with a history of cocaine use, we hypothesize that these NE-dominant regions will deviate from the canonical neurovascular relationship defined by local Ca^{2+} activity alone.

In this study, we used mesoscopic optical imaging in awake mice to simultaneously measure (1) NE release, (2) local neural Ca^{2+} activity, and (3) changes in hemoglobin concentration and oxygenation across the dorsal cortex during both spontaneous and visual stimulus evoked activity—before, during, and after four weeks of daily cocaine administration. Using our established computational framework, we assessed how the neurovascular relationship differs between spontaneous and stimulus-evoked activity and whether this relationship, characterized in primary visual cortex, can be generalized to other cortical areas. Additionally, we evaluated the contributions and shape of the Ca^{2+} and NE IRF kernels during cocaine administration and withdrawal, observing stronger deviations from the canonical neurovascular relationship in the barrel and motor cortices.

We conclude that chronic cocaine use alters the neurovascular relationship in the barrel and

motor cortices by enhancing the influence of the NE kernel. In future analyses, we aim to examine whether these effects persist during withdrawal after cessation of cocaine use.



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Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR187.01/LL6

Topic: I.01. Attention

Support: Honda R&D Co., Ltd.

Title: Neural Correlates of Individual Differences in Risk Assessment in Driving: An fMRI study using an MR-compatible driving simulator

Authors: ***M. CHO**¹, S. MURAKAMI¹, E. TSUMAYA², D. MATSUYOSHI³, Y. YOMOGIDA³, R. KANAI³, Y. AIZAWA⁴, M. YAMADA⁴;

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Abstract: Honda has set a goal to achieve zero fatalities in traffic accidents by 2050. To achieve this goal, it is essential to identify and eliminate the causes of human errors by drivers. Previous studies have suggested that risk perception—the extent to which drivers perceive a traffic environment as dangerous—affects the level of risk in their driving behavior. However, little is known about the cognitive and neural processes underlying the relationship between drivers' behavior and risk perception. To investigate this, we conducted two experiments. In Experiment 1, we recorded fMRI and eye-tracking data while healthy adults (aged 22-78 years old) operated a driving simulator. The driving simulator was constructed inside an MRI scanner and consisted of a steering wheel with turn-signal buttons, an accelerator pedal, and a brake pedal. Participants drove in the target or other trials. In target trials, a road with risks, such as a car in the adjacent lane passing the participants' driving car, was presented, and participants were required to safely change lanes to the right. At the end of a trial, a traffic light in front of an intersection turned red, and participants had to put on the brake pedal to stop. In the other trials, participants drove on the road with a lane change to the left or without a lane change or drove straight on a road without any other objects. In Experiment 2, participants were shown videos of someone driving in a virtual space using a driving simulator. They were asked to press a button whenever they perceived a situation in the video to be dangerous. We evaluated drivers' risk perception performance based on the results of Experiment 2 and analyzed the relationship between risk perception performance and driving behavior observed in Experiment 1. The behavioral data showed that the risk perception performance was negatively correlated with the maximum deceleration. Next, we investigated what neural processes underlie this relationship. The fMRI data showed that the risk perception performance positively modulated activations in the V4 and negatively modulated activations in the supramarginal gyrus at the first fixation to a risky car in Experiment 1. In previous studies, it has been established that the V4 is associated with the visual processing of color and shape, while the right temporo-parietal junction, including the supramarginal gyrus, is related to stimulus-driven attention. These results suggest that drivers who can appropriately assess risks tend to carefully observe other traffic participants, whereas those who cannot are more likely to rely on bottom-up attention, which may lead to dangerous driving behavior.

Disclosures: **M. Cho:** A. Employment/Salary (full or part-time): Honda R&D Co., Ltd. **S. Murakami:** A. Employment/Salary (full or part-time): Honda R&D Co., Ltd. **E. Tsumaya:** A. Employment/Salary (full or part-time): Honda R&D Co., Ltd. **D. Matsuyoshi:** A. Employment/Salary (full or part-time): ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **Y. Yomogida:** A. Employment/Salary (full or part-time): ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **R. Kanai:** A. Employment/Salary (full or part-time): ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards);

Honda R&D Co., Ltd.. **Y. Aizawa:** None. **M. Yamada:** 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.; Honda R&D Co., Ltd..

Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR187.02/LL7

Topic: I.01. Attention

Support: Honda R&D Co., Ltd.

Title: Memory-based risk prediction is associated with reduced impact of exogenous attention decline in older drivers

Authors: ***S. MURAKAMI**¹, M. CHO¹, D. MATSUYOSHI², Y. YOMOGIDA², R. KANA¹², Y. AIZAWA³, M. YAMADA³;

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Abstract: Exogenous attention is known to decline with age (Ling et al., 2013), which may negatively impact risk detection during real-world driving. Here, we report that older adults performed comparably to younger adults in risk detection while driving—a critical component of safe driving—despite showing reduced performance in the exogenous attention task in the laboratory setting. Consistent with this, Curran et al. (2001) reported that older adults who were able to identify highly reliable cues maintained top-down attentional functions at levels comparable to those of younger adults. However, little is known about the cognitive and neural mechanisms related to the exogenous and endogenous attentional processes of older drivers. To gain further insight into this issue, we analyzed brain regions whose activation has been associated with the performance differences between the exogenous attention task and risk detection during the driving task. This analysis aims to uncover the underlying neural mechanisms supporting these distinct attentional processes. In the exogenous attention task, participants were instructed to fix their gaze and respond to visual markers presented on a hemispherical display. Performance was evaluated based on reaction times to stimuli appearing in the horizontal ultra-peripheral visual field (60-110 degrees in visual angle). In the driving task, participants operated a driving simulator integrated into the MRI scanner, following a course designed to reflect high-risk traffic conditions in Japan. Risk detection performance was assessed by the time taken to detect a vehicle approaching from behind during lane changes. We focused on the brain activity when participants gazed at a risk-related target during the driving task. Significant activation was observed in the medial prefrontal cortex (mPFC) and inferior frontal junction (IFJ). The mPFC is associated with memory, decision-making, and inhibitory control (David et al., 2012), while the IFJ supports the selection of task-relevant, non-spatial information

and flexible updating of behavioral rules (Bedini et al., 2023). These findings suggest that older drivers capable of safe driving compensate for age-related exogenous perceptual decline by utilizing memory-based risk prediction (mPFC) and directing attention based on those predictions (IFJ), allowing for the identification of highly reliable cues in complex environments. This study provides insight into how cognitive functions support attention in older adults, underscoring the potential value of further research to clarify the contributions of these neural activations to adaptive cognitive behavior.

Disclosures: **S. Murakami:** A. Employment/Salary (full or part-time): Honda R&D Co., Ltd. **M. Cho:** A. Employment/Salary (full or part-time): Honda R&D Co., Ltd. **D. Matsuyoshi:** A. Employment/Salary (full or part-time): ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **Y. Yomogida:** A. Employment/Salary (full or part-time): ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd. **R. Kanai:** A. Employment/Salary (full or part-time): ARAYA Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ARAYA Inc.. F. Consulting Fees (e.g., advisory boards); Honda R&D Co., Ltd.. **Y. Aizawa:** None. **M. Yamada:** 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.; Honda R&D Co., Ltd..

Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR187.03/LL8

Topic: I.01. Attention

Support: National Natural Science Foundation of China (grant number: 32271078)

Title: The auditory predictive coding during walking

Authors: *X. CHEN^{1,2}, J. LUO¹, S. SUN¹, L. CAO^{1,2};

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Abstract: Comparing expectation with pending input is an important neural computation performed throughout the brain and is the key of predictive processing. In many situations, when sensory stimuli are self-generated and thus highly predictable, neural responses to these stimuli are attenuated, a phenomenon known as sensory attenuation. However, when these predictions are violated, the attenuation can diminish or even reverse, resulting in an enhanced neural response known as a prediction error signal. While those prediction-based

effects were robustly observed in simple, small motor actions such as button presses and speak, its presence during natural, continuous, and ecologically meaningful larger body movement such as walking remains unclear. Specifically, it remains unknown whether natural and stable footfalls during walking enhance the processing of naturally predictable stimuli, and how this might influence prediction-based effects. To answer those questions, in a mobile EEG experiment, participants listened to footstep-triggered tones that were either expected or unexpected during natural walking. A control condition involved passive listening to the same previously tones while standing still. Results showed a clear prediction error effect during walking as well as standing: unexpected sounds elicited a stronger auditory N1 component across frontal electrodes than expected sounds. However, this effect was smaller during walking compared to standing. A reduced mismatch negativity component was also found during walking compared to standing. Importantly, no evidence of sensory attenuation was found. N1 responses to self-generated sounds were similar between walking and standing. These findings suggest that prediction error mechanisms remain during walking but can be modulated by movement states. Unlike simple motor actions, walking involves complex, spatially extended, and goal-directed movements, which may require a different balance between prediction and sensory input. This study thus extends predictive coding theory to natural locomotion and highlights the dynamic nature of sensory processing in real-world behaviors.

Disclosures: X. Chen: None. J. Luo: None. S. Sun: None. L. Cao: None.

Poster

PSTR187: Human Attention in Everyday Life

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Program #/Poster #: PSTR187.04/LL9

Topic: I.01. Attention

Support: DENSO CORPORATION

Title: Driver's eye gaze prediction using a deep learning model

Authors: *R. YOSHIE¹, F. NAKANISHI², Y. OHSAWA¹, M. YAMATAKA², T. KOHAMA¹;
¹Grad. Sch. of Biology-Oriented Sci. and Technol., Kindai Univ., 930 Nishimitani, Kinokawa-shi, Wakayama, Japan; ²Advanced Res. and Innovation Ctr., DENSO CORPORATION, 500-1 Minamiyama, Komenoki-cho, Nisshin-shi, Aichi, Japan

Abstract: With the development of automated driving technology, driver assistance systems are progressing rapidly. However, because the intervention of these systems can cause instability in driving behavior, systems facilitating cooperation between humans and machines are expected to be realized. Prediction technology for eye gaze, a biological signal that reflects human intention, is attracting attention, and there are high expectations for the development of technology to understand the driver's state by applying eye gaze prediction technology. Previous deep learning

models for predicting driver's eye gaze have been developed under constrained conditions, such as accident scenarios, which limits their general applicability across diverse situations. In this study, we designed a deep learning model to predict driver gaze based on the hypothesis that gaze direction is influenced by both bottom-up factors derived from image feature values and top-down factors involving higher-order cognitive processes such as the integration of contextual information. The proposed model applies scale adjustment parameters to the image features, optical flow, and object information. Following information enhancement and suppression, these elements are integrated and convolved in the temporal direction. To train the model, we used driving scenes continuously captured by an in-vehicle camera while driving on motorways and urban streets along with eye movement data that were measured simultaneously. The probability of gaze distribution for the final frame in a set of consecutive input frames was predicted, and the training process was performed to minimize the difference between the predicted and actual gaze distributions using the k-fold method. The simulation results indicated that the cross-correlation coefficient between the measured and unlearned data exhibited a broad distribution, with higher values observed on motorways than on urban streets. It was also demonstrated that the object information employed for training differed between motorways and urban streets, confirming that information was acquired under specific road conditions. These findings suggest that the proposed model effectively predicts the driver's gaze position.

Disclosures: **R. Yoshie:** 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.; DENSO CORPORATION. **F. Nakanishi:** A. Employment/Salary (full or part-time): DENSO CORPORATION. **Y. Ohsawa:** 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.; DENSO CORPORATION. **M. Yamataka:** A. Employment/Salary (full or part-time): DENSO CORPORATION. **T. Kohama:** 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.; DENSO CORPORATION.

Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR187.05/Web Only

Topic: I.01. Attention

Title: Prediction of stress reactivity of athletes and military servants according to psychophysiological indicators using the electroencephalography method

Authors: *S. FEDORCHUK¹, O. KORBUSH²;

¹Natl. Univ. of Ukraine on Physical Educ. and Sport, Kyiv, Ukraine; ²Natl. Univ. of Ukraine on Physical Educ. and Sport, Kiyv, Ukraine

Abstract: Stress is characterized by negative effects on various systems of the human body, including the nervous, immune, cardiovascular and digestive systems. Even with a significant number of studies devoted to the study of stress using electroencephalography (EEG), there are no comprehensive guidelines on the relationship between EEG function and stress assessment methods. The purpose of the work is to determine the state of psychophysiological functions of operators of unmanned aerial vehicles (UAVs) based on indicators of electrical activity of the brain using a mobile electroencephalograph. The diagnostic complex "Diagnost-1" (M. V. Makarenko, V. S. Lyzogub) was used to determine the state of the psychophysiological functions of the respondents. The authorities' respect for the additional corrective tests using the Landolt Coil method was carried out using the second complex of psychological and psychophysiological diagnostics "BOS-test professional". The SMARTING (mBrainTrain, Serbia) mobile electroencephalographic system was used to record the electrical activity of the brain. 6 UAV operators aged 20-38 participated in the study as subjects. Based on the data of the spectral power of the electroencephalogram, the following indicators were calculated: the brain load index (defined as the ratio of the spectral power of the theta range in the frontal-central lead to the spectral power of the alpha rhythm in the parietal central lead); attention level index (defined as the ratio of spectral powers of theta and alpha range to beta and gamma range in the left prefrontal abduction); index of emotional expression (defined as the ratio of spectral power of theta and alpha range to beta and gamma range in the right temporal lobe); index of motor control (defined as the spectral power of the alpha range in the vertex central lead). Conclusions: The results of the investigation revealed that the level of respect among combat participants tended to increase during the testing period. This can indicate fatigue and limited brain capacity to adapt to stressful minds. The investigation also confirmed the connections between psychophysiological indicators and the effectiveness of the test, which indicates possible problems of adaptation to stress. These results are important for the development of effective rehabilitation methods aimed at enhancing the adaptation of combat participants to stressful situations and enhancing their cognitive functions.

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Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR187.06/LL10

Topic: I.01. Attention

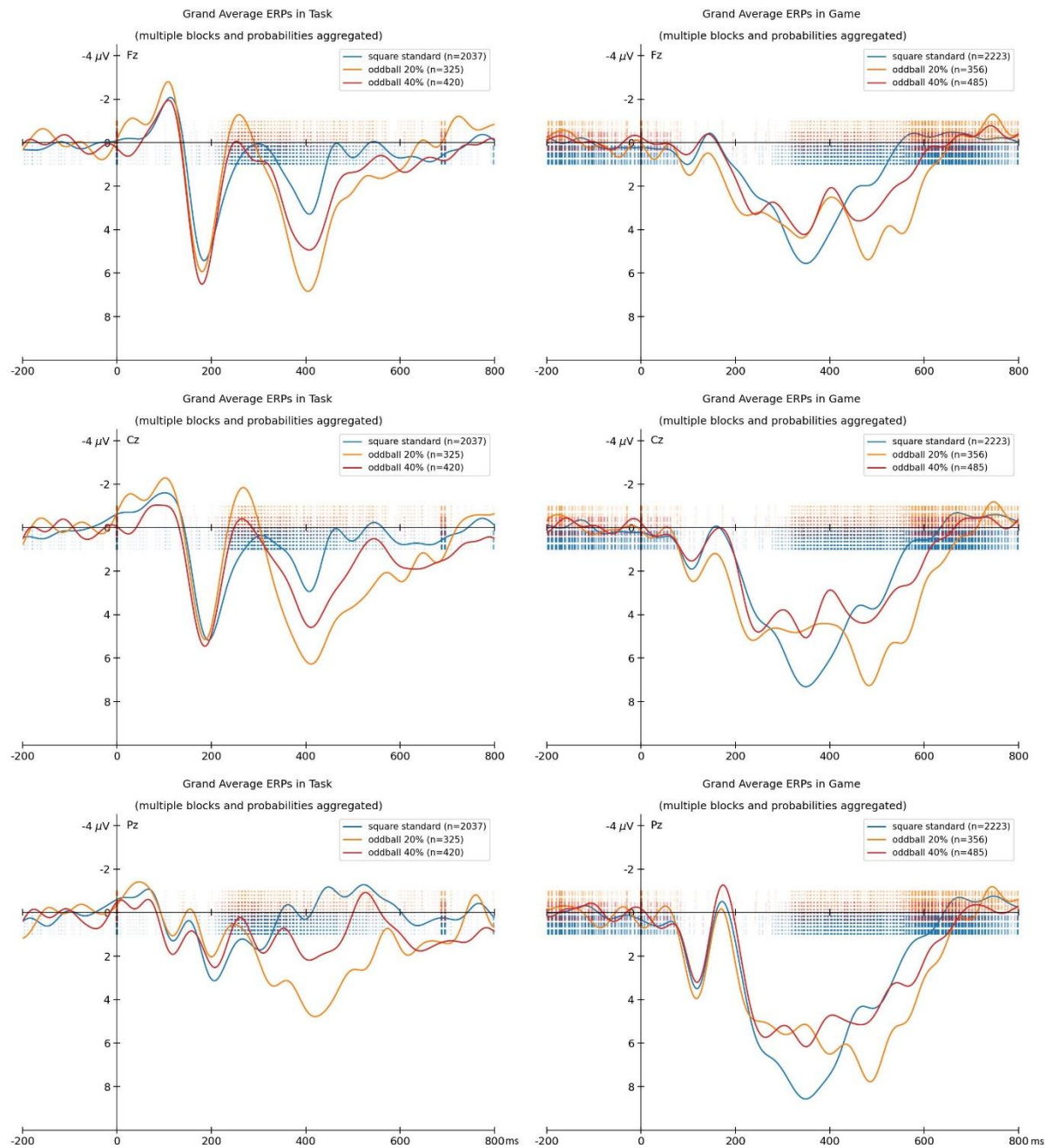
Support: NSF IIS 1817226
NSF IIS CRCNS 2208362

Title: Gaming the Brain: P300 Differences in Task vs. Game Paradigms

Authors: *A. D'AMICO¹, V. R. DE SA²;

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Abstract: Decades of human cognitive neuroscience experimentation has been conducted using parsimonious tasks. While these tasks allow for strict control of variables, they're often contrived and not representative of the complexity of everyday events encountered in modern society. Leveraging the rich history of standard tasks alongside modern computational and recording techniques as well as paradigm design concepts from experimental psychology and game design, we are well positioned to begin studying cognition with complex, naturalistic paradigms such as video games. In the present pilot study, we recorded electroencephalography (EEG) from participants (n=6) while they completed an oddball-like task designed to elicit the most well-studied event-related brain potential (ERP) component - the P3b - as well as a simple game that was designed to elicit the same events as the task. The P3b has been shown to be sensitive to various factors, most notably subjective and sequential probability. In the present study, our primary goal was to examine if the P3b's sensitivity to target-to-target intervals (TTIs) varied between the game and the task. Both the task and game had various blocks designed around a two stimulus oddball paradigm, however, blocks varied in the standard and oddball probabilities, as well as the responses required to the oddball stimuli (no response, respond once, or respond twice). While our primary goal was to investigate the TTI impacts on the P3b, we found a more striking initial finding; although the task replicates standard P3b findings, the game exhibits considerable differences, including a large P3-like component to standard stimuli and a late P3-like component to oddball stimuli that seems to be modulated by the same factors as the P3b. These preliminary findings are discussed in an attempt to explain these game/task differences by examining how they fit in P3 theory including the triarchic model (Johnson, 1986), the context updating hypothesis (Donchin & Coles, 1988), the context-closure hypothesis (Verleger, 1988), and Polich's integrative theory (2007).



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Poster

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Topic: I.01. Attention

Support: BPI I-Nov Innovation Competition grant DOS0192291/00 -
DOS0192292/00

Title: Closed-loop VR neurofeedback for cognitive recovery: arousal biomarkers and sleep deprivation study design

Authors: M. JOMAA¹, R. KHOUDRA¹, F. ZEIDAN², *M. LOUVIGNE¹;
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Abstract: Virtual Reality (VR) combined with real-time EEG-based neurofeedback (NF) holds promise for restoring cognitive function through targeted modulation of brain states. We recorded high-resolution EEG (64 channels) from 34 healthy human adults (ages 18-60; 50% female) immersed in emotionally engaging VR scenarios combining dynamic environments and affective images. Using a 7-channel EEG montage (F3, F4, C3, Cz, C4, P3, P4), we identified robust biomarkers of medium arousal, a state hypothesized to support sustained attention and optimal cognitive engagement. Feature extraction focused on advanced measures of neural dynamics and inter-regional communication, including phase transfer entropy, envelope correlation, intrinsic mode function (IMF)-based features, and weighted permutation entropy. These features, combined with an ensemble classification strategy involving 151 Random Forest models, achieved real-time arousal level classification with an accuracy of at least 73% (depending on subject), laying the groundwork for adaptive feedback and closed-loop modulation. Building on these findings, we developed a real-time NF system that integrates wearable EEG with adaptive VR environments. The system continuously estimates arousal and modulates the visual and auditory VR scene to promote and sustain a medium arousal state through immersive interaction. We are currently validating this system in a study designed to assess cognitive recovery following acute sleep deprivation. Each participant completes two sessions, each including two visits: one after a night at home of normal sleep, and one after a night at home restricted to 3 hours of sleep (validated by polysomnography and actigraphy). During the sleep-restricted visit, participants undergo a 20-minute NF session, either real or sham, in a randomized, counterbalanced, and double-blinded design. Cognitive and EEG assessments (resting-state EEG, Psychomotor Vigilance Task [PVT], and Attention Network Test [ANT]) are performed before and after each NF session. These assessments are complemented by EEG-based spectral and connectivity analyses, as well as validated mindfulness scales, including the State Mindfulness Scale (SMS) and Toronto Mindfulness Scale (TMS). Results from the biomarker study are presented here. Data from the ongoing validation study will be completed prior to the conference and presented in full at the poster session. This work supports the development of accessible, scalable neurotechnologies to enhance cognitive resilience under fatigue and stress-related conditions.

Disclosures: M. Jomaa: A. Employment/Salary (full or part-time): Healthy Mind. R. Khouadra: A. Employment/Salary (full or part-time): Healthy Mind. F. Zeidan: F. Consulting Fees (e.g., advisory boards); Healthy Mind. M. Louvigne: A. Employment/Salary (full or part-time): Healthy Mind.

Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

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Program #/Poster #: PSTR187.08/LL12

Topic: I.01. Attention

Support: U.S. Department of Defense (DoD) Hearing Restoration and Rehabilitation Program grants awarded to I.C. (HT9425-23-1-0912) National Institute on Deafness and Other Communication Disorders (NIDCD) P50 (DC000242 37) awarded to I.C., T.D.G., B.M., and Bruce J. Gantz
National Research Foundation of Korea grant funded by the Ministry of Science and ICT (RS-2024-00461617)

Title: Neurofeedback Training of Auditory Selective Attention for Improving Speech Perception in Noise: A Multi-Site, Multi-Language Study

Authors: *J. HAM^{1,2}, J. KIM³, V. VISWANATHAN⁴, H. JOO⁵, D. LUONG⁵, J. WOO⁶, B. SHINN-CUNNINGHAM⁴, I. CHOI²;

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Abstract: Understanding speech in noise is cognitively challenging, especially for people with hearing loss. Conventional hearing aids, focused on amplifying sound to ensure audibility, fail to aid listening in noisy settings, which underscores the role of central auditory processing. Auditory selective attention is a fundamental aspect of central, non-linguistic processing that modulates the neural representation to favor a target compared to background noise. Prior studies have found that individual differences in attentional modulation of cortical auditory evoked potentials (CAEP) are associated with speech-in-noise performance. Our previous neurofeedback training (NFT), designed to strengthen the attentional modulation, improved word-in-noise perception in normal-hearing English speakers. Here, we aim to investigate whether such training can generalize to speakers of different languages and to the sentence-in-noise (SiN) task. Normal-hearing English and Korean native speakers underwent three NFT sessions with a gamified audiovisual brain-computer interface. They were told to attend one of the two speech streams—a female saying "Up" five times and a male saying "Down" four times—presented simultaneously. The target speech was marked by a series of coins placed above or below a center line. According to their attentional state, decoded from single-trial EEG, the rocket icon moved up or down, either gaining or missing the coins. Before and after training, we evaluated the speech-in-noise perception via SiN tasks, where participants repeated sentences presented in multi-talker babble at various signal-to-noise ratios (SNRs). The speech corpora from QuickSIN were used and adapted for Korean speakers. After the training, attentional modulation has been strengthened, indicated by an increased attentional modulation index—the ratio of CAEP amplitude to the onsets of attended vs. ignored speech. The SiN performance, measured by the

number of accurately repeated keywords, also improved in challenging SNR conditions. These results support that NFT can enhance sentence-based speech-in-noise perception in both English and Korean speakers. Continued research on larger populations, including those with hearing loss, will contribute to the development of evidence-based rehabilitation of speech-in-noise perception, which could improve the quality of daily communication.

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Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR187.09/LL13

Topic: I.01. Attention

Title: Neurofeedback training to improve processing speed in younger adults

Authors: *A. WEBER¹, K. M. VISSCHER², K. MCGREGOR³;

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Abstract: Processing speed is defined as the amount of time it takes to extract, synthesize, and respond to presented information. Like other cognitive domains, processing speed declines with age. This age-related decline in cognitive functioning, including deficits in working memory, may be partially explained by a general slowing of information processing, though the underlying mechanisms remain poorly understood. Older adults often report difficulties with everyday tasks that require suppressing irrelevant or distracting visual information, potentially interfering with processing efficiency. A proposed mechanism by which the brain selectively inhibits irrelevant visual processing is believed to be represented by alpha oscillations (8-12 Hz) in the occipitoparietal cortex. Alpha activity, as measured by electroencephalography (EEG), can be thought of as a “sensory gate” to incoming stimuli, with increases in activity to suppress distractors and decreases in activity to enhance targets in visual attention tasks. Older adults typically exhibit less robust alpha modulation as compared to younger adults, yet limited research suggests stronger overall alpha modulation correlates with a greater ability to suppress irrelevant information. The goal of this analysis is to evaluate the effects of occipitoparietal alpha band EEG neurofeedback on cognitive performance, including processing speed, in younger adults. The baseline session consists of cognitive and behavioral assessments including a visual attention assessment utilizing EEG. Participants are randomized into either the neurofeedback group or a no-contact control group. Participants in the neurofeedback group return for three subsequent 30-minute neurofeedback training sessions involving alpha modulation using EEG. Participants in both groups repeat behavioral and visual attention assessments at their final session. We show that participants can learn to modulate alpha using our neurofeedback training

paradigm. Preliminary data in 2 healthy younger adults suggest that performance on the visual attention task and SDMT improve after training. This knowledge will contribute to the development of cognitive interventions for older adults, potentially improving functional performance in instrumental activities of daily living.

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Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

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Program #/Poster #: PSTR187.10/LL14

Topic: I.01. Attention

Title: Analysis of Longitudinal Variations in Brain Oscillations for Breath-Focus and Mantra-Based Meditation

Authors: A. LI¹, T. LIU², M. ZHANG³, B. COHEN⁵, *S. RAVISHANKAR⁴;

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Abstract: This study investigates how focused attention (FAM) and mantra-based (MBM) meditation differentially impact the longitudinal development of brain oscillations in novice practitioners. While our previous pilot studies and other research showed meditation's potential (often comparing experts to novices), less is known about how attentional focus and its neural underpinnings evolve during sustained practice of different methods. Building on our previous findings, this research, employing an enlarged cohort, seeks more definitive insights into these long-term effects.

We conducted a 6-week longitudinal study with 30 healthy college participants, screened for minimal prior meditation experience, and randomized to FAM (Breath focus meditation) or MBM (either SA-TA-NA-MA or Hare-Krishna) groups. Initial training was video-guided, followed by structured daily practice (escalating from 5-15 minutes), with adherence monitored via online journaling. A mid-point coaching check-in allowed participants to discuss progress and questions. Pre- and post-intervention 64-channel EEG data were collected during sessions that included an initial 4-min eyes-closed rest (ECR1), an 8-min group-specific eyes-closed meditation with motion (alternate nostril switching) or sound, a subsequent 4-min eyes-closed rest (ECR2), and an 8-min final silent meditation (SM) (internal mantra repetition for MBM groups, breath focus for FAM group).

Two primary spectral analyses were performed. The first, comparing post-intervention ECR1 with SM, aimed to distinguish the trained meditative state from general rest. Analysis revealed ECR1 exhibited higher individual alpha power (IAP) than SM across all groups, prominent in parietal areas. Notably, in the Hare Krishna (HK) group, SM showed lower prefrontal IAP compared to ECR1, and the individual alpha frequency (IAF) in the occipital area exhibited the most pronounced ECR1-SM differences. SM for MBM also shows reduced low-beta band power

(15-20 Hz) than ECR1 for both groups compared to BFM. The second analysis compared pre- to post-intervention SM recordings to assess training-induced neuroplasticity. While overall, pre-SM and pos-SM IAP showed non-significant difference, alpha frequencies trended slower post-training. The HK group uniquely showed a significant longitudinal increase in frontal beta band power during SM after the training period. These alpha/beta modulations and IAF shifts serve as objective markers of state differentiation and training-induced neural changes. For instance, the HK group's increased frontal beta power may suggest enhanced attentional engagement or cognitive processing.

Disclosures: A. Li: None. T. Liu: None. M. Zhang: None. B. Cohen: None. S. Ravishankar: None.

Poster

PSTR187: Human Attention in Everyday Life

Location: SDCC Halls B-H

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Program #/Poster #: PSTR187.11/LL15

Topic: I.01. Attention

Title: Quantifying improvements in cognitive skills, stress, and mindfulness from mantra-based and breath-focus meditation techniques

Authors: A. LI¹, *A. SYED², K. IKA³, B. COHEN⁴, M. ZHANG¹, S. RAVISHANKAR²;
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Abstract: With rising mental health issues in young adults, contemplative meditation practices have been gaining more attention due to their perceived effects on stress, attention, and concentration. The current study analyzes the psychological and neurophysiological impacts of three meditation techniques over a period of six weeks of training and practice: Breath-Focus (BF) meditation and Japa (mantra-based) meditation with one of two mantras: Hare Krishna (HK) or SA-TA-NA-MA (SA). The effects are analyzed against a no-meditation (NM) control group. Data on 65 healthy college students was recorded before and after the meditation intervention. Attention-related brain responses were monitored via event-related potentials (ERP) during a classical visual oddball task. Psychological outcomes were evaluated via standard self-report questionnaires: the Perceived Stress Scale (PSS), Five Facet Mindfulness Questionnaire (FFMQ), and the revised Multidimensional Assessment of Interoceptive Awareness (MAIA-2). The Wilcoxon test was used for all before-after differences, with the significance level set at .05. Prior research has shown that shorter ERP latencies are associated with increased levels of attention. The latency difference between pre- and post-meditation training showed a mean change (in ms) of -19.96, -16.5, -6.2, and 1.27 for the BF, SA, HK, and NM groups, with p values of .064, .025, .295, and >.5, respectively, suggesting improved focus in all meditating groups but not in the control group with significance reached only in SA. All meditation groups showed reduced stress (PSS) but not the NM group; only the BF group's decrease was

significant. With respect to the FFMQ, the BF group showed a significant gain in Acting with Awareness; HK improved on all subscales, but not significantly. Interoceptive awareness (MAIA-2) improved across all subscales for all meditation groups. In particular, improvements in the attention regulation, self-regulation, emotional awareness, and trusting subscales were significant for (SA), (BF, SA), (HK, BF), and the (HK, BF) groups, respectively. However, the NM group did not show significant improvement in any of the subscales. Our data suggests that even short, daily meditation sessions can yield measurable changes in underlying brain activity and mental well-being. SA meditation excelled at bolstering attention-related neural activity, while the HK and BF groups showed enhanced emotional body awareness. These results add to the emerging literature suggesting that contemplative methods can be used as low-cost and easy to implement interventions to improve mental and emotional well-being among young adults.

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Poster

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Topic: I.01. Attention

Support: ANR grant ANR-22-CE33-0009

Title: Assessing the impact of multimodal stimulation on attentional networks

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Abstract: Attentional state is constantly challenged during daily life and especially when driving. This can lead to increasing traffic accident or error judgment notably by the augmentation of fatigue, distraction, cognitive load, and even low frequencies vehicle vibration. Maintaining optimal vigilance is therefore essential for driving security. Here, we investigated whether delivering multisensory information improves the efficiency of the three attentional networks (alerting, orienting, executive control), as well as reaction time and number of responses. Building on the original Attention-Network Test (ANT) and different variants, we compared unimodal visual cues, unimodal vibrotactile cues and a combined visual and vibrotactile (multimodal) cues. 25 participants were seated on a vibrating chair and completed a modified ANT in 3 conditions: visual, vibrotactile and multimodal. Each trial began with one of four cue types—no cue, double cue, valid spatial cue or invalid spatial cue—followed by five arrows that could be congruent or incongruent. Alerting, orienting and executive control scores were computed, reaction times and accuracy were analyzed. No modality effect emerged for

alerting or executive control. However, orienting was reduced in vibrotactile condition compared to both visual and multimodal conditions and was significantly enhanced in multimodal condition compared to visual condition. Reaction times were slower in vibrotactile condition than visual or multimodal condition, which did not differ from each other. Although, accuracy was higher in the multimodal condition than either unimodal condition with no difference between them. In sum, vibrotactile condition resulted in slower reaction times, reduced orienting, and no accuracy benefit compared to vision, highlighting their limited utility when used alone. However, combining visual and tactile information preserves the rapid response times associated with visual condition while improving decision accuracy compared to unimodal conditions. Among attentional networks, only the orienting shows a graded benefit from vibration to visual to multimodal condition, indicating that multisensory redundancy specifically improve spatial orienting without altering other attentional subsystems. These findings highlight the value of multimodal integration for warning systems, as it boosts decision accuracy and spatial orienting—without compromising reaction times or other attentional functions. Future works should validate these advantages in a driving simulator and under more ecological conditions with fatigue, distraction, and realistic traffic scenarios.

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Poster

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Program #/Poster #: PSTR187.13/LL17

Topic: I.01. Attention

Title: Smartphone presence increases EEG beta activity in proportion to phone use and problems

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Abstract: We are investigating how the presence of one's smartphone influences attention-related EEG (electroencephalographic) activity. Participants are undergraduates scoring above the median on at least 2 of 3 phone-related survey measures including Phone Time (hours of usage per day), Phone Reliance (dependence on one's phone), and Nomophobia (fear of lacking functional access to one's phone). Participants first perform a classic oddball task, attending and responding to infrequent targets (oddballs) but not frequent nontargets (standards); we have found the expected P3 effect (a larger attention-related ERP component evoked by oddballs), but not the predicted attenuation of this effect in the presence of one's phone as compared to a control object. Next, participants passively view their phone (versus a control object). We observe decreased alpha activity (8-13 Hz; associated with a relaxed, inwardly-focused state) over anterior and posterior sites. We also observe a relative increase in beta activity (13-32 Hz; associated with an externally-oriented state of arousal/attention) over posterior electrode sites

that is positively correlated with participants' Phone Time, Phone Reliance, and Nomophobia. We did not, however, observe correlations between alpha or beta and self-reported attention difficulties. While these findings do not necessarily demonstrate a negative impact of smartphones on EEG correlates of attention, they do suggest recruitment of attentional resources that is proportional to phone use and related problems.

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Poster

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Program #/Poster #: PSTR187.14/LL18

Topic: I.01. Attention

Support: John A. Widtsoe Grant 2024

Title: The impact of social media consumption on sustained attention and episodic memory

Authors: *J. MCFARLANE¹, J. A. NIELSEN²;
²Psychology, ¹Brigham Young Univ., Provo, UT

Abstract: Much is still unknown about the impact of long-term social media use on human cognition. In this study, we aimed to uncover the effects of long-term social media use on human attention and memory. Participants were excluded on the basis of neurological and psychiatric conditions, history of brain injury, English non-fluency, and colorblindness. We used a time-tracking app called Stay Free to collect two weeks of mobile device social media use data from healthy young adults (n=99, 63 female; age 18-25, avg. 20.8), then compared their average daily social media consumption (min/day) to their scores on the Sustained Attention to Response Task (SART) and the Mnemonic Similarity Task (MST). These tasks were designed to quantify each participant's sustained attention and episodic memory ability, respectively. Linear regression analyses showed no correlation between social media consumption and either sustained attention score on the SART (P=0.4168) or episodic memory score on the MST (P=0.2264). We concluded that social media consumption time across a two-week period is not associated with sustained attention or episodic memory abilities in young adults. Continued research is needed to determine whether social media use differentially impacts vulnerable populations (such as individuals with ADHD).

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Poster

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Program #/Poster #: PSTR187.15/LL19

Topic: I.01. Attention

Title: Cognitive Performance is associated to the screen time and the kind of internet use in adults from a University in the South of Mexico

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Abstract: The harmonics of the neurological networks that allow accomplishing a task and thus making decisions are in a delicate balance between pathophysiology and life style. Under healthy conditions, individuals confer their neurocognitive performance to the lifestyle determinants. Diet, physical activity and cardiometabolic state are supposed to model the brain architecture from macro to microscopic view. Nevertheless, sleeping quality and screen time are believed to affect cognition, in fact, attention and memory are severely affected by extended electronic display devices exposition. In contrast, it has also been suggested that positive emotions could be enhanced in as a direct function of display exposition. In this context, in this contribution, we focused on the relation between lifestyle parameters and neurocognitive performance in adults. The methodology included an open call participation for adults with no report for previous cognitive impairment, neurological disorder or chronic degenerative diseases (such as autoimmune diseases or cancer), where 45 participants were enrolled. Anthropometric variables were documented, as well as total cholesterol, triglycerides and arterial blood pressure. Additionally, a self-administered structured questionnaire for lifestyle, a Montreal Cognitive Assessment (MOCA), Go/ No Go task (G/NG), and Hanoi Tower (HT) tests were applied. The results showed that HT errors correlate positively with screen time (TV or videos) (*Pearson's R* 0.332, *p* 0.029). A positive relation of HT errors was found with the preponderance of self-promotion in social networks (*Pearson's R* -0.316, *p* 0.039). In the case of G/NG, the time of response was prolonged in association to the use of social media, specifically to make political announcements and disseminate diverse content (*Pearson's R* 0.3, *p* 0.03). HT proved to be the most sensitive tool to assess the incidence of display exposition and internet use profile, in cognitive performance, since this test focuses in the problem-solving, planning, and memory skills from individuals, who were assumed to have a normal cognitive status, as was confirmed from total MOCA scores.

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Poster

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Topic: I.01. Attention

Support: CAPES Foundation (Brazil) – Doctoral Exchange Fellowship [PDSE Program]

Title: Neurovisceral correlates of socioemotional attention: Heart rate variability and trait empathy shape visual attention to images of suffering

Authors: *G. CAMPELO¹, D. ANJOS¹, A. ARMELIN¹, P. MOTA¹, B. KING², A. C. SKWARA², G. CASTILHO¹, R. DE MORAES JR¹, C. D. SARON²;

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Abstract: How physiological and dispositional factors interact to influence attention to suffering deserves further exploration. This study examined how heart rate variability and individual differences in empathic concern (EC) and personal distress (PD) affect visual attention to suffering and threat using an Attentional Engagement/Disengagement Task (AEDT). Fifty-two participants (69% fem., m. age = 22.16) completed the AEDT while webcam-based eye-tracking and wearable physiology was recorded. Trial-level HRV was measured as the RMSSD. The AEDT presents 56 emotional-neutral image pairs (suffering-neutral or threat-neutral) for 8s each. Engagement trials began with a central fixation cross before image pairs appeared; disengagement trials displayed the cross on the side where the emotion image would appear. For engagement trials, rolling window GLMMs revealed an $HRV \times EC \times PD$ interaction for suffering scenes from 300-1500 ms (β s: -6.53 to -13.92 , FDR- p s $< .05$). Predicted probabilities of gaze at emotion probed the interaction at $\pm 1SD$ levels. For individuals with low EC/low PD, decreased engagement occurred in high HRV trials ($z = -2.49$, FDR- $p = .013$), while for low-EC/high-PD ($z = 9.1$) or high-EC/low-PD ($z = 6.06$), more engagement occurred under high HRV (FDR- p s $< .001$). No interaction was found for high-EC/high-PD, nor for threat. For disengagement trials, there was an $HRV \times EC \times PD$ interaction for suffering, up to 400 ms, and for threat, up to 1150 ms (FDR- p s $< .05$). For suffering, high-EC/low-PD people did not disengage under low HRV ($z=2.94$, FDR- $p=.04$), while high-EC/high-PD did ($z = -3.98$; FDR- p s $< .001$). For threat, higher HRV co-occurred with disengagement for most trait levels (FDR- p s $< .008$) except for individuals with low-EC/low-PD ($z = 7.84$, FDR- $p < .001$). Modeling the 8s visualization in all trials, the $HRV \times EC \times PD$ interaction remained. For high EC/low PD and high EC/high PD, dwell time on suffering co-occurred with low HRV (FDR- p s $<.001$). For low EC/low PD and low EC/high PD, dwell time co-occurred with high HRV (FDR- p s $<.001$). Together, these results reveal that trial-level HRV fluctuations moderated attention to suffering in trait-dependent ways. HRV's relationship to attention was temporally-specific, correlating with early engagement/disengagement (300-1500ms) but also sustained dwell time (8s) in opposing directions contingent on empathy-distress profiles. These findings suggest that HRV is not uniformly related to increased attention to suffering; instead, it interacts with dispositional empathy and personal distress, potentially implicating distinct neurovisceral pathways for initial versus sustained attention to social scenes.

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Poster

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Topic: I.01. Attention

Title: Scanpath generation using a deep learning visual system model

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Abstract: Human vision is the sense that processes the most information among the five senses. Therefore, eye gaze, which facilitates visual input, serves as a significant biological indicator of an individual's mental state and encompasses aspects such as consciousness and attention. Gaze prediction technology is expected to lead to the development of methods for estimating human psychology, with applications in various research fields including commerce, medicine, and educational engineering. However, most studies on gaze prediction have failed to adequately consider the dynamics of information processing in the brain. To address this concern, we developed a deep learning visual system model based on neuroscientific findings, following a constructivist framework. The proposed model is designed to replicate the dynamic characteristics of human gaze shifts (scanpaths) using object information, such as faces and textual content present in the image, to predict areas that are likely to direct eye gaze. A retinal filter was applied to the image to represent the photoreceptor density distribution, and the variation in resolution according to eccentricity was calculated. Additionally, a recurrent neural network mechanism suitable for processing time-series information was employed to provide a working memory function. We then compared the model's predictions with the actual gaze movement data. The training outcome of the proposed model shows that gaze shifts with temporal variations occur for objects and features that rapidly capture attention within the image. The correlation coefficients between the simulated gaze distribution and actual data showed positive correlations for both the mean and median values. In assessing the dynamic characteristics of gaze shifts using MultiMatch, the scores of the proposed model significantly surpassed those of the baseline, including Itti's classical saliency map, across all indicators. The predicted trajectory of the gaze initially converged at the center immediately after the presentation of the image information and subsequently dispersed towards the periphery over time. An analysis of the amplitudes and angles of the saccades generated by the proposed model revealed that the angular profiles matched well, albeit with a slightly higher frequency of short-amplitude saccades than the actual data. These findings confirmed the validity of the scanpaths produced by the proposed model. This suggests that our model effectively relates image statistics

to the temporal characteristics of scanpaths and accurately extracts features present in the actual data, such as angles and temporal changes in gaze shifts.

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Poster

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Topic: I.01. Attention

Support: NICHD R01 HD108325-01A1

Title: Gaze entropy as a tool for understanding attention in complex learning environments

Authors: *T. MARCUS^{1,2,3}, J. KING^{2,3}, J. MARKANT^{1,3};

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Abstract: Multimedia lessons include visual features (e.g., lesson content, visual cues, videos of the instructor and students) that shape how students direct attention and learn. Lesson-relevant stimuli like instructor videos or visually cued text support learning (King et al., 2022), while peer videos are lesson-irrelevant and can distract and impair performance (Marcus et al., in prep). A common but understudied feature in multimedia learning is the video of the learner's own face (i.e., the self-face). Although the self-face reliably captures attention more than stranger faces in visual search tasks (Bredart et al., 2006), its impact in multimedia lessons remains unclear. We investigated how the presence of the self-video and visual cues impacted attention during multimedia lessons, and whether these effects depended on individual differences in selective attention. We recorded college students' (N = 68) eye movements as they viewed pre-recorded lessons comprising a slide deck with lesson content and a video of the instructor providing narration. Across lessons, we manipulated the presence of visual cues and either a peer or self-video. Participants completed a recognition memory test to measure learning and the Flanker task (Eriksen & Eriksen, 1974) to assess selective attention abilities. We computed eye movement entropy to index the randomness of participants' scanning of the visual features on the screen. Preliminary analyses indicated that more distributed scanning of the slide decks (i.e., increased entropy) related to increased learning of lesson content at a trend-level ($r(68) = .22$, $p = .066$). We also examined how gaze entropy changed when visual features were added to the lesson (visual cues, self-video, or their combination). Gaze entropy increased when at least one visual feature was added (cue, self-video, or both; p 's < .032), but these effects did not vary across feature type or interact with selective attention abilities (p 's > .220). Overall, these results suggest that adding visual features to multimedia lessons may increase gaze entropy to a similar extent, regardless of their relevance to task goals. Ongoing analyses will examine how gaze entropy and selective attention interact with each other across conditions to predict learning outcomes.

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Poster

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Program #/Poster #: PSTR187.19/MM1

Topic: I.01. Attention

Title: Monitoring mental effort during reading: Pupil diameter reflects task-evoked autonomic modulation

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Abstract: Recent advances in psychophysiology highlight the autonomic nervous system (ANS) as a central mechanism for regulating stress, attention, and emotional responses. Pupil diameter, in particular, has emerged as a promising non-invasive marker of sympathetic arousal and cognitive effort. However, its temporal dynamics and sensitivity to endogenous versus exogenous drivers remain underexplored in structured cognitive tasks. This study examined whether pupil diameter reflects task-evoked autonomic modulation during reading comprehension. Thirty-nine healthy adults (mean age = 27.0 years) completed four trials of a 3-minute silent reading task, each preceded by a 2-minute rest period. Pupil diameter and galvanic skin response (GSR) were continuously recorded. Each trial was segmented into three 1-minute phases (early, middle, late) to assess temporal effects. Linear mixed-effects modeling revealed a consistent positive association between GSR and pupil diameter across all phases, indicating robust sympathetic coactivation. Trial number negatively predicted pupil size during early and middle phases, reflecting habituation. While task accuracy was not a strong predictor overall, it contributed to individual variation, suggesting residual cognitive modulation even under adaptive physiological downregulation. These findings position pupil diameter as a dynamic index capturing both initial autonomic mobilization and sustained engagement. Importantly, the combination of pupillometry and electrodermal activity offers a multimodal framework for tracking attentional and emotional states in real time. Our study provides methodological insight into isolating cognitive demand from sensory confounds and supports future applications in neuroadaptive systems, educational monitoring, and clinical assessment of attentional control.

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Poster

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Program #/Poster #: PSTR187.20/MM2

Topic: I.01. Attention

Title: My brain predicts incoming signals in the mind wandering state, but not in the focused attention state

Authors: *A. BRAGIN;
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Abstract: Rationale. I use my brain as an investigative tool to explore electrographic correlates of mental states. **Methods.** This study used a simple paradigm. Set 1 started with a 3-minute Mind Wandering (MW) mental state, and after a click, I switched to the Focused Attention (FA) mental state for the next 3 minutes. In set 2, I remained in the MW state after the click. In set 3, I was in the FA mental state before and after a click. Global field strength (Σ), generalized frequency (Φ), spatial complexity (Ω), power spectrograms, and microstate analysis were performed to characterize MW and FA mental states. **Results.** The duration of the evoked potentials to the click was 500-600 msec. Global field strength increased at the beginning of the FA state for 8-10 seconds. At the same time, the generalized frequency decreased. Power spectra of the delta frequency band increased for 4 seconds, while the power of alpha, beta, and gamma decreased. Microstate analysis revealed that, in set 1, in addition to an increase in Global Field Power (GFP) after the click, a predictive response was observed 10 seconds before the click. This phenomenon was observed only during the MW state, but not during the FA state. These changes in GFP were accompanied by an increase in the duration of microstates B, C, D, and E, as well as a decrease in the occurrence of microstates A, B, C, F, and G. **Conclusion.** Based on the applied analysis of the EEG signal, I claim that at the steady condition, the MW and FA states are indistinguishable. There is a transition period during the switch from the MW to the FA state, characterized by an increase in global field strength and a decrease in global frequency. In the current experimental paradigm, my brain can predict a signal arriving at a 3-minute interval during a mind-wandering state, but not during a focused attention state.

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Poster

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Program #/Poster #: PSTR187.21/MM3

Topic: I.01. Attention

Support: NSF grant BCS2318984

Title: Ongoing alpha oscillations bias decision-making in willed attention

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Abstract: It is well established that ongoing alpha oscillations (8 to 12 Hz) influence visual stimulus processing. In this study, we investigated whether and how ongoing alpha oscillations biased decision making in willed attention. Electroencephalography (EEG) and functional magnetic resonance imaging (fMRI) data were recorded from participants performing a cued visual spatial attention task. Each trial started with one of three cues. Two of them instructed the participant to covertly attend a spatial location in the left or the right visual field (instructed attention). The third cue prompted the participant to spontaneously decide which spatial location to covertly attend (willed attention). Following a variable cue-target interval, the participant discriminated the spatial frequency of a grating appearing at the attended location and ignored the grating appearing at the unattended location. Subjecting the distributed pattern of EEG alpha-band power in the pre-cue time period (-500 to 0 ms) to multivariate pattern analysis (MVPA), we found that (1) for instructed attention, the accuracy of decoding the direction of attention was at chance level, as expected and (2) for willed attention, however, the accuracy of decoding the direction of attention was significantly above chance level and significantly correlated with the cue-evoked fMRI activities in the salience and the central executive networks. These results revealed that (1) ongoing alpha oscillations biased decision making in willed attention and (2) it was doing so by modulating the activity in the frontoparietal decision-making networks.

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Topic: I.01. Attention

Support: European Research Council Grant 810580

Title: Revealing the neural signatures underlying the temporal variations of flow state: an MEG study

Authors: *B. TIAN^{1,2,4}, F. GUIBERT^{2,4,5}, J. DAMAS^{2,4}, D. WANG¹, D. VAN DE VILLE^{5,3}, D. BAVELIER^{2,4};

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Abstract: Flow refers to a state of deep concentration in which performance is optimized. This state has been of high importance in the psychological literature, given its unique status in achieving extraordinary performance (Nakamura & Csikszentmihalyi, 2002). Yet, the neural bases of flow remain largely under studied (Alameda, Sanabria, Ciria, 2022). An early conceptualization, the Hypofrontality hypothesis (Dietrich, 2004) proposed reduced recruitment of top-down networks of attention during flow. More recently, taking note of its association with high reward and positive valence, Weber and Fisher (2020) have proposed a Synchronization hypothesis whereby heightened connectivity between attention and reward networks is expected. Finally, noting its intrinsic attentional nature, several authors have proposed it may be better conceived of as an effortless state of attention (Marty-Dugas & Smilek, 2019) which like other attentional states fluctuate over time (Nobre & van Ede, 2023). To capture flow fluctuations in a seamless way, we present a novel experimental paradigm combining a gamified motoric finger-pressure task with a simultaneous auditory oddball detection task. Every 25 or so trials, participants were stopped and probed with flow questions, providing a reference flow level. Through behavioral modeling, we establish a link between self-reported flow level and task performance metrics. Notably, focusing on pressing trials during which an auditory target co-occurs, we show that better pressing performance is linked to faster auditory target detection. The finding that both tasks co-vary positively is in accordance with a common state of flow. Building on these observations, we derive a computational model that predicts on a trial-by-trial basis temporal variations of flow level based on task performance. This model accurately predicts the flow levels reported at our interspersed flow probes, providing the needed data analysis framework for our subsequent MEG study. Using the same dual-task paradigm, we recorded MEG (MEGIN Oy, with 306 sensors) signals along with 3T structural MRI scans (N = 34, 22 males). For each participant, we then use the predicted flow variation vector to define time windows corresponding to higher-flow and lower-flow states. Neural comparisons between these states revealed differences in event-related fields (ERF) and time-frequency power distributions associated with the dual-task events. MEG source reconstruction based on the individuals MRI-informed head models enabled us to observe how attentional, reward and emotional valences brain networks contribute to the dynamic transitions between flow states.

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Poster

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Program #/Poster #: PSTR188.01/MM5

Topic: I.04. Executive Functions

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CityUHK SGP 9380157

Title: Relearning in a complex context refines task representation

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Abstract: In everyday life, the same task is often performed across different contexts, for example, making a decision while sitting quietly versus while driving. The theory of compositionality suggests that tasks sharing functional elements engage overlapping neural substrates. However, it remains unclear whether reusing these neural modules across contexts requires ongoing adaptation of their internal representations. To investigate this, we trained mice to perform a Go/No-Go auditory discrimination task in two contexts: a simple condition (task alone) and a complex condition (task performed concurrently with a background motor task). In secondary motor cortex (M2), we identified neuronal populations active in both contexts, consistent with reuse of compositional neural modules. To test whether the same neural representations support task processing across contexts, we trained linear decoders on neural activity from one context and assessed their ability to decode trial types in the other. Decoders trained on complex-task activity successfully generalized to the simple condition, but not vice versa. These findings suggest that learning in more demanding environments could refine task representations to support flexible performance across contexts. Such dynamic reorganization may underlie the brain's capacity to adapt task execution across contexts of varying complexity.

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Poster

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Program #/Poster #: PSTR188.02/MM6

Topic: I.03. Decision Making

Support: R00 DA047419

Title: Dopaminergic representations of behavioral flexibility

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Abstract: Midbrain dopamine (DA) signaling in the striatum is critically involved in reward-based learning and behavioral flexibility, processes essential for adapting to dynamic environments and implicated in psychiatric conditions such as substance use disorder (SUD), obsessive-compulsive disorder (OCD), and schizophrenia. Impaired behavioral flexibility is a prominent feature of various psychiatric disorders, notably substance use disorder (SUD), where

persistent maladaptive decision-making contributes significantly to continued drug use and relapse vulnerability. Understanding the neurobiological underpinnings of behavioral flexibility, particularly the dynamics of striatal DA during reversal learning, is crucial because current therapeutic strategies often lack specificity, failing to adequately address the neural mechanisms driving maladaptive behaviors. Identifying precise DA signaling dynamics could enable more targeted, effective treatments for disorders characterized by impaired flexibility. We hypothesize that phasic striatal DA release during the initial stages of reversal learning facilitates updating response-outcome associations, thus improving decision-making and adaptive behavior. To test this, we employed an operant probabilistic reversal learning (PRL) paradigm in two complementary experiments. In Experiment 1, we recorded phasic DA dynamics using fiber photometry in the dorsal striatum (DS) and nucleus accumbens (NAc) of mice expressing the genetically-encoded dopamine biosensor, GrabDA. Animals were trained to discriminate between levers with distinct reward probabilities, and once trained, the reward contingencies were reversed across the levers. We observed dynamic alterations in DS and NAc DA signaling during the early phases of reversal, indicative of DA-mediated behavioral updating. Experiment 2 employed a closed-loop optogenetic approach to causally probe the role of striatal DA during reversal learning. We selectively activated DA neurons projecting from the ventral tegmental area (VTA) and substantia nigra pars compacta (SNc) to the NAc and DS, respectively. Optogenetic stimulation during select trials during reversal learning significantly enhanced accuracy and promoted optimal choice strategies. Collectively, these findings demonstrate the crucial involvement of phasic striatal DA signaling in supporting behavioral flexibility. Such insights into DA's role in adaptive learning have significant implications for understanding and ameliorating cognitive deficits observed in disorders like SUD.

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Poster

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Title: Neural codes for world and task structure in prefrontal and entorhinal networks

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Abstract: Flexible behaviour requires representing common structure in our experiences of the world and transferring it to new scenarios. Both prefrontal regions and the hippocampal formation (including entorhinal cortices) have been implicated in these processes, with debate over the precise nature of their task and world structure representations and the conditions under which they arise. To get at this division of labour, we designed a behavioural paradigm in which animals learn many examples of a task - a repeating sequence of four goals in a grid-maze - but differ in the specific goal locations (the ABCD task). This paradigm is well suited to disentangling world and behaviour via the decorrelation of both world- and task-space distances, and the specific behavioural policies that are optimal for each task example. Recording from prelimbic cortex in mice performing the ABCD task, we find that spatial structure and task structure are combined in a single representation whereby neurons track task progress from a single behavioural step. For example, a neuron that is active when the mouse was rewarded in the central port (a spatial variable) two rewards ago (a task structure variable). Using a representational geometry approach to query the precise nature of PFC spatial tuning, we find that PFC primarily and strongly splits locations by their abstract features: the centre, corners, and locations on the cardinal axes. The overall maze topology is only recoverable when more dimensions of the neural subspace are included. Recent theoretical work suggests that medial entorhinal cortex (mEC) may represent abstract task structures and solve new examples via associative binding with place cells in the hippocampus. When we record from mEC, we do not yet see evidence of a pure task abstraction in the form of neurons (or population states) that consistently code for a particular sequence position across tasks. However, we observe that a large fraction of neurons preserve their task tuning relative to each other. While this may indicate the presence of a single task-structured ring in mEC, it is not yet clear to what extent this effect is explained by multi-peak purely spatial tuning. Future analysis of this data involving ring-rotated decoding will distinguish these two possibilities. Lastly, we present preliminary recordings from lateral entorhinal cortex, a region whose anatomical projections and multi-scale temporal coding places it as a strong candidate for holding our pure task abstraction. This work begins to tease apart how PFC and distinct entorhinal subregions differentially encode spatial and abstract task variables to support rapid generalisation.

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Poster

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Topic: I.03. Decision Making

Support: U19NS123716

Title: Altered use of prior expectations shapes behavior and neural dynamics in a mouse model of autism

Authors: *M. F. DAVATOLHAGH¹, J. COUTO¹, M. MELIN¹, L. OESCH¹, C. FINDLING², P. MORALES¹, I. HONG¹, I. BRAIN LAB¹, A. K. CHURCHLAND¹;
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Abstract: In dynamic environments, updating beliefs based on past experiences—priors—is essential for efficient decision-making. Prior utilization is often impaired in psychiatric disorders, affecting perception and behavior. We investigate how Neurexin1 α (Nrxn1 α) loss-of-function disrupts this process, providing insight into circuit deficits underlying sensorimotor dysfunction. While Nrxn1 α 's synaptic role is well studied, its impact on network dynamics - and how these neural changes translate to behavioral deficits - remains unclear. Using widefield calcium imaging, we assess cortex-wide activity in mice performing a two-choice task that requires integrating sensory evidence with prior expectations. In this task, stimulus side probabilities alternate in blocks (80:20 or 20:80), encouraging reliance on prior knowledge, especially when sensory contrast is low or absent. We find that Nrxn1 α KO mice underutilize priors in decision-making and are slower to update their choices based on feedback (WT: n=6, KO: n=6). To investigate the neural basis of this behavior, we examined cortex-wide dynamics during task performance. Nrxn1 α KO mice exhibited increased variability in cortical responses and disrupted coordination between regions, particularly between sensory and decision-making areas (WT: n=4, KO: n=3). To disentangle movement-related calcium signals from those related to task variables (e.g. stimulus onset) or cognitive signals (e.g. the strength of prior beliefs), we employed a linear encoding model. This analysis revealed that a larger proportion of neural variance in KO mice was explained by movement variables, suggesting altered sensorimotor integration. Together, our findings suggest that core computations underlying decision-making, such as integrating past experience with current evidence, depend on intact synaptic mechanisms shaped by genes like Nrxn1 α . Ongoing work will explore whether Nrxn1 α KO mice disproportionately weigh immediate sensory information over learned information (prior) indicating sensory inputs are stronger in guiding behavior.

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Poster

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Topic: I.03. Decision Making

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Title: Brain-wide neuronal computation for rule inference during flexible decision-making

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Abstract: A hallmark of intelligence is the ability to infer rule changes in the external environment and adjust behavior accordingly. However, it remains unclear how hundreds of interconnected brain regions coordinate to represent task rules and update the representations based on external feedback. In particular, it is important to determine whether rule representations are distributed across large-scale networks or confined to certain regions such as the prefrontal and parietal cortex, and the neural substrates of task feedback that enable rule inference. To address these questions, we performed high-density electrophysiological recordings using Neuropixels probes, capturing the activity of 27,457 single units across 46 brain regions in mice engaged in a rule-switching flexible categorization task. In each trial, mice need to decide whether a pure tone stimulus belongs to the low- or high-frequency category by licking left or right. The categorization rule changes across blocks of trials by shifting the category boundary between two frequency values. Well-trained mice promptly adjust their internal boundary by inferring rule changes based on behavior outcomes. Using neuronal encoding models, we found that sensory information is primarily encoded in sensory and premotor regions, whereas choice-related activity propagates extensively throughout the brain. Crucially, task-rule representations are not confined to classical association areas but are widely and hierarchically organized across sensory, motor, and higher-order regions. Prediction error signals—derived from behavioral outcome and essential for inferring rule changes—are sparsely encoded in restricted brain regions, including the lateral orbitofrontal cortex (ORBl) and the secondary motor area (MOs). These error signals span diverse temporal periods after the behavior outcome, suggesting multiple timescales for accumulating evidence and inferring rule changes. Together, our results provide a cellular-resolution, brain-wide map of rule inference computations underpinning flexible decision-making. Future work will focus on inter-regional communications by examining functional connectivity and the direction of information flow to reveal how brain networks coordinate the representation of dynamic rules.

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Poster

PSTR188: Neural Mechanisms: Adaptive Choice

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Program #/Poster #: PSTR188.06/MM10

Topic: I.03. Decision Making

Title: The contribution of the corticostriatal projections from lateral orbitofrontal cortex to choice bias in perceptual decisions

Authors: *S. C. RYU¹, C. JI¹, J. MCGUIRE³, A. J. CHRISTENSEN⁴, A. KEPECS²;
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Abstract: Adaptive behavior relies on learning from outcomes to update the value of different options and to refine the strategies that lead to success. This dual learning process—evaluating "what we want" and "how to get it"—is central to goal-directed behavior. The orbitofrontal cortex (OFC), and in particular its interaction with the striatum, is essential for calibrating how outcomes shape future actions, yet how signals carried by this circuit mediate these processes is not well understood. To address this, we trained rats to perform a hybrid perceptual and value-based decision-making task in which rats must discriminate mixtures of two auditory stimuli while the amount of water reward associated with each option vary on a block-wise basis. Subjects bias their decisions towards the side with the larger reward in proportion to stimulus difficulty. We performed in-vivo calcium imaging in freely moving rats in excitatory neurons of the lateral OFC (3 male rats, 150 neurons per rat) as well as target-specific recordings of lateral OFC neurons that project to the striatum (6 male rats, 5~0 neurons per rat). As previously observed (Hirokawa et al. 2019), we found IOFC-STR neurons characterized by sustained activity from the end of a trial up until the initiation of the next stimulus signaling positive and negative outcomes. Using unsupervised clustering, we observed additional heterogeneity in temporal dynamics of OFC neural activity during this intertrial interval when the process of outcome evaluation and action updating is likely to unfold. IOFC neurons grouped into fast-response and slow-response types for both correct and error trials. While fast-responding outcome cells were preferentially tuned to the value of the outcome, slow-responding cells responded differentially for 'switch' and 'repeat' sequences of decisions. At the population level, we were able to decode from intertrial interval IOFC activity whether the current outcome was the result of a switch or repeat. In comparison to the general population of IOFC neurons, IOFC-STR neurons were enriched for both fast and slow types of outcome cells and exhibited higher decoding accuracy. These results provide evidence that the IOFC separates information about the value of the current outcome from evaluation of the choice strategy that generated the outcome, and that this is conveyed to the striatum to mediate the IOFC's well-documented role in outcome-based learning, behavioral flexibility, and the balance between goal-directed and habitual behavior.

Hirokawa, J., Vaughan, A., Masset, P. et al. Frontal cortex neuron types categorically encode single decision variables. *Nature* 576, 446-451 (2019).

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Poster

PSTR188: Neural Mechanisms: Adaptive Choice

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Program #/Poster #: PSTR188.07/MM11

Topic: I.03. Decision Making

Support: R01NS100996

Title: Conflict and Control in the Basal Ganglia: GPi Activity Revealed by Intraoperative Recordings

Authors: ***R. SHANTI**^{1,2}, J. BOWERSOCK², T. STEWART², K. E. GARTNER², R. FERNANDEZ-GAJARDO², N. C. VAN WOUWE², J. S. NEIMAT²;
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Abstract: The globus pallidus internus (GPi) is a primary target for deep brain stimulation (DBS) in Parkinson's disease (PD) and plays a key role in both motor function and cognitive control. While its role in movement is well characterized, its contribution to processing during conflicting action impulses remains unclear. In this study, we recorded single neurons within the GPi of patients with PD while they performed the Simon task, which induces response conflict through spatial incongruence. Intraoperative microelectrode recordings were acquired during clinically indicated DBS implantation. We have preprocessed data from seven subjects with a total of 26 well-isolated single units. Spike sorting was performed using Plexon Offline Sorter with both manual and semi-automated approaches. Spiking activity was aligned to stimulus onset and movement execution. Trials were categorized as congruent or incongruent based on behavioral code markers. Stimulus-locked and response-locked spike raster plots and peristimulus time histograms (PSTHs) were generated for each unit. We applied z-score normalization using a pre-stimulus baseline (–250 to 0 ms) to compare condition-specific modulation. We conducted permutation testing across trials to assess significant differences in firing rates and performed paired t-tests. We identified a population of neurons exhibiting increased firing during incongruent trials. We are currently examining whether this includes post-response modulation, as prior LFP studies have shown shifts in GPi activity following incongruent trials. Ongoing analyses aim to further validate condition-specific effects and determine the timing and nature of GPi involvement in cognitive-motor regulation. These findings may improve our understanding of the basal ganglia's function in decision-making and inform the refinement of DBS targeting strategies.

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Poster

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Topic: I.03. Decision Making

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Title: A subcortical switchboard for perseverative, exploratory and disengaged states

Authors: *M. AHMADLOU^{1,2}, M. YASAMINSHIRAZI², P. ZHANG², I. ROGERS², J. J. DZIUBEK^{3,2}, M. YOUNG², S. B. HOER⁴;

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Abstract: Animals must flexibly adapt their behaviour to survive in dynamic environments, selecting between strategies such as persevering with a current option, exploring alternatives, or disengaging altogether. While forebrain regions have been implicated in encoding choice value and guiding optimal decisions, the mechanisms by which the brain implements distinct behavioural strategies remain unclear. Here, we identify the median raphe nucleus (MRN) as a central node for flexible behavioural control. Using cell-type-specific optogenetics, fibre photometry, and circuit tracing in mice engaged in both instinctive and learned tasks, we show that the MRN's principal neuronal populations—GABAergic, glutamatergic (VGluT2+), and serotonergic neurons—exert dissociable control over perseverance, exploration, and disengagement, respectively. Suppression of MRN GABAergic neurons, driven by inhibitory input from the lateral hypothalamus, promotes perseveration, whereas activation of MRN VGluT2+ neurons drives exploratory behaviour. Serotonergic neuron activity is required for general task engagement and is suppressed by aversive input from the lateral habenula, leading to disengagement. These findings position the MRN as a behavioural switchboard regulating alternative strategies, with implications for understanding the neural basis of flexibility and its disruption in psychiatric disorders such as depression and obsessive-compulsive disorder.

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Poster

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Program #/Poster #: PSTR188.09/MM12

Topic: I.03. Decision Making

Support: NIH R21MH126359

Title: Cerebellar inactivation effects on forebrain network connectivity and 2-cue reversal learning

Authors: *A. SINGH¹, S. VANDER DUSSEN², N. HARRIS³, P. J. MATHEWS⁴;

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⁴Neurol., Lundquist Institute/UCLA, Torrance, CA

Abstract: Roughly 500 million individuals worldwide suffer from a reduced mental capacity to adaptively shift learned behaviors to new environmental contexts, a phenomenon called cognitive or behavioral inflexibility. Loss of this ability can impose developmental delays, suicidal tendencies, and is associated with several challenging neuropsychiatric disorders in both children and adults (e.g., autism spectrum and schizophrenia). The underlying mechanisms giving rise to this behavioral phenomenon are not well understood, but changes in the normal function of forebrain areas involved in goal-directed behavior like the prefrontal, anterior cingulate, and parietal cortices, as well as the thalamus, basal ganglia, and hippocampus are postulated. Recently, cerebellar dysfunction has been implicated as a causal or at least contributing factor in behavioral inflexibility by several clinical and basic science research studies. This includes the common finding that neurons in the ‘cognitive cerebellum’ are damaged in those with mental disorders linked to behavioral inflexibility. Moreover, forebrain areas linked to behavioral flexibility are now being identified as targets of cognitive cerebellar projections, thus providing a path for the cerebellum to impact this adaptive behavior. Here we address essential knowledge gaps regarding mechanisms by which abnormal cerebellar activity contributes to behavioral inflexibility. We will use advanced approaches including chemogenetics, neuroimaging, dense electrode arrays, and a stimulus-reward reversal learning paradigm in mice. Our over-arching hypothesis is that abnormal cognitive cerebellar activity impedes downstream forebrain subregions from enabling adaptive shifts in previously learned behaviors. Prior studies and our own preliminary data link disruptions in the neural activity of cerebellar lobule VI and crus I to behavioral inflexibility. It is unclear however, whether these effects arise from: 1) a loss in essential signals needed for flexible behavior (i.e., loss of information); 2) abnormal cerebellar output that disrupts normal functions of downstream forebrain areas involved in flexible behavior (i.e., dominant negative effect); or 3) some combination of both. Here, we establish how these mechanisms of action differentially effect cognitive flexibility. Specifically, we test the hypothesis that chemogenetic suppression of Purkinje neuron (PN) activity in lob. VI decreases the rate of learning in a stimulus-reward reversal learning paradigm by altering neural output of the cerebellum. We observe that the lobule VI inhibition did not result in motor impairments.

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Poster

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Program #/Poster #: PSTR188.10/MM13

Topic: I.03. Decision Making

Support: HHMI

Title: Cognitive graphs of latent structure in rostral anterior cingulate cortex

Authors: M. MANAKOV¹, ***M. PROSKURIN**¹, H. WANG¹, E. KULESHOVA¹, S. DRUCKMANN², D. G. TERVO¹, A. Y. KARPOVA¹;

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Abstract: Mental maps of environmental structure enable the flexibility that defines intelligent behavior. We describe a striking internal representation in rat prefrontal cortex that exhibits hallmarks of a workspace for constructing goal-specific, cognitive graphs for sequences of abstract states that animals must traverse through their actions. As rats uncover — unguided — complex sequential patterns, neural ensemble activity in rostral Anterior Cingulate Cortex develops a highly structured yet compact, scalable representation anchored in states at the start and end of self-organized sequences. Graphs are organized to reflect relational similarities across contexts, and individually, permit flexible refinement of component states. The representation's crystalline organization permits instantaneous inference of the animal's current state within self-generated sequences, offering insights into the algorithmic and representational principles underlying unguided parsing of open-ended problems.

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Poster

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Topic: I.03. Decision Making

Support: R01 MH132064

Title: Neural circuit mechanisms of top-down influences on reward learning

Authors: F. M. STOLL¹, Z. R. ZEISLER², ***P. H. RUDEBECK**²;

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Abstract: Our internal goals and knowledge of the environment shape how we learn. While it has been appreciated that knowledge can be used in a top-down manner to enhance learning, the precise neural mechanisms and pathways involved remain unclear. To address this, we trained three rhesus macaques to perform a probabilistic stimulus-reward learning task in which animals learned the probabilities of receiving a juice reward associated with 3 unique stimuli in each session. Reward probabilities were systematically reversed over the course of a session and these changes in contingency were occasionally signaled using a salient stimulus, indicating that the probability changed without providing information about the new stimulus-probability contingencies. Computational modeling of macaques' choices using reinforcement learning models as well as estimation of monkeys' transitive strategy using a Bayesian framework

revealed faster behavioral change following signaled compared to unsignaled switches. This confirmed that their learning could be enhanced in a top-down manner. While subjects performed the task, we recorded the activity of more than 5,000 neurons in orbitofrontal cortex (OFC), ventrolateral prefrontal cortex (vlPFC), agranular insula (AI), amygdala and striatum using semi-chronic microdrives. We found that neurons in vlPFC/amygdala were more likely to represent the expected value of choosing the individual stimuli while OFC/amygdala neurons were more likely to encode the stimulus identity. Importantly, amygdala neurons were the first to represent the transitive strategy that monkeys employed on a given trial, while vlPFC neurons were the first to represent monkeys' change in strategy following switches. Furthermore, changes in population activity within vlPFC could be observed on the trial immediately following signaled compared to unsignaled switches, leading changes in representations within other areas. Thus, our study reveals a central role for vlPFC in mediating top-down influences on stimulus-reward learning.

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Conte Center on the Neurocircuitry of OCD MH10643

Title: Medial dorsal thalamus regulates prefrontal cortex networks and cognition

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Abstract: Brain states—distinct spatiotemporal patterns of neuronal firing and functional connectivity—shape cortical information processing. Although these states critically support cognitive operations and behavioral control, how they are regulated remains poorly understood. We investigated the function of the mediodorsal thalamus (MD) in the regulation of behavioral

states and functional connectivity in prefrontal cortex (PFC) in primates. We recorded simultaneously from MD and its mutually interconnected prefrontal areas - anterior cingulate cortex (ACC; area 24) and ventrolateral prefrontal cortex (VLPFC; area 47/12o) in monkeys as they chose among decision offers associated with different reward size, uncertainty, and informativeness (i.e., ability to resolve reward uncertainty earlier rather than later delivery of uncertainty-resolution by visual cues). We found that many MD neurons exhibited ramping activity anticipating uncertainty resolution, peaking when uncertainty was resolved by informative uncertainty-resolving cues or by uncertainty-resolving reward delivery or omission. This signal was also observed in the ACC and VLPFC, but emerged earlier in the MD, suggesting that the MD may drive PFC anticipation of incoming information. To test causality, we inactivated MD regions enriched with information-related neurons. Before inactivation, monkeys preferred offers with higher expected reward, greater uncertainty, and earlier uncertainty resolution via informative cues. Strikingly, after inactivation, their preference for uncertainty resolution (information) declined, whereas their preference for greater reward or uncertain/risky offers was relatively unchanged. Proportion of neurons preferring informative offers in the ACC and VLPFC also significantly decreased, highlighting MD's causal role in PFC computations of uncertainty-resolution (information-seeking). Also, MD inactivation altered behavioral states when the task was not on, and the monkeys passively rested. MD inactivation reduced stable eye-close rest bouts and increased transitions between eye-close and eye-open rest states. Importantly, MD inactivation significantly increased functional connectivity within and across ACC and VLPFC in a structured manner that may support the monkey's behavioral changes. To further study this issue, we constructed a computational model that illuminates these effects and reveals novel insight into the MD-PFC circuitry mechanisms. Together, these data show that the primate MD thalamus plays a causal role in coordinating long-range prefrontal network dynamics to support cognition and maintain internal states.

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Poster

PSTR188: Neural Mechanisms: Adaptive Choice

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Title: High cognitive flexibility associated with low strategy engagement across rodents and monkeys

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Abstract: Impaired decision making is a key phenotype in alcohol use disorder, which can be driven by a lack of cognitive flexibility. Cognitive flexibility is required to make adaptive, goal-directed decisions based on changing environmental conditions. Impairment in cognitive flexibility has been established as a risk factor for future alcohol use and may contribute to difficulty in abstaining from drinking after initiation. The attentional set shifting task requires mastery of multiple changing rules and has been widely used in clinical and animal models to assess cognitive flexibility. The present project resulted in the development of an analysis approach that could be applied to both rodent and monkey attentional set shifting data, allowing for translation across species. Specifically, the analysis approach used Bayesian inference to assess the utilization of different strategies to solve the attentional set shifting task. Poorer task performance was associated with a higher use of spatial strategies, while better task performance was associated with a lack of dominant strategy. Critically among the high performers, strategy use peaked partway through training but then decreased as the animals developed ways to solve the task that do not involve locking into a single strategy. This training effect was not observed in low performers, who retain high spatial strategy use. These observations are consistent across monkeys and mice. Ongoing work is focused on the cognitive flexibility consequences of alcohol consumption, comparing strategy use and task performance across alcohol naïve and post-drinking timepoints. Preliminary work suggests that prolonged alcohol drinking in monkeys facilitates reemergence of spatial strategy reliance akin to what is seen in baseline low performers.

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Title: Evidence accumulation from experience and observation in the cingulate cortex

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Abstract: We use our experiences to form and update beliefs about the hidden states of the world. When possible, we also gather evidence by observing others. For example, when choosing which restaurant to dine in, we may combine information from our last visit with testimonials from others. However, how the brain integrates experiential and observational evidence is not understood. The anterior cingulate cortex (ACC) has been implicated in a variety of cognitive and social processes, including hierarchical decision making, conflict monitoring, and reward-monitoring for self and other agents. We studied the dynamics of ACC neural activity and evidence integration in a two-player game with volatile hidden states. The game was designed such that players could benefit from integrating evidence across experiences of self and other. Each trial consisted of two phases. In phase 1, both players were presented with two arenas and each made a choice between them. On every trial, only one arena could yield reward, and the correct option changed covertly after 12-25 trials. As such players had to choose judiciously using evidence from previous trials. In phase 2, one player was randomly assigned as the “actor” and had to collect tokens in its chosen arena using a joystick, while the “observer” watched. The actor could receive reward only if it had chosen the correct arena with a probability that increased with the number of collected tokens. The observer received no reward but could observe the actor playing and the trial outcome. Both humans and monkeys successfully updated their beliefs based on the history of choices and outcomes while playing the game and observing their partner, though less effectively when observing. Electrophysiological recordings in animals revealed that ACC integrates independent sources of experiential and observational outcome into a coherent neural representation of dynamic belief about the environment's state. The geometry of population activity revealed the computational architecture of this integration and provided a neural account of the behavioral asymmetry between experiential and observational evidence accumulation. Specifically, the encoding axis of cumulative evidence was more aligned with that of self-experience than observed other-experience. Recurrent neural network modelling suggest mixed inputs of actor and observer outcome drive evidence integration. This work lays the groundwork for understanding the neural mechanisms underlying evidence accumulation in social contexts within the primate brain.

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Title: Neuronal prediction of other agents' intentions evolves over repeated social interactions to guide behavior

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Abstract: Social interactions entail complex and dynamic decision making, as social agents integrate past interactions and their outcomes to build and continuously update their representation of the ever-changing social environment. This internal model is used to predict other agents' intentions in order to inform and guide one's own behavior accordingly. While understanding the prediction of another agent's decisions is critical in both typical and atypical cognition, little is known about the neural substrate of social prediction and how it is used to guide decision making. Here, dynamic social decision-making between two social agents was studied through an iterated prisoners' dilemma game. Pairs of rhesus macaques were trained to perform this task in hour-long sessions, while electrophysiology data from the dorsal anterior cingulate cortex (dACC) was simultaneously recorded. This allowed us to probe how the neuronal representation of another agent's decisions evolves through repeated interactions, as well as how this internal model relates to dynamic cooperation behavior. By training a model to predict their partner's upcoming decision on a trial-by-trial basis using only an agent's recorded neural activity, we first evaluated how an agent's internal model of their partner's behavior adapts over accumulated interactions. We then compared this neural-based model of the other's upcoming decisions to a strictly behavioral model, trained using only past interaction history. We find that the accuracy of the neural-based model of the other's intentions significantly improves as the session progresses. Trial-by-trial analysis further reveals that the predictions of the neural and behavioral models of the other's intentions are correlated. Additionally, we find that agents are less likely to cooperate on trials where the models predict the other's upcoming decision with low confidence, and that this tendency becomes exacerbated over accumulated interaction history. Taken together, these results represent new evidence showing that the model of the other's behavior within the dACC dynamically adapts during social interactions as a function of past interaction history. They also show how macaques modulate their own behavior based on their confidence in the outcome of a social interaction.

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Poster

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Title: The thalamus reconfigures prefrontal substrates of hierarchical reasoning in humans

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Abstract: Cognitive flexibility—the ability to adapt to changing environments by shifting between different thoughts and action plans—is essential for survival. Failure to adjust effectively to changes in contingencies can lead to reduced efficiency and perseverative errors, both hallmarks of cognitive rigidity observed in psychiatric conditions such as schizophrenia. Central to cognitive flexibility is the mental representation of the external world (context representation) and the ability to track context changes, which organize the mapping between perceptual inputs and their meanings. However, the neural correlates underlying context representation and change remain unknown.

To address this gap, we collected behavioral and fMRI data from 14 human subjects (56 sessions in total) performing hierarchical decision-making tasks where the context can abruptly change. Subjects had to adjust their behavior following these abrupt context changes based on feedback. Our data revealed that the blood oxygen level-dependent (BOLD) signal pattern in the mediodorsal thalamus (MD) could decode the context, a low-dimensional latent variable representing the relationship between the perceptual cue and the task rule. In contrast, the prefrontal cortex (PFC), the cortical counterpart of the MD, decoded not the latent context but concrete task variables such as the perceptual cue and task rule. To further investigate context change, a hallmark of cognitive flexibility, we developed a Bayesian-based computational model to simulate human behavior during context changes, capturing the context prediction error. When this context prediction error was used as a regressor in the analysis of BOLD signals, a general linear model (GLM) identified a cluster in the MD with enhanced activity corresponding to high context prediction error. In fact, this thalamic region is the only brain structure that jointly encodes task context and context prediction error. Functional connectivity analysis indicates that mediodorsal prediction errors drive prefrontal reconfiguration underlying task execution. Collectively, our data highlights the unique computational role of the human mediodorsal thalamus in regulating prefrontal activity in flexible cognition.

To our knowledge, this is the first dataset to demonstrate that human MD encodes contextual representations and plays a role in switching across latent cue-to-rule mappings. Our results highlight the critical role of MD in supporting cognitive flexibility in humans.

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Topic: I.03. Decision Making

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Title: Multivoxel Patterns in the Posterior Putamen Predict Individual Differences in Habitual Control

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Abstract: Goal-directed or habitual strategies may guide instrumental actions, but the neural signatures distinguishing these modes of control remain unclear. We developed a novel outcome devaluation task and utilized fMRI with cross-subject multivariate pattern analysis (MVPA) to identify neural patterns predictive of individual differences in decision-making strategies. Healthy participants (N = 144; post-exclusions) performed a trackball-based free-operant task over 20 training blocks, followed by a devaluation manipulation and a choice test. A devaluation ratio (DR) indexed the degree of goal-directedness (DR $\approx$ 1.0) vs. habitual responding (DR $\approx$ 0.5). We categorized the participants into Goal-Directed and Habitual groups using a threshold of DR $\geq$ 2/3. We divide the participants into a Cross-Validation (MVPA) Set (N = 108, Goal-Directed = 59) to train and test classifiers and an independent Held-Out Set (N = 36, Goal-Directed = 21) (for final validation). During training, swiping rates increased and plateaued, with goal-directed participants showing steeper initial learning curves. To identify neural correlates, we applied MVPA using 4 mm spherical searchlights on subject-wise beta maps, which reflected the average voxelwise activation across all training blocks. A 4-fold cross-validated linear discriminant classifier achieved significant decoding of goal-directed vs. habitual participants within the left posterior putamen (Area Under the Receiver Operating Characteristic Curve (ROC AUC) = 0.62), confirmed using permutation-based cluster correction (Family-wise Error Rate (FWER) $p < 0.003$, and $p < 0.03$ after Bonferroni correction for 11 ROIs). This effect was specific to the left posterior putamen and not observed in other a priori ROIs or whole-brain analyses. Decoding performance generalized to the Held-Out sample (ROC AUC = 0.62, $p < 0.03$), demonstrating robust out-of-sample prediction. The decoding remained significant after regressing out motor confounds (e.g., swiping rate) and univariate activation. These findings elucidate that multivoxel patterns in the posterior putamen can decode individual differences in decision-making strategy across subjects, revealing its role in encoding stable behavioral phenotypes beyond stimulus-response mappings.

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Topic: I.03. Decision Making

Support: Hong Kong Research Grants Council (15105522)

Title: Dissociable roles of the anterior cingulate cortex and lateral frontopolar cortex in encoding counterfactual option value

Authors: *J. Y. TO, C.-K. LAW, B. K. CHAU;
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Abstract: In everyday life, we frequently encounter counterfactual options - options that we may not choose at the present moment, but we may wish to pursue at later opportunities. Past neuroimaging studies in macaques and humans have shown that the value of the counterfactual options may be encoded in the anterior cingulate cortex (ACC). Intriguingly, compared to macaques, humans show an additional signal in the lateral frontopolar cortex (FPI), a region that is uniquely well-developed in the human brain. Currently, it is unclear why in the human brain these two regions share such similar encoding and whether they have dissociable roles in influencing choice behavior. Here, we investigated the respective roles of the human ACC and FPI in decision-making involving counterfactual options in a human functional magnetic resonance imaging (fMRI) experiment (n=33). In a decision-making task, three abstract visual symbols were included, each associated with a hidden reward probability that changes over the course of the experiment. On each trial, participants were shown two stimuli, with the third stimulus being unavailable, and were asked to choose the stimulus that leads to the most reward. We applied reinforcement learning models to the participants' behavioral data to model how participants learn the reward values associated with each stimulus. We found that the double-update Rescorla-Wagner model that learns from both chosen and unchosen reward prediction error describes participants' choice behavior better than a classical single-rate model, suggesting that the values of the unchosen alternative option are inferred from feedback and influence future decisions. Next, we examined the fMRI data and focused on testing the ACC and FPI activities by regressing them against model-derived subjective values. Both regions showed similar signals related to the values of the chosen option and the more relevant counterfactual options (that was either the better one or the available but unchosen one). Interestingly, the two regions employed different frameworks encoding the counterfactual options. The difference in coding between the ACC and FPI may imply a difference in their roles in choice behavior.

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Poster

PSTR188: Neural Mechanisms: Adaptive Choice**Location:** SDCC Halls B-H**Time:** Monday, November 17, 2025, 8:00 AM - 12:00 PM**Program #/Poster #:** PSTR188.19/NN4**Topic:** I.03. Decision Making**Support:** R01AA030728**Title:** Late Error-Related Activity as a Computational Proxy for Internal Error Monitoring and Adaptive Control**Authors:** ***R. BOARDMAN**^{1,2}, P. J. BRANCALEONE², B. BARTHOLOW²;²Psychological and Brain Sci., ¹Univ. of Iowa, Iowa City, IA

Abstract: The brain's ability to detect and correct motor errors is critical for adaptive behavior. This function depends on the dynamic allocation of cognitive control in response to performance feedback. Two event-related potentials (ERPs), the frontomedial error-related negativity (ERN) and the later parietocentral error positivity (Pe), are linked to early error detection and post-error awareness, respectively. However, these signals are often studied in isolation, and their computational relationship remains poorly understood. We propose that the ERN reflects an early prediction error signal, while the Pe encodes confidence in the validity of that error. Together, these signals contribute to a dynamic internal estimate of error occurrence that supports behavioral adjustments such as post-error slowing (PES) and post-error increases in accuracy (PEIA). 172 participants (aged 14-19; 55 male, 117 female) completed a 300-trial arrow flanker task while electroencephalogram (EEG) was recorded. A regression disaggregation procedure separated between-person (average) ERP amplitudes from within-person (trial-to-trial) fluctuations. Multilevel models were conducted to assess PES and PEIA on a given trial as a function of previous-trial ERP amplitudes. Between-subject ERN amplitude significantly predicted PES ($b = -2.72$, $p = .003$), suggesting that individuals with stronger error monitoring signals slow more following errors. However, ERN amplitude did not predict trial-level PES or PEIA. In contrast, both previous-trial Pe amplitude ($b = 0.01$, $p = .048$) and between-subject Pe amplitude ($b = 0.08$, $p < .001$) significantly predicted PEIA, consistent with Pe reflecting a confidence-weighted signal that updates the internal estimate of error occurrence. A hierarchical Bayesian model formalized these dynamics by estimating a trial-wise posterior probability of error occurrence, conditioned on ERN and Pe amplitudes. Pe amplitude reliably predicted this posterior ($\beta = 0.01$, HDI = [0.01, 0.03]), whereas ERN amplitude did not ($\beta = -0.01$, HDI = [-0.01, 0.03]). The posterior variable predicted PEIA ($\beta = 1.29$, HDI = [0.69, 1.96]) but not PES ($\beta = 0.01$, HDI = [-0.01, 0.03]). These findings position the Pe as a computationally meaningful confidence signal that enables adaptive cognitive control.

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Topic: I.03. Decision Making

Title: Investigating Domain-General Neural Mechanisms of Decision-Making across Perception and Memory

Authors: *A. TSVINEV, A. PILIPENKO, J. SAMAHA;
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Abstract: Humans frequently make decisions based on either sensory input from the external environment or information retrieved from memory. The centro-parietal positivity (CPP), an event-related EEG potential, has been widely identified as a neural correlate of sensory evidence accumulation during perceptual decision-making tasks. However, it remains unclear whether this component also reflects evidence accumulation during decisions based on long-term memory. The present study investigated whether the CPP serves as a domain-general signal of evidence accumulation across both perceptual and semantic memory-based decisions. 22 participants completed 320 trials each of a perceptual and a memory task. In the perceptual task, participants discriminated between the luminance of two alphanumeric character strings across three levels of difficulty. In the memory task, participants compared the populations of two U.S. states, selected and binned into three difficulty levels using US census data. After each decision, participants rated their confidence on a scale from 1 (very low) to 4 (very high). To control for motor-related EEG artifacts, response and confidence keys were counterbalanced within subjects and tasks. Additionally, stimuli gradually ramped up over 300 ms to their final luminance levels in both tasks to minimize confounding early visual EEG activity. Critically, stimulus- and response-locked analyses revealed CPP-like components in both tasks. A 2×3 repeated-measures ANOVA on CPP slope in each time-locked analysis showed significant main effects of Task and Difficulty, along with a robust Task $\times$ Difficulty interaction and similar pattern in reaction times. Confidence ratings were significantly modulated by difficulty but showed no task-related effects or interactions. These results indicate that the CPP is sensitive to task context while still reflecting core computations shared across decision domains. Collectively, the findings support the CPP as a domain-general neural marker of evidence accumulation that adapts to the demands of both perceptual and memory-guided decisions.

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Poster

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Title: Spatial organization of effector-selective beta oscillations during perceptual decisions revealed by human intracranial EEG

Authors: ***S. GHERMAN**¹, N. MARKOWITZ², G. TOSTAEVA³, E. ESPINAL⁵, E. FREUND⁴, J. WINFIELD¹, S. JOHNSON², A. D. MEHTA⁶, S. KELLY⁷, R. G. O'CONNELL⁸, S. BICKEL⁹;

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Abstract: Voluntary movements are preceded by a gradual decrease in beta-band (13-30 Hz) oscillatory power over the sensorimotor areas, which culminates when the movement is initiated. When perceptual decisions are reported with specific movements such as a button press, beta activity recorded with noninvasive electrophysiology has been shown to track information about the ongoing decision, consistent with an effector-selective bounded evidence accumulation process. While the spatial correlates of sensorimotor beta have been mapped previously in the human brain, the extent to which these regions also track decision formation is unclear. Here, we sought to characterize the spatial organization of decision-related sensorimotor beta with high spatial precision, using intracranial EEG.

Presurgical epilepsy patients (N=19) judged the direction (up vs. down) of random-dot visual stimuli and reported their choice with a button press, in a speeded reaction time paradigm where each choice option was mapped to one of the responding effectors (left vs. right hand). In line with previous findings, effector-selective beta desynchronization was distributed across the sensorimotor areas and extended into the supramarginal gyrus, superior parietal lobule, and medial frontal regions. On average, the profile of this activity showed a gradual buildup that reached a reaction time invariant level at the time of motor response, and the rate of which was predictive of subjects' response speed, mirroring observations from noninvasive approaches. Importantly, this pattern could be observed consistently across these extended regions. Electrical stimulation data was used to categorize functionality at a subset of recording sites, confirming that this pattern was present in primary motor areas, and, interestingly, also in areas consistent with somatosensory function.

Our findings highlight the ability of intracranial EEG to spatially characterize effector-selective beta activity in the human brain and show that dynamics consistent with bounded evidence accumulation are more widespread than previously demonstrated.

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Title: The interaction between information capacity and algorithmic complexity in human decision-making

Authors: *K. LI¹, J. A. PARKER¹, J. W. KABLE¹, J. I. GOLD²;
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Abstract: Suboptimal performance on decision-making tasks is often attributed to constraints in cognitive resources, but the exact nature of those constraints is not well understood. Here we compare the effects of two types of constraints that reflect the complexity of the underlying decision process, in related, but distinguishable, ways. The first, which we term information capacity, governs the amount of information used in making a decision. The second, which we term algorithmic complexity, governs the number of computational and memory operations used to implement a decision process (or “strategy”). We propose that both factors have substantial effects on the variability of decisions across individuals and tasks, including the use of a small number of decision strategies that vary in algorithmic complexity but are each implemented across a range of information capacities.

We analyzed the behavior of human participants performing decision tasks online. Our analyses used the Information Bottleneck (IB) framework, which computes an upper bound on performance as a function of information capacity called the IB bound. Using variations of a classic inference task that involves choosing between two equally likely latent states based on some probabilistic evidence across a series of trials, we found that between-subject variation in performance could be explained largely by variation in information capacity that followed along the IB bound. In other words, for these tasks people tended to use information-efficient decision strategies, equivalent to Bayesian optimal inference corrupted with various amounts of a particular form of (logistic) choice noise.

However, a small number of participants performing those tasks tended to use more information-inefficient strategies (i.e., they fell off the IB bound). These strategies were consistent with the use of a suboptimal heuristic but similarly corrupted with various amounts of logistic choice noise. To further examine these heuristic strategies, we designed a new version of the task that uses different forms of evidence that require different degrees of algorithmic complexity to process appropriately. Preliminary results suggest that individuals prefer algorithmically simpler heuristics to more complex ones when both are equally information efficient. Furthermore, people tend to change their strategy to simpler heuristics when the task demands increase. Together, these findings allow us to better understand interactions between information capacity,

algorithmic complexity, and performance, and more generally the specific information-processing constraints that underlie bounded rationality.

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Topic: I.03. Decision Making

Title: Distinct Signatures of Naturalistic Pursuit and Avoidance in Human Intracranial Electrophysiology

Authors: *B. VAIL¹, S. KOENIG², S. M. YOO³, B. Y. HAYDEN⁴, A. B. HERMAN², D. P. DARROW²;

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Abstract: Reward pursuit and threat avoidance are fundamental building blocks of behavior which can be disrupted in psychiatric disorders. The anterior cingulate cortex (ACC), amygdala, and orbitofrontal cortex (OFC) have been shown to anticipate rewarding and threatening outcomes, but ongoing pursuit and avoidance of these outcomes are rarely assessed with naturalistic tasks or invasive recording in humans. The objectives of this study are to define behavioral states of pursuit and avoidance, and to characterize differences in ACC, amygdala, and OFC activity in humans during these states. Local field potentials (LFP) were recorded from the ACC, amygdala, and OFC of neurosurgical patients during a task in which they simultaneously pursued “prey” and avoided “predators”. Pursuit (PRS) was defined by player trajectories more similar to the player-to-prey angle than to the predator-to-player angle. Avoidance (AVD) comprised trajectories that were more similar to the latter. Hilbert analytic amplitude (HAA) was extracted from single-trial LFP for the gamma (30-150 Hz), beta (13-29 Hz), and theta/alpha (4-12.5 Hz) bands, then aligned to the beginning of PRS/AVD epochs. Each timepoint from -250 to +500 ms of epoch onset was analyzed using a linear mixed effects model with HAA as a function of PRS-vs-AVD and random effects for subjects and channels. Windows of adjacent time points with $p < .05$ (cluster-based permutation testing, Bonferroni correction) were considered to differ significantly between PRS and AVD epochs. All PRS and AVD results are reported relative to AVD and PRS, respectively, rounded to 50 ms. In ACC (9 subjects, 74 channels), gamma power was elevated -250-200 ms before AVD onset and increased periodically throughout AVD - decreasing at corresponding times during PRS. Beta power increased at +100-150 ms of AVD, while theta/alpha power increased after +250 ms of PRS. In the amygdala (13 subjects, 89 channels), gamma power decreased at AVD onset (+50 ms), then sharply peaked at +250 ms. Beta and theta/alpha power decreased at +350 ms of AVD. In OFC (11 subjects, 156 channels), gamma power preceding PRS was consistently lower than AVD,

converged with AVD at epoch onset, and repeatedly decreased during PRS - increasing at corresponding times during AVD. Beta power decreased -250-100 ms prior to PRS and alternately increased and decreased throughout AVD. Theta/alpha power decreased after +200 ms of AVD. These divergent activity patterns, absent of experimental cues, point to distinct neural states underlying naturalistic pursuit and avoidance. The use of human intracranial data additionally enhances the study's potential for psychiatric translation.

Disclosures: **B. Vail:** None. **S. Koenig:** None. **S.M. Yoo:** None. **B.Y. Hayden:** None. **A.B. Herman:** None. **D.P. Darrow:** None.

Poster

PSTR188: Neural Mechanisms: Adaptive Choice

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR188.24/NN9

Topic: I.03. Decision Making

Support: MVLS DTP
BBSRC, BBN010956/1

Title: Shared Spatial Generators but Distinct Temporal Dynamics in Perceptual Decisions and Physical Inference

Authors: ***B. MONTABES DE LA CRUZ**, L. S. PETRO, L. MUCKLI, M. G. PHILIASTIDES;
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Abstract: Physical inference - our ability to predict future states of objects based on internal computations - is thought to depend on a frontoparietal network that overlaps with regions implicated in perceptual decision-making tasks, where participants rely on external sensory information. We investigated whether physical inference decisions engage similar accumulation-to-bound mechanisms as those established in perceptual decision-making. We conducted an EEG study (N=31) using both a perceptual decision-making task and a physical inference task. The perceptual task used a dynamic face-vs-categorization task, while the physical inference task involved briefly presenting images of tower blocks designed to be physically unstable—collapsing to the left or right under the force of gravity. Each tower was shown prior to collapse for 300ms, and participants were asked to predict the future collapse direction (left/right). We manipulated task difficulty by varying the percentage of image phase coherence in the face-vs-car task, and the proportion of tower blocks biased towards left-vs-right collapse direction. We first applied a multivariate decoding analysis on response-locked EEG data from the perceptual task, which identified spatial electrode weights giving rise to a time-resolved build-up of activity in a central-parietal positivity electrode cluster. To test the extent to which accumulation-to-bound dynamics observed in perceptual tasks also emerge in physical inference decisions, we subsequently applied these spatial weights on response-locked data from the physical inference

task (i.e. cross-decoding). We identified significant cross-decoding within a transient window - rather than a gradual build-up of activity - centered around 340 ms prior to the response. Our findings suggest that physical inference may recruit similar spatial generators to those involved in perceptual decisions but the underlying decision-making mechanisms might not involve the same continuous temporal integration processes. We propose that this difference may reflect the top-down nature of physical inference—driven by internal models and predictive simulations—as opposed to the more bottom-up sensory-driven processing characteristic of classic perceptual decisions.

Disclosures: B. Montabes de la Cruz: None. L.S. Petro: None. L. Muckli: None. M.G. Philiastides: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.01/NN10

Topic: I.04. Executive Functions

Support: NSF CAREER BCS-2048066

Title: Sensory-biased processing dissociates association networks

Authors: *K. ZENDEHROUH KERMANI¹, Z. LADWIG³, E. HOUSTEAU³, M. E. MITCHELL², N. R. LABORA⁵, G. WULFEKUHL⁵, J. HERNANDEZ⁴, M. DORN⁴, C. GRATTON²;

²Psychology, ¹Univ. of Illinois Urbana-Champaign, Urbana, IL; ³Northwestern Univ., Chicago, IL; ⁴Northwestern Univ., Evanston, IL; ⁵Florida State Univ., Tallahassee, FL

Abstract: Precision fMRI has provided insights into how large-scale functional networks divide into smaller subcomponents, including dividing the traditional “dorsal attention network (DAN)” into DAN-A and DAN-B components (Du et al., 2024). Here, we set out to examine functional distinctions between these two networks. We hypothesized that the sub-networks may differentially exhibit amodal versus modality-preferential (auditory or visual) cognitive control signals, based on comparisons to prior work on dissociable visual and auditory-biased higher-order processing regions in the PFC and parietal cortex (Michalka et al., 2015; Noyce et al., 2017). We collected a dataset of 10 highly-sampled participants (5 female, ages 18-33), each of whom completed over 2 hours of resting-state fMRI, ~36 minutes of a Visual and Auditory Sustained Spatial Attention task (Michalka et al., 2015), and ~36 minutes of a Visual and Auditory Working Memory task (Noyce et al., 2017), in addition to a number of other tasks. We then compared individuals' task activations with their functional network organization, based on individualized network maps derived from resting-state fMRI data. Individuals' visual-biased attention and working memory regions corresponded with the spatial arrangement of their DAN-B subnetwork across all participants. We did not observe a differential activation in DAN-A

based on modality, providing a dissociation between these two sub-networks. Future steps include further examination of the correspondence between auditory-biased regions and individual functional network organization, as well as investigation of which task demands recruit DAN-A over DAN-B. This work suggests that the DAN-A and DAN-B subnetworks are functionally dissociable, with the DAN-B being preferentially recruited for visual-biased higher-order processing. These findings advance our understanding of the functional specialization of association networks within individuals, suggesting a relative hierarchy of modality preference within the dorsal attention network.

Disclosures: K. Zendehrouh Kermani: None. Z. Ladwig: None. E. Housteau: None. M.E. Mitchell: None. N.R. Labora: None. G. Wulfekuhle: None. J. Hernandez: None. M. Dorn: None. C. Gratton: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.02/NN11

Topic: I.04. Executive Functions

Support: NSF Grant

Title: Functional Neuroarchitecture of Brain Activation and Network Organization in Bilinguals During Native and Second Language Processing

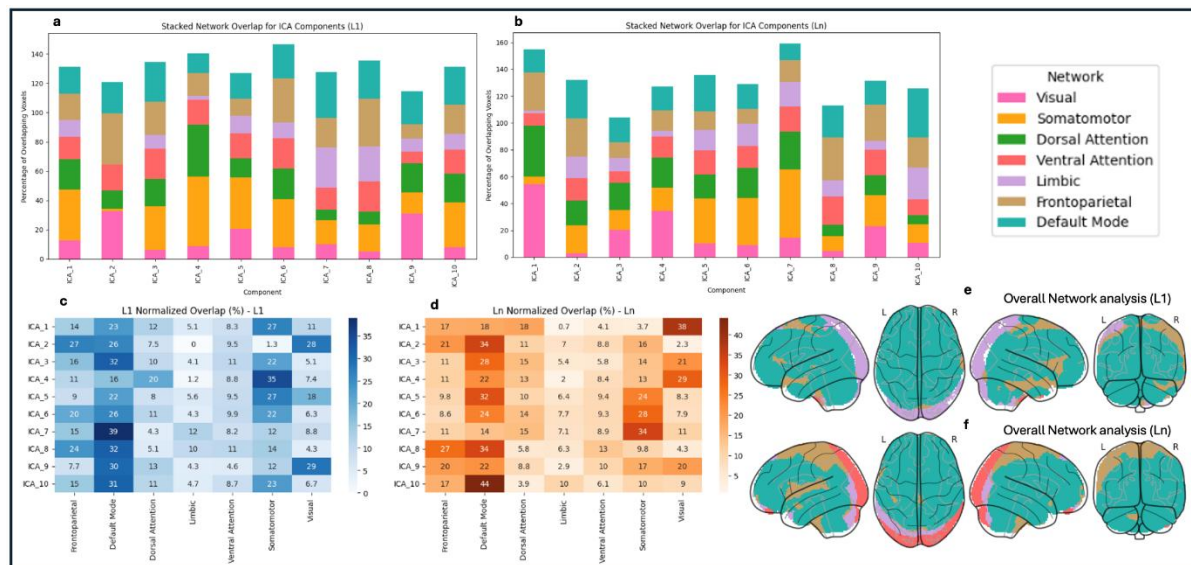
Authors: *O. R. NARAYANA MUDALIGE DON¹, J. SANCHEZ¹, A. SHEPHERD¹, L. L. OWEN²;

¹Computer Sci., ²Psychological and Brain sciences, Univ. of Montana, Missoula, MT

Abstract: Understanding how the brain processes language in both primary and secondary languages is essential for unraveling the neural mechanisms of bilingualism and language learning. In this study, we investigate how bilingual speakers with a primary language of Spanish (L1) and secondary language of Basque (Ln) recruit large-scale brain networks while performing a semantic animacy judgment task. Using Independent Component Analysis (ICA) and Yeo 7-network parcellation (Yeo et al., 2011), we examined functional brain activity patterns associated with L1 and Ln to explore differences in network engagement during second language use. We analyzed an open fMRI dataset from 34 Spanish-Basque bilingual adults (Gurunandan et al., 2019). Participants completed six runs of a semantic task in both Spanish and Basque, classifying words as living or non-living using button presses. Functional images were preprocessed and analyzed using Nilearn's CanICA algorithm (n components = 10) (Abraham et al., 2014). ICA components were mapped onto the Yeo 7-network parcellation to identify engaged brain networks and compare L1 vs. Ln processing.

Results showed that second language (Ln) processing elicited broader and distinct patterns of brain network engagement compared to native language (L1). While both languages activated

core networks such as the Default Mode Network (DMN), Ln use was marked by increased recruitment of visual, ventral attention, and control networks, and decreased somatomotor involvement. Observed differences are shown in stacked overlaps (Fig. 1a-b), network heatmaps (Fig. 1c-d), and cortical maps (Fig. 1e-f). These findings suggest that second language use, especially in less-proficient speakers, involves a shift in network dynamics—marked by increased cognitive demand and reduced articulatory efficiency. The results underscore the adaptability of the brain in response to bilingual language demands and emphasize the role of attentional and sensory networks in supporting Ln comprehension (Tao et al., 2021).



Disclosures: O.R. Narayana Mudalige Don: None. J. Sanchez: None. A. Shepherd: None. L.L. Owen: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.03/NN12

Topic: I.04. Executive Functions

Support: INBRE Grant P20GM103474

Title: Quantifying network dynamics with archetypes

Authors: *L. L. OWEN¹, E. F. STONE²;

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Abstract: Disentangling how the brain supports narrative comprehension under varying conditions remains a fundamental question in cognitive neuroscience. In this study, we use Archetypal Analysis (AA) to investigate differences in brain activity during an fMRI task (Simony et al., 2016) that manipulates the coherence of auditory input: participants listen to a spoken story presented either intact or scrambled at multiple temporal resolutions (paragraph and word) or scanned during rest. AA, a geometric, unsupervised learning method, identifies extremal activation patterns—or “archetypes”—that capture dominant modes of brain activity across the dataset. By projecting each condition's fMRI data onto a common archetypal space, we uncover latent neural profiles associated with high-level comprehension (intact story) versus disrupted or low-level processing (scrambled conditions) or rest. Our results reveal that intact narrative comprehension engages a distinct set of archetypal brain states, particularly within the default mode network and language-selective regions, while scrambled conditions elicit alternative archetypes reflecting more sensory-driven or fragmented processing. These findings demonstrate how AA can expose the structure of cognitive state differences in naturalistic tasks, offering a compact and interpretable framework for modeling the neural basis of language comprehension.

Disclosures: L.L. Owen: None. E.F. Stone: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.04/OO1

Topic: I.04. Executive Functions

Support: MH122066
MH096773
MH129616
MH121518
NS110332
MH121276
MH124567

Title: Identifying novel functional brain networks in individuals using precision functional mapping

Authors: *A. DWORETSKY¹, D. J. NEWBOLD¹, A. N. NIELSEN¹, R. J. CHAUVIN¹, A. C. MEYER¹, S. M. NELSON², A. Z. SNYDER¹, S. MAREK¹, T. O. LAUMANN¹, N. U. F. DOSENBAACH¹, E. M. GORDON¹;

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Abstract: Recent work using functional MRI (fMRI) to investigate the organization of the human brain has revealed a set of robustly validated large-scale functional systems that are

largely conserved across individuals. Network templates derived from group-average data are often used to identify these canonical systems in new individuals. However, such templates may fail to capture important individual-specific variation in brain networks, particularly in highly variable regions like the temporoparietal junction (TPJ) and lateral frontal cortex. Further, recent work in individuals has described novel network structures in both association and primary cortex, suggesting that other network structures may remain unrecognized. However, canonical network templates by definition cannot be used to identify novel or unknown networks. Here, we developed a framework to identify novel functional networks in individuals using a combination of template-constrained and data-driven methods. Using precision functional mapping (PFM) data from 16 healthy controls across three datasets, each with ≥ 2 hours of resting-state fMRI, we first adapted a template-matching approach to assess how well each cortical location in an individual corresponded to each of 19 canonical network templates. This approach revealed not only the regions with an expected strong match to a known network, but also regions without a strong match to any known network. These low-match network patterns were then clustered within and across individuals to identify novel, previously unknown networks.

The clustering analysis identified both novel networks that were spatially consistent in many individuals ("commonly unknown" networks) and others that were observed in only one or very few individuals ("idiosyncratically unknown" networks). Commonly unknown networks appeared in regions such as the TPJ and lateral frontal cortex, and in some cases spatially overlapped with existing task-based descriptions of functional responses (e.g., vision and language). Idiosyncratically unknown networks exhibited a wide distribution throughout association cortex. These findings highlight the limitations of predefined canonical network templates in capturing the diversity and hierarchy of functional network organization. Importantly, idiosyncratically unknown (individually unique) networks may represent an important and previously unrecognized correlate of individual behavioral variability. These results demonstrate the value of refining existing network definitions and offer a principled approach to achieving more complete and individualized descriptions of functional brain organization.

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Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

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Program #/Poster #: PSTR189.05/OO2

Topic: I.04. Executive Functions

Support: NIH Grant PA19091

Title: How Integrated Uncertainty Modulates Thalamocortical Functional Connectivity for Cognitive Flexibility

Authors: *S. E. STOKES, S. LEACH, K. HWANG;
Psychological and Brain Sci., Univ. of Iowa, Iowa City, IA

Abstract: Flexible cognition requires that actions and decisions be determined by multiple sources of information, which may include sources from latent cognitive states and external sensory inputs. These information sources are often stochastic and carry uncertainty, yet it remains unclear how such uncertainty modulates the brain's communication architecture. Here, we address this question with a particular focus on the thalamus, a network hub structure we hypothesized both detects uncertainty in task-relevant signals and exerts widespread influence over cortical processing through its connectivity profile. We developed a cognitive flexibility paradigm in which human participants integrated latent cognitive representations and sensory evidence to select one of two tasks on each trial. A computational model provided trial-by-trial estimates of uncertainty of both the latent cognitive representation as well as the sensory cue. Critically, the combined uncertainty of these inputs can be calculated with a trial-by-trial entropy. These trial-by-trial regressors can be used to determine whether the thalamus responds to uncertainty and can be used as a covariate for functional connectivity analysis. Fifty-nine participants underwent 3T fMRI scanning while performing the task. First, we found that uncertainty is robustly encoded in medial and posterior thalamic nuclei. This is consistent with our prediction that the thalamus is well positioned to detect and encode uncertainty from multiple sources given its connectivity architecture. Next, we implemented a customized beta-series functional connectivity analysis: for each trial, we extracted beta estimates from thalamic seeds and from cortical regions of interest (the fusiform face area [FFA] and parahippocampal place area [PPA]) and regressed their coupling on the entropy regressor as an interaction term. We observed that higher trial-by-trial entropy predicted strengthened functional connectivity between thalamic regions and both the FFA and PPA. These findings indicate that the thalamus not only monitors uncertainty across input information streams but also dynamically adjusts its interactions with task-relevant cortical regions in response to that uncertainty. This thalamocortical interaction mechanism may enable flexible reconfiguration of large-scale networks to promote cognitive flexibility.

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Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

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Program #/Poster #: PSTR189.06/Web Only

Topic: I.04. Executive Functions

Support: TÜBİTAK Grant 120K924

Title: The demands of beginning of extended tasks are categorically different from control demands during their subsequent execution

Authors: *A. YAZICI¹, A. A. FAROOQUI²;

¹Psychology, ²Psychology, Bilkent Univ., Ankara, Turkey

Abstract: Goals are typically achieved through extended tasks. While numerous previous studies have shown that frontoparietal multiple-demand (MD) regions activate during the execution of such tasks, what happens at the beginning of these tasks is unclear. This is important because starting extended tasks involves configuring cognition in relation to the entirety of the ensuing task, a key additional demand compared to their subsequent execution. We investigated the response of brain regions to this demand. We had participants who either executed a loosely organized sequence of nine 3-back trials (Group 1) or a well-defined extended task where nine similar trials had been cohered towards a defined goal - counting the total number of 3-back repeats. We found that while the beginning of the loosely organized trial sequence activated MD regions, that of the defined extended task deactivated them, suggesting that starting an extended task may have unique demands that deactivate MD regions. We then tested this thesis through a third group of participants who executed an identical but less demanding, well-defined task requiring keeping a count of 2-back repeats across six trials. In line with the above thesis, beginning these tasks deactivated MD regions less compared to beginning the 3-back extended task (Group 2) but more compared to beginning the 3-back trial sequence (Group 1). These findings suggest that the beginning of extended tasks may involve a distinct kind of domain-general demands compared to those involved in the subsequent execution of such tasks, which are known to activate MD regions.

Disclosures: A. Yazici: None. A.A. Farooqui: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.07/OO3

Topic: I.04. Executive Functions

Title: Using Connectome-based Predictive Models to understand executive function contributions to the attentional blink and N-back paradigms

Authors: *Y. D. CHUA¹, A. P. WONG², C. L. ASPLUND¹;

¹Yale-NUS Col., Singapore, Singapore; ²Univ. of Queensland, Brisbane, Australia

Abstract: Executive functions (EFs) are essential to cognition, in that they rely on the successful control of the encoding, filtering, manipulation, and formation of memories to achieve behavioral goals. Two visual paradigms that have been used to study EFs are the N-back and the Visual Attentional Blink (VAB). Poor scores on these tasks have been attributed to a failure of working memory control. Here, we used Connectome-based Predictive Models (CPMs) of fMRI-

based functional connectivity (FC) to investigate how the coordination of brain networks associate with individual differences in task scores. The study consisted of three main parts. We first tested whether FCs could predict individual differences in task scores reliably. To do so, we constructed CPMs of VAB and 2-back from three datasets that successfully predicted behavioral scores from their corresponding task-based FCs. There were: 1) VAB CPM ($r_s=0.31$, $p=.011$, $n=73$) using Wu et al. (2020)'s dataset, 2) 2-back CPM ($r_s=0.48$, $p<.001$, $n=2252$) using Adolescent Brain Cognitive Development Study's dataset (ABCD; Casey et al., 2018) FCs from Chen, Tam et al. (2022), and 3) 2-back CPM ($r_s=0.39$, $p<.001$, $n=773$) using Human Connectome Project - Young Adults (HCP-YA; Van Essen et al., 2013) FCs from Ooi et al. (2022). We then tested the generalizability of the models by applying them across datasets. The Wu et al. (2020) VAB CPM predicted 2-back scores from the ABCD dataset modestly ($r_s=0.05$, $p=.014$). The 2-back CPM trained on the ABCD predicted VAB scores from Wu et al. (2020) non-significantly ($r_s=0.13$, $p=.29$). Finally, we characterized the patterns of predictive networks underlying the tasks. To do so, we compared the top 10% and bottom 10% predictive network edges across CPMs. The top 10% of VAB CPM edges from Wu et al. (2020) and ABCD overlapped significantly at 17.7%, and the corresponding bottom 10% overlapped significantly at 12.4%. Here, we found that inter-network edges between Default and either Salience Attentional (SA) or Somatomotor (SM) regions predicted higher VAB and 2-back scores. On the other hand, negative scores were predicted more by edges within Dorsal Attentional (DA), as well as between DA and either SA or SM regions. In sum, our findings are dissimilar from our initial hypothesis, such that coordination across networks underlie successful predictions of executive function tasks.

Disclosures: Y.D. Chua: None. A.P. Wong: None. C.L. Asplund: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

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Program #/Poster #: PSTR189.08/OO4

Topic: I.04. Executive Functions

Support: World Premier International Research Center Initiative (WPI), MEXT,
Japan
IRCIN-Daikin SCP

Title: Enhancing Brain Flexibility for Divergent Thinking: Creativity Potential Network and Oxygen-Based Modulation

Authors: *Y. T. HUANG^{1,2}, T.-L. LIU², C.-T. WU³, Z. C. CHAO²;

²Intl. Res. Ctr. for Neurointelligence, ¹Univ. of Tokyo, Tokyo, Japan; ³Dept. of Occup. Therapy, Univ. of Florida, Gainesville, FL

Abstract: Creativity is often defined as the ability to generate ideas that are both novel and useful. As artificial intelligence continues to demonstrate capabilities in solving complex problems, understanding the unique mechanisms underlying human creativity becomes increasingly important. Furthermore, oxygen inhalation has been shown to facilitate not only physical performance but also cognitive processes. However, little is known about how creative potential is represented in resting-state brain dynamics (Study 1) and influenced by oxygen intervention (Study 2). In Study 1, 49 participants completed the Alternative Uses Test (AUT), a measure of divergent thinking that asks participants to generate unusual uses for everyday objects. Resting-state 128-channel EEG data were recorded before each trial. The novelty and feasibility of each response were evaluated using an automated GPT-based method, which was then used to categorize EEG power and coherence. We find that interactions between brain regions, rather than activity within individual regions, are significantly associated with subsequent creative performance. Specifically, higher degree centrality in theta-band functional connectivity within the right parietal and occipital regions is associated with greater novelty, while degree centrality in the right middle and inferior frontal areas is linked to more feasible responses. To our knowledge, these findings are the first to identify the Creativity Potential Network (CPN) that predicts upcoming creative performance in two distinct domains. In Study 2, 34 participants were randomly assigned to inhale either high-concentration oxygen (n = 18) or normal air (n = 16) for one minute before each of six out of 30 AUT trials. We find that exposure to short pulses of high-concentration oxygen significantly enhances the novelty of answers while preserving their corresponding feasibility. Notably, the oxygen group shows significant improvement in low-novelty responses, with only marginal gains in already high-novelty responses. This “lower-bound” enhancement is also reflected in CPN, showing increased theta-band coherence during trials that yield the low-novelty solutions. Together, these studies highlight the promise of using neural markers to monitor, and high-concentration oxygen to enhance creative performance, suggesting potential applications for neurofeedback systems in real-world settings such as the workplace.

Disclosures: Y.T. Huang: None. T. Liu: None. C. Wu: None. Z.C. Chao: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.09/OO5

Topic: I.04. Executive Functions

Title: Does the drummer's brain work differently?

Authors: *O. T. BAYAZIT;

Physiol. and Biophysics Dept., Istanbul Aydin Univ. Fac. of Med., ISTANBUL, Turkey

Abstract: This study aimed to compare the neuroelectrical activity of drummers and non-musicians during the basal session to investigate the neuroelectrical basis of artistic creativity

using a brain dynamics and psychophysiological approach. Fifteen drummers and 15 non-musicians participated in this study. The EEG of the participants was recorded from the prefrontal and central regions of the brain. The EDA was obtained via disc electrodes placed on the little and ring fingers. Electrophysiological recordings were made during the basal, drumming, and listening sessions in drummers and only during the basal session in non-musicians. EEG was analyzed in the alpha1 (α_1 ; 8-10.5 Hz), alpha2 (α_2 ; 10.5-13 Hz), beta1 (β_1 ; 13-20 Hz), beta2 (β_2 ; 20-30 Hz), and gamma (γ ; 30-40 Hz) frequency ranges. The basal EDA of the drummers was lower than that of the non-musicians ($p < 0.01$). Prefrontal α_2 , prefrontal, and central β_1 and β_2 in drummers were found to be higher than in non-drummers in the basal session ($p < 0.001$). The drummers had higher α_2 and β_2 during the performance ($p < 0.001$). A comparison of the bilateral electrodes shows that the basal C3 γ of non-musicians was smaller than C4 ($p < 0.01$). The baseline α_1 in C4 was higher than C3, and the C3 β_2 was higher than C4 in the drummers ($p < 0.05$; $p < 0.01$). Having lower EDA in drummers may be an indication that drummers who are prepared for the stage and show exhibit lower excitement and emotional excitability in the basal state. Having a high α_2 may be considered an indicator of memory, attention, or artistic creativity in drummers. The increase in α_2 and β_2 during performance may be due to the complex movements required to compose the rhythm of the music. The lower γ in C3 in the basal may be due to the dominance of the hemisphere of right-handed non-musicians. The higher Fp2 δ may be due to the processing of memory, signal detection, decision making, and updating of memory during the predominant processing of tonal transition information in the right hemisphere during the listening of music in right-handed drummers.

Disclosures: O.T. Bayazit: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.10/OO6

Topic: I.04. Executive Functions

Support: R00 MH125021

Title: Deviation from scale invariant brain criticality increase with cognitive effort

Authors: *L. LIM¹, A. WESTBROOK²;
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Abstract: Scale-invariant activity indicates proximity to criticality in the brain, with implications for how flexibly the brain responds to cognitive demands. We applied d_2 , a metric quantifying deviation from brain criticality in terms of scale invariance (Sooter et al, 2024), to EEG data from a task-switching paradigm and n-back working memory task. First, we validated d_2 as an indicator of distance to criticality in oscillatory systems by simulating critical dynamics with a neural mass model. Second, we tested for changes in d_2 as a function of task load and task

performance in our data. In the task-switching paradigm, trials were either regular (repeat) or switch types (targeted switch, distractor, voluntary switching). Following stimulus onset, d_2 was lower in regular trials than in switch trials, suggesting that engaging in more demanding switch trials involves greater deviation from scale invariance and brain criticality. Performance metrics revealed contrasting relationships: in regular trials, operating closer to criticality was linked to higher accuracy and faster responses, reflecting efficient, stable processing. In switch trials, deviating farther from criticality was linked to improved accuracy, suggesting that deviating from criticality supports successful switching. Additionally, faster responses in switch trials but slower responses in regular trials were associated with greater d_2 before stimulus onset, indicating that shifts in brain dynamics may facilitate more vigorous behavioral engagement in switch trials but maintaining scale-invariant dynamics may be more optimal for executing default tasks. Similarly, we showed increased d_2 with increasing load in n-back task, consistent with the previous finding of greater deviation from criticality with rising cognitive demand. Together, these results suggest that the d_2 metric offers a scale-sensitive marker of how neural dynamics adaptively shift with cognitive control demands and effort exerted on control demanding tasks.

Disclosures: L. Lim: None. A. Westbrook: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

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Program #/Poster #: PSTR189.11/OO7

Topic: I.04. Executive Functions

Support: Masonic Cross-Departmental Award

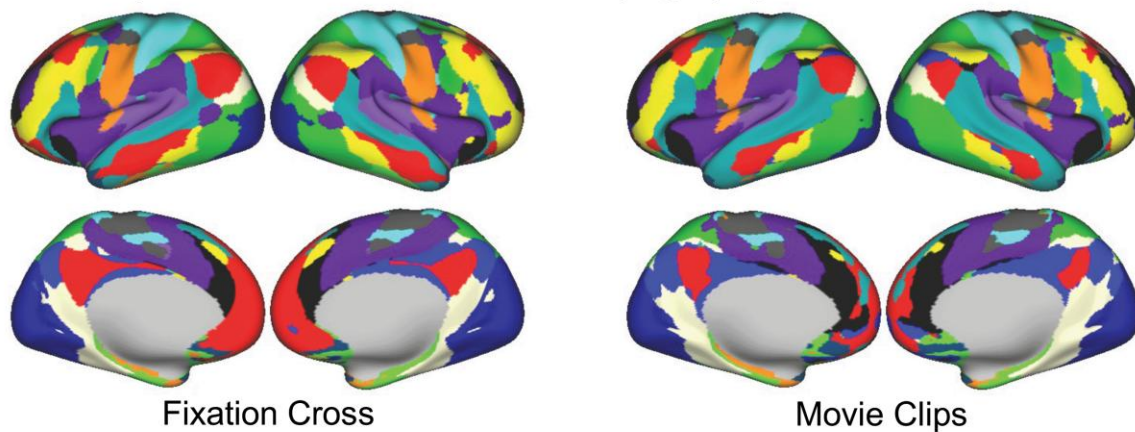
Title: Common and specific large-scale fMRI network representations during passive viewing of crosshair fixation and movie clips

Authors: *K. J. GODFREY^{1,2}, G. GRIMSRUD^{2,3}, S. HODAPP¹, J. S. B. RAMIREZ², M. GELL^{1,2}, C. CONELEA^{1,2}, B. TERVO-CLEMMENS^{1,2}, S. M. NELSON^{2,3};
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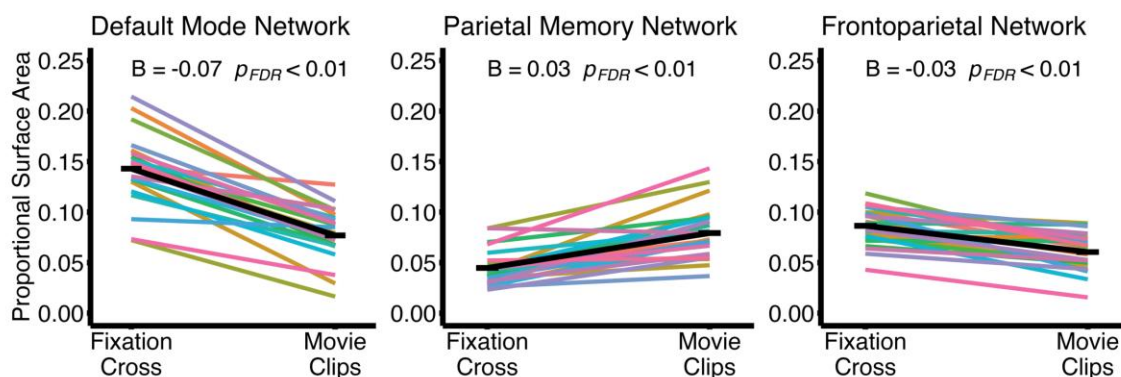
Abstract: Recent functional MRI (fMRI) research suggests stability in inter-individual functional network topography, including relatively high consistency when topography is estimated across conditions or task acquisitions. However, prior reports regarding viewing condition effects are limited by single echo, relatively short (~15 minutes), per-condition acquisitions with suboptimal reliability. Understanding fMRI network representations across viewing conditions is critical to improve fMRI data collection in high-motion populations more amenable to movie watching. Data were analyzed from a human transdiagnostic adolescent cohort, $n=25$ (10M/15F, aged 9-18 years) with ≥ 1 DSM-5 disorder, who completed a precision and high reliability 3T fMRI protocol (4-echo multi-phase) at two sessions <1 month apart. On

average, 28 minutes of post-censored ($FD < 0.2\text{mm}$) fMRI data were available per-participant across sessions for each of resting state (eyes open fixation) and movie clips (short, disparate, children's movie clips). Network detection, via template matching, was used to generate individual functional network maps for each participant per condition. Overlapping group- and individual-level large-scale network patterns were observed, with the majority ($M = 80\%$, range = 70-92%) of within-condition reliable vertices also shared across viewing conditions. Yet, several significant and split-half reproducible viewing condition effects on network surface area were observed in multiple networks including default mode, parietal memory, and frontoparietal (cf., Figure 1). These findings align with prior reports of group- and individual-level stability across conditions for a large proportion of vertices, suggesting movies as valid acquisition conditions for network mapping in high-motion cohorts. While relatively small, but across-participant consistent, viewing condition effects on functional networks could provide new insight into network connectivity dynamics that remain relatively unexplored in studies applying popular group-derived network parcellations.

A. Group-Level Functional Network Topography Across Conditions



B. Group- and Subject-Level Network Surface Area Across Conditions



Disclosures: K.J. Godfrey: None. G. Grimsrud: None. S. Hodapp: None. J.S.B. Ramirez: None. M. Gell: None. C. Conelea: None. B. Tervo-Clemmens: None. S.M. Nelson: None.

Poster

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Title: Deep Learning Approach to Video-Based Behavioral Classification with Neural Recordings

Authors: *C. E. MACLAREN¹, S. N. JACKSON¹, O. E. FRUCHET¹, R. A. VOLKMAN¹, S. K. INATI², K. A. ZAGHLOUL¹;

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Abstract: Drug-resistant epileptic patients are brought to the Clinical Center at the National Institutes of Health for seizure monitoring, where they are monitored 24/7 via a live-stream camera with intracranial EEG recordings. However, throughout a patient's stay, only 8% of all data is being analyzed for research, as the main access is through behavioral testing sessions. Through deep learning advancements, there is opportunity to access behavioral information throughout a patient's entire stay, outside research sessions. There exist current methods for identifying human action in videos, but little advancements in behavior in a hospital environment, where patients are monitored 24/7 via a live-stream camera. With new advances in machine learning and computer vision, different deep learning models can now identify objects and track their movement throughout a video. Through such, human movement - described as human pose - can be extracted in videos, creating opportunity for tracking and classifying different actions. Pre-trained human pose models achieve very high mean average precision (mAP) and are useful for transferring to different datasets. Utilizing a pre-trained network and fine-tuning for refined features, we can identify more positional information to the standard pre-trained network for our non-uniform environments, where patients may be in different settings with various obstructions, such as staff and family interruptions, blankets, tables, etc. We can achieve a strong mAP, and can, thus, extract precise locations of body parts and joints. This can then serve as strong features for an additional deep learning network. By leveraging a Long Short Term Memory (LSTM) architecture, we can extract spatiotemporal information from our human pose inputs, training a model to learn movement of body parts across multiple frames in a video. Through this second deep learning network, we can classify the movement of the patient in a low-level space into behavioral categories. By correctly identifying human movement in videos, we can cluster different behaviors alongside precise neural data. Through such, we tap into a larger set of annotated data, allowing us the opportunity to correlate behavior and neural activity, specifically outside the scope of our behavioral testing sessions.

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Title: Identifying and mapping human neocortical laminar ensemble dynamics during arousal, task engagement and visual perception

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Abstract: The layered architecture of the neocortex forms the fundamental basis for complex neural computations. However, identifying these layer-specific subcircuits and deciphering their functional contributions in the human brain remains challenging. Recent advances in high-resolution neural recording technologies now permit investigation of human cortical layers and their circuit composition with unprecedented detail. Using Neuropixels probes (N=17 participants) and "thumbtack" laminar electrodes (N=7 patients) in human frontal and temporal cortex with positioning and relationships to cortical layers verified through precise imaging techniques and histology, we identified robust patterns of neurophysiological activity, including local field potential co-modulation and spectral features, that consistently segment the cortical column into its distinct layers. We found that neurons within these physiologically defined layers possess distinct electrophysiological profiles (waveforms, firing patterns, spatiotemporal dynamics), reflecting diverse underlying cell types. These cell-types form layer-specific ensembles exhibiting characteristic oscillatory coupling patterns both within and across laminae. Furthermore, these layer- and cell-type-specific subcircuits demonstrate distinct engagement profiles during baseline activity, across fluctuations in arousal state, and during task performance, including visual perception. This work provides a validated framework for mapping laminar circuits in vivo and reveals the functional composition and architecture of layer-specific cellular dynamics in the human neocortex at unprecedented detail, which multiplexes in service of distinct cognitive functions and brain states.

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Poster

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NIMH R01 MH117155

Title: Ripples as biomarkers of cortical language processing

Authors: *D. R. CLEARY¹, I. VERZHBINSKY², Y. TCHOE³, C. DICKEY⁵, A. BOURHIS⁶, M. GANJI⁷, J. LEE⁸, S. LEE⁹, B. Q. ROSEN¹⁰, D. SOPER¹¹, S. S. CASH¹³, A. C. PAULK¹², A. M. RASLAN¹⁴, S. DAYEH⁴, E. HALGREN¹⁵;

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Abstract: Introduction: Brain-computer interfaces for use in speech prostheses rely on electrophysiological recordings from cortical regions that process speech. Current cortical recording methods use high frequency and wide-spectrum recordings to capture a wide range of data, but this process also generates a large of amount of data that requires intensive computational processing post-hoc. Here, we used high-channel count and high spatial resolution thin-film electrodes to record from the surface of the auditory cortex during awake craniotomy, and found discrete, high gamma electrophysiological biomarkers of speech

processing. **Objective:** To better understand the fundamental processing of receptive speech, we designed an intraoperative experiment to perform high-resolution recordings from human cortex while awake patients listened to auditory stimuli. **Methods:** We used custom-designed high-density, conformal parylene surface arrays with 1024 channels made of platinum nanorods (array of 16x64 channels at 200 um pitch). During surgery, clinical mapping first grossly identified areas that produced evoked potentials from receptive language, and then the custom high-density arrays were placed on the cortical surface, usually at or around superior temporal gyrus. After recording started, patients listened to a series of consonant-vowel combinations or noise-vocoded sounds for 5 minutes. **Results:** Auditory stimuli produced variable degrees of activity across the electrode. Evoked gamma-band activity allowed for gross discrimination between words and noise. Additionally, short bursts of temporally symmetric activity in the 70-110 Hz band (ripples) were found to occur in conjunction with auditory stimuli. When compared to higher and lower frequency gamma-band activity, the ripple-band was found to be a superior modality for decoding the response to auditory stimuli. **Conclusions:** We report a novel finding from the superior temporal gyrus, that functional LFP responses are detected with the highest effect size and discriminability in the ripple segment of the gamma frequencies. Knowing these biomarkers of cortical processing facilitates the creation of precisely targeted speech prostheses for optimized electrode, amplifier and analysis choices, and would minimize the amount of data transmission.

Disclosures: **D.R. Cleary:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cortical Science, Inc. **I. Verzhbinsky:** None. **Y. Tchoe:** None. **C. Dickey:** None. **A. Bourhis:** None. **M. Ganji:** None. **J. Lee:** None. **S. Lee:** None. **B.Q. Rosen:** None. **D. Soper:** None. **S.S. Cash:** None. **A.C. Paulk:** None. **A.M. Raslan:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cortical Science, Inc. **S. Dayeh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cortical Science, Inc. **E. Halgren:** None.

Poster

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Topic: I.04. Executive Functions

Support: F31MH135645

Title: Task related modulation of cross-region human single neuron co-firing is mediated by ripple oscillations

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Abstract: Ripple oscillations (70-100Hz) may facilitate communication between distant brain regions during cognition. We analyzed intracranial recordings from epilepsy patients performing a Sternberg working memory task to investigate whether co-occurring ripples coordinate neuronal firing across brain regions and support memory processes.

We analyzed a previously collected dataset (Daume et al, Nature, 2024) of single-unit activity and local field potentials from microwire electrodes implanted bilaterally in hippocampus, amygdala, vmPFC, ACC, and preSMA. Data from 36 patients yielded 1373 single units from 1927 microwire channels. Patients viewed 1-3 images (encoding), maintained them in memory (maintenance), then indicated whether a probe matched the set (retrieval).

Ripple rates increased across all regions during encoding (13%), maintenance (10%), and retrieval (36%) relative to baseline. Critically, ripple co-occurrence between distant regions (up to 220mm) increased during these phases, particularly under high memory load (100% increase during retrieval, load 3 vs load 1, $p=3.2e-6$).

Co-occurring ripples dramatically enhanced cross-regional unit co-firing. During co-ripple periods, unit pairs showed substantial increased co-firing vs baseline (50%, $p\approx 0$), while no-ripple periods showed minimal change (2%, $p=1$). This enhancement occurred equally for nearby and distant neurons, challenging expectations of distance-dependent decay. Memory load further modulated this effect: high-load trials showed greater co-firing during co-ripples than low-load trials (maintenance: 13%; probe: 19%, $p<1e-38$).

Remarkably, co-ripples promoted reinstatement of stimulus-specific firing patterns during retrieval. When probes matched encoded stimuli, co-firing patterns from encoding were more likely to repeat during retrieval co-ripples than mismatches (0.26% vs 0.20%, $p=8.5e-13$). This effect was attenuated during no-ripple periods (0.13% vs 0.11%, $p=3.4e-5$).

These findings reveal that ripple oscillations orchestrate long-range neural communication during human cognition, providing temporal windows for enhanced information transfer that scale with cognitive demand and support memory-specific neural representations. By facilitating coordinated activity across distributed brain networks, ripples may serve as a fundamental mechanism for binding neural representations during complex cognitive operations.

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Poster

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Support: BRAIN initiative NS109553

Title: Inter-hemispheric coordination of ripples during a naturalistic task

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Abstract: Ripples are brief (~70ms) high-frequency (~90Hz) oscillations that have been observed to coordinate and phase-lock across widespread cortical and subcortical regions, forming large-scale networks that are modulated by various kinds of tasks. While ripple synchrony has been described to occur throughout the human brain, the nature of their cross-hemispheric coordination has not been directly explored. Here, we investigate whether co-ripples form coordinated networks across hemispheres, and whether cross-hemispheric coordination differs from within-hemispheric coordination in time or space. To address these questions, we analyzed stereo-electroencephalography recordings (SEEG) from a publicly available dataset (Keles et al., Scientific Data 2024) in which patients with bilateral implants watched a 6.5-minute movie and later completed a frame recognition task. The dataset's symmetric bilateral electrode coverage provides an ideal opportunity to assess hemispheric ripple network dynamics during a naturalistic task. Using established methods to detect and quantify co-ripples and phase-locking, preliminary findings suggest that co-ripples coordinate across hemispheres, with possible distinctions in temporal and spatial features compared to within hemisphere co-ripple networks. These findings may provide insight into how the brain coordinates distributed activity across hemispheres during cognitive processing and provides stronger evidence for the putative role of co-ripples as a mechanism for facilitating cortical integration.

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Poster

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Topic: I.04. Executive Functions

Title: Recording Ripples Noninvasively in Healthy Subjects Using Scalp EEG and MEG

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Abstract: Cortical ripples (~90 Hz, 60-120 ms) are high-frequency brain oscillations associated with processes like memory and decision-making. Normally, these oscillations are recorded invasively using intracranial electroencephalography (iEEG), placing electrodes inside the brain. This project aims to study if these ripples can be observed noninvasively with scalp EEG and/or magnetoencephalography (MEG). We analyzed data from the COGIGATE dataset, with 64-

channel EEG and 306-channel MEG recordings from a total of 97 subjects, and intracranial data for comparison. Participants performed a visual detection task where they were presented with sequential stimuli, with each block requiring the detection of two target stimuli. Targets were from the categories of faces, objects, letters, and false fonts. They were presented along with nontargets. Stimulus detection varies from 500 to 1500 ms. The participants' gaze was monitored. Preprocessing using artifact removal and Independent Component Analysis (ICA) was used to suppress artifacts caused by eye blinks and muscle contractions. Previously described intracranial methods for ripple detection were applied across trials, leveraging the knowledge that ripples become synchronous in specific task stages. A major challenge is that ripples are small, focal, and infrequent, so we averaged over electrodes and people. Further, we selected contacts at scalp locations with no underlying muscle tissue. A quality check for detected ripples involves ensuring they are around 90 Hz in frequency and 60-120 ms long, and were consistent with the intracranial dataset and previous intracranial descriptions of ripples. The COGIGATE dataset includes intracranial patients completing the same task, allowing for a reliable comparison. In the future, ripple detection could be used to explore behaviors across conditions such as schizophrenia and autism, or study the effects of alcohol, psychedelics, etc.

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Poster

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Topic: I.04. Executive Functions

Title: Analyzing the Role of Cortico-Cortical Co-Ripples in Information Integration in Mice

Authors: *Y. BU¹, I. VERZHBINSKY³, S. WILSON³, A. NUNEZ¹, J. YANG¹, E. HALGREN²;

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Abstract: The neural mechanisms underlying cortical integration remain incompletely understood. Recent human studies identified cortical ripples, high-frequency oscillations (~90 Hz), as key events that synchronized activity across cortical areas via near-zero phase-lag co-occurrence ("co-ripples"), suggesting a mechanism for integration (Dickey et al., 2022; Verzhbinsky et al., 2023). In this study, we investigate cortical ripples in mice to characterize their properties, inter-area interactions, and modulation of neuronal activity, aiming to extend our understanding of ripple mechanisms beyond what is accessible in human studies. We analyzed 70 mice (WT, Vip-IRES-Cre, Sst-IRES-Cre) from the Allen Institute's Visual Behavior Neuropixels dataset, which includes recordings from six visual cortical areas, hippocampus, and thalamus, capturing >200,000 units. Ripples were detected from current source density signals

within the 120-200 Hz range and quantified for density, frequency, duration, amplitude, timing, and co-occurrence. We found that ripples exhibit distinct temporal dynamics across different task conditions, which include an active change detection task, where mice viewed natural images and licked for reward, and passive viewing sessions involving natural images, Gabor patterns, or full-field flashes without a required response. In the active condition, the posteromedial visual cortex (VISpm) showed increased ripple activity early in the session that declined over time, while the primary visual cortex (VISp) showed the opposite trend. This suggests shifting contributions of visual areas as mice engage with and learn novel stimuli. Co-ripple density across all visual area pairs increased more than tenfold during hit trials relative to pre-stimulus baseline and was 30-50% higher than in miss trials, paralleling findings in humans (Garrett et al., 2024). Notably, co-ripples during hit trials were especially frequent between layers 5 and 2/3 across visual areas, particularly from VISp layer 5 to layer 2/3 in other areas, indicating a preferred bottom-up projection pathway. Overall, these findings validate mouse cortical ripples as a suitable model to study ripple-mediated integration observed in humans and highlight their synchronizing role during tasks. Ongoing analyses of ripple propagation and neuron-type specificity will further illuminate the fundamental process of cortical integration.

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Poster

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Topic: I.04. Executive Functions

Support: AVIAN MIND, ERC-2020-ADG, LS5, GA No. 101021354 (OG)

Title: From Sleep to Active Behavior: fMRI Mapping of Neural Networks in Pigeons

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Abstract: Animal-fMRI is a powerful method to understand neural mechanisms of cognition at the systems level. But it requires to scan actively participating small animals under low-stress conditions in the scanner. We established a comprehensive platform to investigate pigeon brain neural mechanisms across the full spectrum of behavioral states, from active behavior to rest and sleep. In the first visual discrimination study in awake, actively participating pigeons, we demonstrated an extensive, largely telencephalic network of sensory, limbic, executive, and motor areas that was active during an operant Go/NoGo color discrimination task. This is the

first time that a complete systems view for an operant visual task was achieved in a bird and opens endless possibilities for similar studies. But our resting-state fMRI technique also provides unprecedented insights into spontaneous neural activity during task-free states. Here, we discovered principles of network organization sharing fundamental similarities with mammalian systems while revealing key differences, particularly in hippocampal connectivity patterns, illuminating both conserved and divergent principles of vertebrate brain organization. Our sleep studies addressed brain maintenance functions across species. Using fMRI in naturally sleeping pigeons, we found ventricular cerebrospinal fluid flow increases during NREM sleep that drop sharply during REM sleep. This suggests REM sleep brain activation may compromise waste clearance functions, revealing potential trade-offs between sleep-related neural processes. Importantly, visual regions were activated during REM sleep, opening the possibility for dream-like states. Taken together, the versatility of our platform allows us to investigate a wide range of neurobiological phenomena. These reach from sensory processing and decision-making with dynamic reorganizations of neural networks across task contingencies up to spontaneous brain activity during rest.

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Poster

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Title: Gamma-band (~40 Hz) information flow dynamics in cat EEG during wakefulness and sleep

Authors: *S. CASTRO^{1,2}, J. GONZALEZ^{3,4,5}, M. CAVELLI², P. TORTEROLO²;
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Abstract: Cognitive processes rely on extensive thalamocortical and corticocortical recurrent interactions. Oscillations within the gamma frequency band (30-45 Hz) of the electroencephalogram (EEG) are associated with these interactions and play a role in cognitive functions. These oscillations have been implicated in the integration of spatially separated yet temporally correlated neural events, leading to a cohesive perceptual experience. On the other hand, it is recognized that top-down processing refers to the brain's ability to use expectations,

attentional focus, and other cognitive factors to influence bottom-up sensory processing. However, the precise directionality of the information flow (bottom up or top down) encoded by gamma band oscillations remains unknown. Therefore, the primary objective of our study is to investigate the direction of information flow in the gamma band during both wakefulness and sleep. To achieve this, 6 cats were chronically prepared for polysomnographic recordings, with electrodes placed in various cortical regions. To examine the directionality of information flow in the gamma band, we employed two approaches. First, we quantified the time lag of amplitude envelopes of gamma oscillations between pairs of EEG channels. Second, we analyzed Granger causality for the same channel pairs. During quiet wakefulness, the predominant direction of information flow in the gamma band was from the dorsolateral prefrontal cortex (Pfdl) to the posterior parietal cortex (Pp), as well as from Pfdl to the primary somatosensory cortex (S1), primary visual cortex (V1), and primary auditory cortex (A1). Furthermore, there was a significant flow from Pp toward the primary cortices (S1, A1, and V1). Furthermore, when examining late gamma oscillations induced 0.5 to 1.5 seconds after a simple auditory stimulus, such as clicks, we observed a predominant bottom-up directionality from the Pp to the Pfdl, as well as from A1 to Pfdl. In contrast, late gamma oscillations induced by complex stimuli, produced a predominant top-down directionality from Pfdl to Pp, A1, and V1 cortex. Hence, during wakefulness, different patterns of information flow emerge depending on the nature of the stimuli. Specifically, bottom-up processing was found to predominate for simple repetitive sound stimuli, while top-down processing prevailed for complex and variable sounds, as well as in the baseline condition (in the absence of stimuli). In addition, no specific directionality in information flow was observed during NREM and REM sleep, suggesting a different mode of cognitive processing during sleep.

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Poster

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Topic: I.04. Executive Functions

Support: ERC starting grant
Einstein research grant

Title: Frontal and posterior divergence in the mouse cortex during different cognitive functions

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Abstract: The cortex is responsible for encoding different cognitive functions, for example sensory integration, learning and working memory. Whereas each cognitive function is shown to involve several cortical areas in a widespread manner, a comparison of cortex-wide patterns

across different cognitive functions is missing. To address this gap, wide-field imaging in behaving mice has become a popular tool to study cortex-wide neuronal patterns during complex behavior. In this talk, I will present results from three studies each investigating brain wide patterns during different behavioral paradigms. The first study focuses on comparing cortex-wide patterns as mice either identify or locate textures using their whiskers (i.e., 'what' vs 'where' processing). The second study compares cortex-wide patterns of different cortical layers (layer 2/3 vs. layer 5) as mice learn to use their whiskers in order to discriminate between two textures. The third study investigates transfer of sensory information and working memory across hemispheres as mice are required to match between two textures presented on different whisker pads. In all three tasks, we find a similar frontal/posterior divergence that is governed by an active movement strategy which shifts responses to the frontal cortex. In the absence of an active strategy, the posterior cortex, specifically posterior lateral areas (i.e., P, LM, POR and LI) encodes different cognitive functions: object identity vs. location, laminar differences during learning, and interhemispheric transfer of sensory information and working memory. Taken together, we hypothesize that posterior lateral areas are a general hub for encoding cognitive function and an active movement strategy shifts activity to frontal areas and suppresses posterior cortex.

Disclosures: A. Gilad: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.22/OO18

Topic: I.04. Executive Functions

Support: Whitehall Foundation, Ref. NO. 2023-08-050

Title: Optogenetic silencing of sparsely labelled CA1 neurons induces widespread network suppression

Authors: *W. SUN¹, S. A. MCKENZIE²;

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Abstract: Optogenetics enables rapid, precise, and potent manipulation of neuronal activity, making it a widely used technique in modern neuroscience. However, neurons function within highly interconnected and dynamic networks, and the network-level consequences of selectively manipulating a small subset of neurons by optogenetics remain poorly understood. In this study, we investigated how optogenetic silencing influences hippocampal network dynamics by combining *in vivo* electrophysiological recordings with temporally restricted and experience-specific optogenetic tagging. Two strategies were used for activity-dependent labelling: (1) wild type mice received injections of an immediate early gene (IEG)-dependent virus (AAV-RAM-

ArchT-eGFP) in the dorsal CA (dCA1) region of the hippocampus, enabling doxycycline (dox)-off dependent tagging of neurons activated during exploration of a novel environment. (2) transgenic mice (FosCreER^{T2}:Ai14) expressing the ‘targeted recombination in active populations’ (TRAP2) system received 4-hydroxytamoxifen (50mg/kg) through intraperitoneal (i.p.) injection in the novel environment. With both strategies, we found that activity-dependent labelling drove native fluorescence in a sparse population of neurons (RAM: 1.3%, n=4; TRAP2: 0.4%, n=6). In all RAM subjects and two TRAP2 subjects, an optogenetic fiber and a silicon probe were co-implanted in dCA1 to allow simultaneous optogenetic stimulation of the inhibitory opsin ArchT and electrophysiological recording. Neural activity was recorded in both the home cage and the tagged context using 100-ms optogenetic pulses. Surprisingly, brief optogenetic silencing of this small subset of tagged neurons led to a significant reduction in firing rate in up to 96% of recorded neurons (50-200 recorded neurons daily over two weeks). In addition, we observed that the ratio of neuronal inhibition to disinhibition was also modulated by the optogenetic laser power, suggesting complex dynamic changes within the network. The mechanisms underlying this widespread impact—whether via direct synaptic connectivity or limitations in the specificity of tagging—remain under current investigation. If fluorescent tagging reflects opsin expression, our findings indicate that manipulating a small number of neurons can exert a disproportionately large effect on the surrounding neural network. This work highlights the importance of considering network-level responses in studies employing sparse optogenetic manipulations.

Disclosures: W. Sun: None. S.A. McKenzie: None.

Poster

PSTR189: Network Activity and Executive Function in Humans and Animals

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR189.23/PP1

Topic: I.04. Executive Functions

Support: Barncancerfonden (PR2018-0122)
Oskarfonden
Linnea & Josef Carlsson
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Kungliga fysiografiska sällskapet
Thorsten & Elsa Segerfalks Stiftelse
Kockska Foundation

Title: Aberrant Neuronal Synchronization Associated with Cognitive Deficits in a Rodent Model of Childhood Cranial Irradiation

Authors: S. A. BARRIENTOS¹, *P. PETERSSON²;

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Abstract: Cranial radiation can be a life-saving therapy for pediatric brain cancer patients but often results in life-long debilitating cognitive deficits. To clarify the underlying mechanisms of these side-effects, we recorded neurophysiological activity in distributed brain networks involved in memory functions and in decision-making processes in adult rats that were exposed to cranial irradiation on postnatal day 21. A decreased power of the Local Field Potential (LFP) was observed in irradiated animals during task execution in the 4-9 Hz frequency band, resulting in reduced single unit entrainment in critical phases of the task. Interestingly, this population activity also showed a small but significant slowing in the irradiated brains resulting in longer time intervals between events of synchronous unit activity compared to controls. Moreover, irradiated rats showed a fragmented pattern of inter-structural coherence across different phases of the task. Based on our results, we propose that cognitive deficits and reduced processing speed following irradiation of the juvenile brain arise as a consequence of changes in long-range functional connectivity, causing abnormally slow and spatially fractionated patterns of coordinated brain activity.

Disclosures: S.A. Barrientos: None. P. Petersson: None.

Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR190.01/PP2

Topic: I.06. Social Cognition

Support: NSER, RGPIN-2018-04699

Title: Rapid estrogenic effects in the medial prefrontal cortex of male mice on social and non-social short-term memory

Authors: *S. MCGUINNESS¹, K. ANDREWS¹, J. MISHRA¹, E. CHOLERIS²;

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Abstract: Sex hormones can rapidly modulate neuronal structure and behaviour. The estrogen 17 β -estradiol (E2) modulates numerous cognitive processes in both sexes showing varying molecular and behavioural effects when administered in different brain regions. One region of interest, the medial prefrontal cortex (mPFC) mediates higher order cognitive processes and is sensitive to sex hormones. One study conducted in female mice found that when E2 was infused into the mPFC, two social cognitive processes were rapidly facilitated (social recognition (SR); social learning (SL)), however two non-social cognitive processes were not (object recognition (OR); object placement (OP)). These results suggest that although the mPFC is involved in both social and non-social cognition, the rapid action of E2 in the mPFC may preferentially facilitate learning and memory involving social stimuli. E2 also produces rapid effects in the male brain often following its local conversion from testosterone by the enzyme aromatase, however the rapid effects of E2 in the mPFC on rapid short-term memory (STM) in male mice remains

unknown. In the present study, CD1 male mice were castrated and received bilateral E2 infusions into the mPFC, targeting the prelimbic and infralimbic subregions. Mice then performed in one of the 40-minute SR, OR or OP paradigms. Interestingly, results show that E2 rapidly facilitates SR, OR and OP in male mice, whereas SR but not OR or OP was facilitated in females. Therefore, there is a potential sex difference in the mPFC's regulation of cognition by E2 and future research may relate these findings to specific sex differences observed in behaviour. Additionally, to complement these results, the rapid effects of E2 on neuronal plasticity were examined through quantifying changes in dendritic spine density in male mice that had undergone the SR STM paradigm. Results show that E2 rapidly increases dendritic spine density in layer 2/3 neurons of the prelimbic subregion, indicating a possible role for dendritic spinogenesis in the rapid facilitation of STM by E2 in the mPFC. The present study provides new insights on the hormonal regulation of STM in the mPFC of male mice. Understanding hormonal brain regulation in males and females provides a basis underlying manifestations of sex differences in behaviour relevant to various psychiatric conditions. Future research should investigate the interplay between sex hormones in the mPFC with other neurotransmitters to understand how behaviour is regulated at a systems level.

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Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR190.02/PP3

Topic: I.06. Social Cognition

Support: JST SPRING, Grant Number JPMJSP2129

Title: Effects of adolescent social isolation on social behavior and brain development in the mice experienced chronic maternal separation.

Authors: *S. KUMAZAKI¹, Y. ITO², J. MOTOYAMA¹;

¹Lab. of Developmental Neurobio., Grad. Sch. of Brain Science, Doshisha Univ., Kyotnabe/Kyoto, Japan; ²Grad. Sch. of Brain Sci., Doshisha Univ., Kyoto, Japan

Abstract: Early-life stress significantly influences social behavior and brain development. Maternal separation (MS) is a widely used rodent model of early adversity which impairs social novelty recognition in adulthood (Wei et al., 2021). Understanding the mechanisms underlying this impairment is crucial for developing strategies to mitigate the long-term effects of childhood stress in humans. While environmental enrichment (EE) during adolescence can mitigate these effects (Wei et al., 2021). Adolescent isolation after MS increases anxiety-like behavior in male rats (Amancio-Belmont et al., 2020), suggesting adolescent social experience modifies adult behavior of post-MS. However, how adolescent isolation affects social novelty and related neural development in MS-experienced animals is unknown. This study examined how adolescent

social isolation affects adult social behavior and neural circuits in MS-experienced mice. We used male ICR mice, applying 4-hour daily MS from postnatal day 2-21, and reared them post-weaning into four groups until 8 weeks: (1) MS-experienced, group-housed (n=12; 4 mice per cage), (2) control, group-housed (n=12; 4 mice per cage), (3) MS-experienced, socially isolated (n=5) and (4) control, socially isolated (n=5). We assessed social behavior using Three-Chamber Test and then quantified oxytocin (OXT)-positive neurons in the paraventricular nucleus (PVN) and GPR54-positive neurons in the supramammillary nucleus (SuM), both involved in social cognition (Menon & Neumann, 2023). ICR mice were chosen for their high sociability and maternal care, possibly increasing sensitivity to social deprivation. Prior work also links social isolation in ICR mice to altered corticosterone and immune-endocrine function (Ortega-Saez et al., 2023). Results showed no behavioral difference between group-housed MS and control mice, suggesting resilience to early MS and adolescent group housing in ICR mice. Isolated control mice displayed longer contact with novel mice, indicating enhanced novelty preference. In contrast, isolated MS mice showed reduced preference for novel over familiar mice and deficits in both sociability and novelty recognition. These findings suggest that early-life MS combined with adolescent isolation specifically impairs social cognition. We are currently analyzing OXT-expressing neurons in the PVN and GPR54-positive neurons in the SuM in these mice to understand how social environments affect the development of the brain in relation to social behavior.

Disclosures: S. Kumazaki: None. Y. Ito: None. J. Motoyama: None.

Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR190.03/PP4

Topic: I.06. Social Cognition

Support: NSERC Grant: RGPIN-2018-04699

Title: The Role of the Rapid Effects of Locally Synthesized Estrogens in the Bed Nucleus of the Stria Terminalis (BNST) on Social Recognition in Male mice

Authors: *A. VARATHARAJAH¹, D. ASPESI³, Z. BROWN¹, L. V. STIMSON¹, J. MISHRA¹, N. J. MACLUSKY², E. CHOLERIS¹;

¹Dept. of Psychology and Neurosci. Program, ²Dept. of Biomed. Sci., Univ. of Guelph, Guelph, ON, Canada; ³Neurosci. Inst., Georgia State Univ., Atlanta, GA

Abstract: Extensive research demonstrates that sex steroids crucially modulate social cognition through both genomic and non-genomic mechanisms to elicit delayed/slow and rapid effects respectively. Sex steroids including testosterone, 17 β -estradiol (E2), and dihydrotestosterone (DHT), can be synthesized by both the gonads and extragonadal organs, including the brain, to work in concert to modulate social cognition. The role of brain synthesized sex steroids is poorly

understood. Previous studies in ovariectomized female mice demonstrates that locally-synthesized E2 in the dorsal hippocampus (dHPC) is required for short-term social recognition (SR) memory and long-term memory consolidation in gonadectomized (GDX) male mice. In gonadally intact male mice, the dHPC E2 synthesis was not required for long-term memory consolidation, suggesting a crucial interplay between gonadal and brain-synthesized sex steroids. The bed nucleus of the stria terminalis, a brain region crucially involved in male social behaviour, shows high expression of G protein-coupled estrogen receptor (GPER), ER α and ER β . The latter two receptors are co-expressed with aromatase enzyme mRNA, responsible for the conversion of T to E2. Exogenous administration of T and E2 targetting the BNST showed rapid facilitation of SR, suggesting a key role of BNST-synthesized E2. In the current study, GDX and gonadally intact young adult male CD-1 mice are bilaterally infused with either an aromatase inhibitor letrozole (0.025, 0.05, 0.1, 0.2 $\mu\text{g}/\mu\text{l}$) or vehicle targetting the BNST 15 minutes prior to being exposed to a rapid short-term SR memory paradigm. Preliminary results demonstrate an impairment of SR in both GDX and gonadally intact males, unveiling a likely role for non-genomic effects of BNST-synthesized E2 on SR. This study will be informative of the interactive role of brain-synthesized E2 and circulating sex steroids in SR and can provide insights into sexually differentiated incidence and manifestation of social disorders.

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Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

Location: SDCC Halls B-H

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Program #/Poster #: PSTR190.04/PP5

Topic: I.06. Social Cognition

Support: NIH R01 MH136228
NIH T32 AG049688

Title: The role of oxytocin in long-term social memory

Authors: *E. LUBBERS, X. WU;
Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY

Abstract: Social memory, the ability to recognize and remember conspecifics, is altered in neuropsychiatric disorders such as autism spectrum disorder and schizophrenia. Social memory deficits impact social behavior but remain untreated. Importantly, long-term social memory in animal models is most comparable to human behavior, but the mechanisms for this memory are incompletely understood. A naturalistic model of long-term social memory is the robust memory pups exhibit for their caretaking dam (dam-pup memory). In this study, we leveraged dam-pup memory to establish a paradigm for circuit- and neuromodulator-level manipulations. Wildtype mice (C57BL/6J) were tested in a three-chamber social memory assay following a two-hour

separation from their mother. Time spent in the chamber or area surrounding a novel or familiar dam under a cup was quantified. At P17, mice exhibited a significant preference for a novel dam compared to a caretaking dam (Paired *t*-test, *n*=15), indicating social memory expression. In contrast, a 2-hour familiarization period with a novel dam was not sufficient to induce 2-hour social memory, which provides evidence that it is not dependent on generalized cues from dams (Paired *t*-test, *n* = 8). To begin establishing the mechanisms underlying dam-pup memory, we confirmed that the dCA2 of the hippocampus, as in other forms of social memory, is necessary. Chemogenetic inhibition of this area significantly decreased ability to discriminate between the caregiving mother and novel mother in mice (Paired *t*-test, *n*=8). Furthermore, oxytocin (OXT) has well-characterized roles in maternal care, sensory processing, and social memory. To test the hypothesis that OXT signaling in the dCA2 is relevant to dam-pup memory, an OXT receptor (Oxtr) antagonist was micro-infused into the dCA2 via bilateral cannula. Multiple infusions of Oxtr antagonist were sufficient to inhibit dam-pup memory (Paired *t*-test, *n* = 11). Additionally, to examine the developmental dynamics of OXT signaling, immunohistochemistry was performed for the Oxtr in the dCA2 by examining expression co-localized to a molecular marker for the CA2. Oxtr expression in the dCA2 was found to increase with age but not by sex or in response to weaning (One-way ANOVA, *n* = 24). Together, these results demonstrate a role for dCA2 OXT signaling in the formation of long-term social memory that independent from upregulation of Oxtr expression during development. Ultimately, by determining the mechanisms underlying enhanced social memory in specific contexts, we aim to elucidate novel treatment targets for social cognitive deficits.

Disclosures: E. Lubbers: None. X. Wu: None.

Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

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Program #/Poster #: PSTR190.05/PP6

Topic: I.06. Social Cognition

Support: NIH Grant R01MH131807
NIMH Grant K01MH109712

Title: Vasopressin-responsive neurons in the central medial thalamus modulate prosocial behavior in a sex-specific manner

Authors: *D. KAHN¹, T. GOOD², B. D. ROOD³;

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Abstract: Humans, along with many animals, rely on social behavior to navigate their livelihoods. Social deficits in various disorders can impede both survival and quality of life. Nevertheless, much is left to be discovered in the complex physiological system underlying

social behavior. The neuropeptide, arginine-vasopressin (AVP), impacts social behaviors ranging from mating to aggression. In the brain, a few different nuclei produce AVP, each of which has distinct functions and AVP projection patterns. In particular, the bed nucleus of the stria terminalis (BNST) plays a role in affiliative (prosocial) behavior and sends AVP afferents to various nuclei such as the central medial thalamus (CM). Unpublished data suggest that cells expressing AVP 1a receptors (Avpr1a) are present in the CM. Further, the CM has different projection patterns along its rostral-caudal extent; the rostral CM projects to regions involved in cognition, emotion and reward motivation, while the caudal CM projects to sensorimotor regions. Previous data in the dorsal raphe (DR), another downstream target of BNST AVP innervation, showed that exposure to a female stimulus animal activates (increases Fos expression in) DR Avpr1a neurons of both male and female subjects. Based on these data, we hypothesized that Avpr1a-expressing cells in the rostral CM, but not in the caudal CM, would influence prosocial behavior. Using a novel mouse model expressing Cre-recombinase under the control of Avpr1a regulatory elements in combination with virally delivered inhibitory DREADDs to the rostral or caudal CM, we tested the hypothesis that chemogenetic inhibition of Avpr1a-expressing cells in the rostral CM would decrease prosocial behavior. Interestingly, our data in the rostral group show increased social behavior in response to a male stimulus in female mice treated with DREADD ligand CNO as compared to vehicle treatment. Specifically, DREADD inhibition in female subjects increased general sniffing and total time spent interacting with a male stimulus. In contrast, no changes in social behavior due to DREADD inhibition were observed in the caudal group. This data suggests that the role of Avpr1a neurons in the CM depends both on sex of the subject and sex of the stimulus, as well as location within the CM nucleus itself. In the future, chemogenetic excitation along with further phenotyping of Avpr1a cells will help us understand the inhibitory/excitatory balance involved in modulating prosocial behavior.

Disclosures: D. Kahn: None. T. Good: None. B.D. Rood: None.

Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

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Program #/Poster #: PSTR190.06/PP7

Topic: I.06. Social Cognition

Support: MIRECC Pala Pilot

Title: Sp4 hypomorphic mice exhibit reduced sensitivity to the pro-social effects of MDMA - Role of mPFC circuitry?

Authors: *T. D. DEXTER^{1,2}, S. BARNES², R. SHARP², D. A. BANGASSER³, M. E. WIMMER⁴, M. VENNIRO⁵, S. B. POWELL², J. W. YOUNG²;

¹Univ. of California San Diego, San Diego, CA; ²Psychiatry, Univ. of California San Diego, La

Jolla, CA; ³Neurosci. Inst., Georgia State Univ., Atlanta, GA; ⁴Psychology, Temple Univ., Philadelphia, PA; ⁵Anat. and Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Deficits in social preference and decision-making are debilitating symptoms present in various mental disorders, warranting the development of targeted therapeutic interventions. Imaging studies have implicated the prefrontal cortex (PFC) in social decision-making, and PFC damage has been shown to impair indexes of social preference across species. Here, we characterized a novel task of social decision-making for mice, confirming: 1) PFC mechanisms underlying social-reward preference; 2) Acute MDMA treatment increases preference for social rewards; and 3) Evidence for abnormal social behavior in the Sp4 hypomorphic model of schizophrenia. **Methods:** Mice were trained to lever press for social rewards, and we tested their preference for choosing social interaction over competing food rewards. Female mice were injected with either GCaMP8f (to measure PFC activity) or GRABDA3 (to measure PFC dopamine) (n=3 each) and a fiber optic implanted into the medial PFC (mPFC). For MDMA experiments, mice (n=8) received i.p. injections of saline, 3 or 7mg/kg MDMA. Lastly, Sp4 hypomorphic mice (n=9 M, 10 F) were compared to littermate controls (n=3 M, 8 F), on tasks of social preference and motivation. Following initial characterizations, Sp4 and control mice were given the same doses of MDMA and evaluated on the social decision-making task. **Results:** mPFC activity was significantly higher at the time of choice between reward types ($p<0.05$), with mPFC dopamine tending to increase during reward collection ($p=0.06$). Interestingly, MDMA (7 mg/kg) increased preference for social rewards in wild-type mice ($p<0.05$). We observed that Sp4 female mice exhibited abnormal social preference and reduced trial counts when increased responses were required ($p=0.01$). Similar to our initial experiments, MDMA treatment increased social preference in Sp4 and control mice ($p<0.0001$). However, we observed significantly higher social preference in control mice treated with the highest MDMA dose compared to Sp4 mice ($p<0.01$). **Conclusions:** MDMA increased social reward preference in mice, and thus may have therapeutic potential for attenuating impaired social drive in disease states. We observed mPFC recruitment during social decision-making, which may serve as a neurobiological target for assessing the effects of pro-social compounds such as MDMA. The Sp4 hypomorphic model of schizophrenia exhibits abnormal social preferences, and a reduced sensitivity to the pro-social effects of MDMA. Future studies characterizing potential neurobiological abnormalities in Sp4 mice will be valuable for identifying how MDMA may be differentially modulating social behavior.

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Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

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Program #/Poster #: PSTR190.07/PP8

Topic: I.06. Social Cognition

Support: Research Apprentice Program - Christopher Newport University
Summer Scholars Program - Christopher Newport University

Title: Zebrafish (*Danio rerio*) Demonstrate Sexually-Dimorphic Responding in Visual Detection of Conspecifics' Reactions to Different Doses of the Synthetic Alarm Substance, Hypoxanthine-3 N-Oxide (C₅H₄N₄O₂)

Authors: *A. J. VELKEY, II¹, K. KINSLOW¹, E. HOFFMAN², R. PAGKALINAWAN², J. MARTIN¹, M. BOWERS², B. SURISSETTY², J. KANAPALA², H. DEWITT¹, T. KIRCHOFF², R. CATERBONE³, M. DWYER⁴, S. CHAARI²;

¹Neurosci. Program, ²Mol. Biol. and Chem., ³Kinesiology Program, ⁴Organismal and Envrn. Biol., Christopher Newport Univ., Newport News, VA

Abstract: Zebrafish (*Danio rerio*) are a common model organism for behavioral neuroscience due to their complex social repertoire which includes shoaling, when fish in a group congregate loosely with each other with little synchrony in movement across the group. Previous research has shown that zebrafish prefer an established social environment and are able to detect subtle movement differences among group members. These findings have been confirmed in several studies using the 3-Chamber Open-Tank Free-Swim Task (OTFST). In the present study using the OTFST, single subjects in the center tank were provided simultaneous visual exposure to a small shoal ($n = 4$, 2 males & 2 females) exposed to synthetic alarm substance in one flanking tank and a similar shoal that remained unalarmed in the other flanking tank. The dose of the synthetic alarm substance delivered to the tank holding the alarmed shoal resulted in a final concentration of 1.5 nM, 3.0 nM, or 5.0 nM of C₅H₄N₄O₂. The movement of each subject in the center tank was digitally recorded during a single session using MediaRecorder; videos were subsequently analyzed using EthoVision XT 16.0. There was more variability in movements among subjects responding to the shoal exposed to the 1.5 nM dose compared to the other doses. At the 1.5 nM concentration, males were significantly more motionless than females across zones, highlighting a sex-dependent behavioral response. However, at 5.0 nM, this pattern reversed in the unalarmed zone, with females showing a marked increase in immobility while males became more active. This interaction suggests that subjects respond to shoals exposed to a higher concentration of C₅H₄N₄O₂ with more anxiety-like behaviors, but they demonstrate the anxiety state with sex-specific responses. This study promises to advance the understanding of mechanisms that produce distinct social behaviors and anti-predation responses in zebrafish.

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Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

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Program #/Poster #: PSTR190.08/PP9

Topic: I.06. Social Cognition

Support: Summer Scholars Program - Christopher Newport University
Honors Summer Research Stipend - Christopher Newport University
Research Apprentice Program - Christopher Newport University
Independent Research Grant - Christopher Newport University

Title: Dose-dependent effects of hypoxanthine-3n-oxide (C₅H₄N₄O₂) on established zebrafish (*Danio rerio*) shoals

Authors: *K. KINSLOW¹, E. HOFFMAN², R. PAGKALINAWAN², M. BOWERS², B. SURISSETTY², J. KANAPALA², H. DEWITT³, T. KIRCHOFF², M. DWYER⁴, S. CHAARI², A. J. VELKEY³;

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³Neurosci. Program, ⁴Organismal and Envrn. Biol., Christopher Newport Univ., Newport News, VA

Abstract: Zebrafish (*Danio rerio*) are a valuable model for studying social behavior due to their highly gregarious nature, which includes shoaling. Shoaling occurs when members of a group of fish congregate loosely with limited coordination of movement among the members. When a predator attacks a shoal member, specialized epithelial cells of the injured fish release an alarm substance (i.e. *schreckstoff*) which can serve as a threat signal to other shoal members. Previous studies indicate that exposure to alarm substances disrupts shoaling and elicits anti-predation responding, including freezing, darting, and bottom-dwelling. The present study explored the responses of small mixed-sex shoals ($n = 4$, 2 males & 2 females each) exposed to varying alarm-substance concentrations as part of a 3-Chamber Open-Tank Free-Swim Test (OTFST). Adult wild-type zebrafish were used in control and experimental shoals in 5L tanks flanking either side of the tank holding a single subject for a related study. The experimental shoals were exposed to 1.5 nM, 3.0 nM, or a 5.0 nM concentration of the synthetic alarm substance while the control shoals remained unperturbed. Digital video recordings were obtained during the OTFST and subsequently analyzed using EthoVision XT 16.0 and DeepLabCut. While the mean inter-individual distances within shoals did not differ significantly across the 3 doses, negative geotaxis, a behavioral marker of anxiety in fish, was more pronounced as dosage increased. Future research should further investigate more complex behavioral patterns such as erratic swimming and darting, which might increase as alarm-substance dosage increases. Understanding these responses in regards to fear contagion has implications regarding anxiety, fear responses, and anti-predation behaviors; better understanding of these mechanisms could potentially contribute to research on animal models of neurodevelopmental disorders affecting social development.

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Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

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Program #/Poster #: PSTR190.09/PP10

Topic: I.06. Social Cognition

Support: NIH Grant K08MH134028

Title: Two dimensions of mouse social behavior: effects of acute isolation and mozart K.448 on reward and interaction

Authors: *A. TURK, J. DELINOIS, C. S. AKAFIA, A. ALLSOP;
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Abstract: Various mental conditions exhibit social interaction deficits and reduced social reward value. Traditional paradigms, such as the Resident-Intruder (RI) test and the Conditioned Place Preference (CPP), are widely used to evaluate social interaction and social reward, respectively. However, CPP does not assess real-time social motivational choices, and RI involves established territories. Conversely, the Modified Social Interaction (MSI) paradigm evaluates spontaneous social interaction in a neutral and familiar environment, whereas in the Operant Social Preference (OSP) paradigm, mice learned to open the door by pushing it, which provided access to a social reward. We used both C57 and CD1 mice (n = 8 per strain, balanced sexes) for MSI and OSP. Experiment videos were manually interpreted by an experienced researcher in a random order. SLEAP, a deep learning-based tool, was also used for automatic tracking of animal behaviors. We trained SLEAP on 375 frames, and the error distance for 90% of the estimated frames was 4.57 pixels, while the mean object key point similarity was 0.85. To test music's behavioral impact, mice were exposed to either Mozart K.448 sonata or white noise for 45 minutes in the home cage, followed by 30 minutes in the MSI. To assess the impact of social isolation (SI) on social reward, OSP-trained mice were socially isolated for 24 hours before the testing day. Rearing (n = 8; CI: -105 to -36), non-social sniffing (n = 8; CI: -75 to -19), and social sniffing (n = 8; CI: -36 to -10) behaviors were reduced in CD1 mice (all $p < 0.01$, Mann Whitney U test) but not in C57 mice (n=8) under the MSI Mozart condition. The median difference (MD) of fecal pellet count (n = 4 in randomly selected subset; MD: -3) and own-grooming behavior (n = 8; MD: -5) decreased in CD1 mice; however, these differences are not statistically significant. Furthermore, white noise increased fecal pellet count. (n = 4; MD: +1.5) In OSP, SI did not significantly change door-opening or attempts for either strain. (all $p > 0.05$, Wilcoxon test) Collectively, Mozart leads to a decrease in general activity and a reduction in fecal pellet count, while white noise increased fecal pellet count. These findings suggest music leads to an anxiolytic-like resting state, which supports potential music-based therapeutic interventions. Interestingly, SI did not alter social reward behaviors in OSP in contrast to CPP. Moreover, deep learning-based pose estimation provides accurate behavioral tracking, which will improve ongoing analysis.

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Poster

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Topic: I.06. Social Cognition

Support: NIH Grant 1S10OD023587-01
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HHMI Freeman Habrowski

Title: Motherhood on the brain: characterizing whole-brain oxytocinergic circuitry

Authors: ***D.-L. K. D. FERGUSON**¹, **B. R. MCRAE**², **N. MIMOUNI**¹, **T. N. ARZUA**¹, **H. IBARRA AVILA**¹, **B. J. MARLIN**³;

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Abstract: An individual's transition into motherhood is characterized by numerous phenotypic changes in the brain, hormones, and behavior. Our goal is to examine how neural circuitry may parallel these changes. In mice, virgin females will not reliably perform maternal behaviors, but mothers and virgins who have been cohoused with mothers do. The neuropeptide oxytocin is involved in the transition from the virgin to the maternal brain that parallels this shift in behavior. For instance, expression of the oxytocin receptor has been shown to fluctuate during pregnancy in rats. Furthermore, virgin female mice injected with oxytocin learn maternal behaviors more quickly. Therefore, examining oxytocinergic circuitry across different maternal experiences will garner greater insight into the mechanisms that support maternal care. We hypothesize that oxytocinergic circuitry will be upregulated in mice that exhibit maternal care behaviors. To that end, we have implemented the iDISCO+ pipeline to carry out whole-brain clearing, staining, and light-sheet imaging of the distribution of oxytocinergic projections. We then used Neurolucida 360 and FIJI analysis tools to precisely map these brain-wide oxytocinergic projections. We have begun to characterize differences in oxytocinergic projections across maternal experience as represented by virgin, surrogate, and maternal female mice. Moreover, to tease apart potential differences in the innate and learned maternal behavior of mothers and surrogate virgins, we have implemented a modified pup retrieval assay. Here, we had mice undergo olfactory fear conditioning, and then tested their latency to retrieve pups on either the control or conditioned odor side of a trichamber. This allows us to determine the lengths to which a maternal figure will go to ensure the safety of offspring. Preliminary results suggest that mothers are likely to retrieve pups more quickly on the conditioned odor side, suggesting that their maternal instincts override their fear response. Determining whether this holds in surrogate virgins will tease apart any potential behavioral differences between the innate and learned maternal experiences, and whether they correlate with changes in oxytocinergic circuitry. Altogether, our findings will provide a clearer picture of how hormonal circuitry and corresponding behavior may be altered with child-bearing and child-rearing, thus identifying key brain regions involved in the transition to motherhood.

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Poster

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Topic: I.06. Social Cognition

Support: NIH Grant T32MH126036
HHMI Freeman Hrabowski

Title: Endogenous opioid neuromodulation of maternal care

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Abstract: Maternal care is crucial for offspring survival, yet costly to the mother: she must redirect energy, time, and resources to her offspring. What, then, motivates an individual to invest in maternal care? In rodents, maternal care is highly dependent on brain regions in the canonical “reward circuit,” which reinforces adaptive behaviors such as mating and parental care. However, this circuit can also reinforce maladaptive behaviors when co-opted by drugs. The expression of opioid receptors within the reward circuit explains why opioids like heroin, morphine, and fentanyl are highly addictive and prone to abuse. The Brain Opioid Theory of Social Attachment, first proposed in the 1980s, posits that the formation and maintenance of close social relationships, and addiction to narcotics, share a largely overlapping neural basis: opioids and their receptors. However, while a significant amount of research has since elucidated the mechanisms by which opioids and opioid receptors lead to addiction, little is known about the function of endogenous opioids—opioids that the brain naturally produces—and how they contribute to the reinforcement of natural behaviors. Inspired by that theory, this novel study bridges a gap between the fields of maternal behavior and opioid use in order to elucidate how reward circuitry shapes natural social behaviors. Previous studies in rats have implicated the mu-opioid receptor (MOR), in particular, as crucial to both social reward and maternal behavior. However, an understanding of the neural mechanisms underlying the role of the MOR in maternal behavior requires a thorough characterization of the neurons that express the receptor and how the activity of those cells drives behavior. To address this knowledge gap, we utilize the genetic, viral, and in-vivo imaging techniques available in mice to investigate how MOR+ neurons participate in the emergence of maternal care. We combine the use of reporter lines and in-situ hybridization to examine brainwide MOR expression throughout pregnancy and postpartum. We also utilize viral tracers to uncover the basic circuitry of MOR+ neurons and to ask if pregnancy induces changes in that circuit. A basic understanding of how endogenous opioid signaling shapes maternal behavior will help us understand how maternal attachments form, how the transition to motherhood might affect susceptibility to addiction, and inform treatments for expectant mothers struggling with addiction. More broadly, this study will provide

insights into how opioid signaling contributes to the formation and maintenance of social attachments.

Disclosures: C.W. Liff: None. B.J. Marlin: None.

Poster

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Topic: I.06. Social Cognition

Support: Chan Zuckerberg Initiative
Howard Hughes Medical Institute

Title: Interrogating the Role for Extracellular Vesicles in Intergenerational Inheritance of Olfactory Fear Conditioning

Authors: *A. V. S. LEWIS¹, B. STECKY², B. J. MARLIN¹;
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Abstract: Fear learning induces heritable changes to sensory systems that influences future behavior and increases chances of survival. Recent work demonstrates that fear learning in rodents alters olfactory receptor choice in main olfactory epithelium (MOE), the sensory organ responsible for smell (Liff et al., 2023). Moreover, this biased choice is inherited by naïve offspring, indicating an intergenerational marker of olfactory fear conditioning. While this work suggests a heritable mechanism by which a stressor influences morphology, the molecular mechanism that biases olfactory cell fate remains unclear. Here, we interrogate the hypothesis that extracellular vesicles (EVs) mediate cell-to-cell communication to bias olfactory neuron identity in the MOE of stressed animals, as well as their offspring. We specifically interrogate the role for a capsid-forming protein, Arc, which is known to encapsulate EVs and is important for learning and memory. We find that Arc is required for maintaining long-term memory of olfactory fear conditioning and that Arc is expressed in the MOE. Our RNA-sequencing data also reveals transcriptional changes to EV machinery in the MOE following olfactory fear conditioning. Collectively, these data support the hypothesis that Arc-encapsulated EVs propagate signals of stress to bias olfactory receptor expression in stressed animals and their naïve offspring.

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Poster

PSTR190: Neuromodulatory Mechanisms of Social Behavior

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Topic: I.06. Social Cognition

Support: HHMI Freeman Hrabowski
NSF GRFP

Title: Understanding the molecular underpinnings of learning and adaptation through the mouse olfactory system

Authors: *B. STECKY¹, A. STUTZMAN¹, A. CARDEIRO¹, S. LOMVARDAS², B. J. MARLIN³;

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Abstract: To survive in a dynamic and often threatening world, animals must interrogate and respond to environmental cues. Odors - chemical signals that convey information about potential food, mates, and predators - are a critical class of sensory stimuli that guide adaptive behavior. Survival often requires learning from salient olfactory experiences. We use the mouse olfactory system to investigate how animals respond to learned odor cues and how this learning alters sensory processing. In order to teach mice to associate a neutral odor with an aversive stimulus, we implement an olfactory fear conditioning paradigm in which odor presentation is paired with a mild foot shock. Experiments were conducted in both wild-type and *gg8-tTA>tetO-P2-ires-GFP* mice - the latter of which expands the population of olfactory sensory neurons (OSNs) that express the P2 olfactory receptor and thus sense the conditioned odor. After conditioning, we assess learned odor aversion in a three-chamber odor preference assay. In parallel, to explore the molecular basis of learned odor aversion, we perform RNA-sequencing on FACS-isolated P2+ OSNs from conditioned *gg8-tTA>tetO-P2-ires-GFP* mice. We show that odor-shock pairing induces measurable changes both in olfactory-guided behavior and in the transcriptional profile of P2+ OSNs. For both genotypes, odor-shock pairing induces robust odor aversion that persists at least fourteen days after olfactory fear conditioning. This behavioral phenotype is coupled with transcriptional changes in P2+ OSNs. Fourteen days after conditioning, we observe significant differential expression of 141 genes in P2+ OSNs in paired mice ($p < 0.05$, paired versus unpaired, mean $|\log_2FC| = 1.50$). Interestingly, upon acute odor re-exposure fourteen days after conditioning, P2+ OSNs from paired mice exhibit substantially fewer transcriptional changes compared to their corresponding home and unpaired comparisons ($p < 0.05$, exposed versus unexposed, home=1076 DEGs, unpaired=484 DEGs, paired=19 DEGs). This suggests that prior odor-shock pairing induces a stable transcriptional state that reduces the need for further transcriptional modulation upon subsequent odor encounters, perhaps lowering the threshold to odor activation. Taken together, these findings argue that odor-shock pairing not only drives long-lasting behavioral adaptation, but also primes sensory neurons at the molecular level, encoding a form of experience-dependent plasticity. Our work highlights a previously underappreciated role for olfactory sensory neurons in storing features of associative learning, expanding the cellular locus of memory to peripheral sensory tissue itself.

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Poster

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Support: NYAS Leon Levy Neuroscience Scholarship (to T.A.)
HHMI Freeman Hrabowski (to B.J.M.)
Columbia Research Initiatives in Science and Engineering (to B.J.M.)

Title: The neuromodulation of stress-induced olfactory plasticity

Authors: *T. ARZUA¹, P. DAVIS², V. LOPEZ¹, D.-L. K. FERGUSON³, B. R. MCRAE⁴, A. STUTZMAN¹, B. J. MARLIN⁵;

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⁴Neurobio. and Behavior, Columbia Univ., New York, NY; ⁵Columbia Univ. Zuckerman Inst., New York, NY

Abstract: The stressors and traumas of our current world can commandeer evolutionarily established circuits in our brains responsible for detecting and responding to threats efficiently. This can lead to conditions such as post-traumatic stress disorder, panic disorder, and generalized anxiety, which altogether comprise the most prevalent classes of psychiatric disorders in the world. Using the mouse's olfactory system, our lab and others have shown that olfactory fear conditioning can induce behavioral and neuroanatomical changes that can be inherited and expressed in naïve offspring. Building on that, this study aims to investigate the roles of the neuromodulators norepinephrine (NE) and dopamine (DA) in this type of plasticity. Produced by the locus coeruleus, NE is crucial in regulating brain-wide responses to stress, including sensory processing. While DA is produced in the olfactory system itself, its role in olfaction is still elusive. To address the gaps in the knowledge of how traumatic experiences are encoded in the brain, we seek to understand how NE and DA can modulate olfactory plasticity caused by stress. To fully dissect these circuits, we have used a combination of olfactory fear conditioning, tissue clearing, and fiber photometry. Using viral tracers and whole-brain clearing, we first show that, on average, 20% of the LC projects to the olfactory bulb across sexes. Using fluorescent GRAB_{NE2h} sensors, we then demonstrate that levels of NE in the bulb dynamically change over the conditioning period when compared to mice that are not conditioned to fear the same odor. Furthermore, upon re-exposure to the conditioning odor, we see increased NE levels, as well as an increase in LC activity. We have also examined the fluctuations of DA using GRAB_{rDA3h} sensors in the olfactory bulb. Future studies will use optogenetic tools to determine if modulation by these two neurotransmitters is necessary and sufficient to induce olfactory plasticity, especially across generations. Together, this work will provide insights into how different

neuromodulators affect the processing and representation of stressful experiences in the brain. From a broader societal perspective, this will be a step toward a more comprehensive and specific response to our ongoing mental health crisis.

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Topic: I.06. Social Cognition

Support: Barnard College SRI Stipend
Howard Hughes Medical Institute

Title: The Role of the Main Olfactory Epithelium During Motherhood

Authors: *E. J. LEE^{1,4}, V. ANDREU², N. MIMOUNI⁵, C. LIFF², R. SEN⁵, B. J. MARLIN^{5,6,2,3},

²Neurosci., ³Psychology, ¹Columbia Univ., New York, NY; ⁴Neurosci., Barnard Col., New York, NY; ⁵Columbia Univ. Zuckerman Inst., New York, NY; ⁶Howard Hughes Med. Inst., New York, NY

Abstract: Motherhood is accompanied by significant emotional, physiological, and behavioral changes which are essential for pup survival. The olfactory system can support essential tasks including pup retrieval and nesting, but the specific neurobiological changes that support the transition to motherhood remain unclear. To characterize the changes in olfactory-guided maternal behavior, we used an odor preference assay with pup urine as the pup-derived stimulus. Mothers at postpartum day 5 showed a preference for pup odor compared to virgin females who showed no specific preference for either stimulus. Interestingly, late-stage pregnant females were tested with the same behavioral paradigm and exhibited no preference for pup odor, suggesting that there may be a shift in olfactory-guided behavior occurring post-partum. Mothers developed a specific preference for pup urine after parturition and this preference was not displayed with other odors, including social and non-social odors. To identify the potential olfactory stimuli that may influence this preference, pup urine was analyzed using gas chromatography-mass spectrometry, revealing distinct volatile compounds that are abundant in pup urine. Altogether, these findings indicate that there are underlying changes in postpartum mice's olfactory systems that support the transition into motherhood. Identifying the specific olfactory changes that support this process can help to better understand social attachment and maternal care.

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Topic: I.06. Social Cognition

Support: HHMI

Title: Whiffing Wonders: understanding the transition to motherhood through the main olfactory epithelium

Authors: *W. YASEN¹, N. MIMOUNI², B. J. MARLIN³;

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Abstract: The transition into parenthood involves significant change. Mothers in particular experience tremendous development to their reproductive, endocrine, and nervous systems to support the nurturing of offspring. Mice rely heavily on their adept sense of smell, and recent work in our lab has demonstrated that, unlike virgin female mice, mothers have a preference toward pup urine, which has implications for mother and pup bonding. Therefore, we hypothesize that hormonal fluctuations as well as pup chemosensory cues result in molecular changes to the main olfactory epithelium (MOE) during pregnancy as well as postpartum. Ongoing work in our lab indicates that bulk RNA sequencing has revealed various differentially expressed genes between PPD5 mothers and virgins. These included the gene *Nr1d1*, a protein associated with hormone secretion, as well as multiple genes related to cell cycle regulation. As there may be implications to neurogenesis, we have examined cell proliferation levels in mothers prior to parturition as well as postpartum. To accomplish this, FIJI was used to analyze EdU in the MOE. This work will help us further understand the ways in which the hormonal changes accompanying pregnancy help mothers adapt to care for their offspring. This information may also provide insight into the postpartum mind, which has further implications in understanding postpartum depression.

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Poster

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Topic: I.06. Social Cognition

Title: Facilitation of Coping Strategy Transitions by Oxytocinergic Neurons

Authors: *Y. GU¹, Z. LIU¹, Y. ZHAO³, N. N. GUAN¹, J. SONG²;

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Abstract: Passive coping, a maladaptive response to ongoing and uncontrollable stress that often results from sustained adversity, is associated with increased psychological distress, including anxiety and depression. Elucidating the mechanisms underlying the transition from passive to active coping, is a fundamental question in neuroscience and psychology. In zebrafish, exposure to conspecific alarm substance (CAS) generated a passive coping states characterized by long-term freezing behavior. Social stimuli by familiar conspecifics switched the passive coping into active support-seeking behavior. Utilizing a combination of state-of-art techniques, we found that oxytocin neurons in the preoptic area are the fundamental elements to mediate the behavioral state transition. The neural representation of passive coping behavioral state is the remarkable synchronization of neuronal activity in the dorsal pallium (Dc, homolog to mammalian cortex). Activation of oxytocin neurons disrupts this synchronized activity pattern by releasing glutamate, which acts on a disinhibitory circuit in the ventral telencephalon (Vv), thereby facilitating the transition from passive coping to active support-seeking behavior. These findings reveal a previously uncharacterized mechanism by which a passive coping state can be switched to an active, solution-seeking state. Oxytocin neurons enable individuals to adapt their behavioral coping strategies, offering significant implications for the development of novel mental health treatments and preventive interventions.

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Topic: I.06. Social Cognition

Title: Roles of the central noradrenergic system in social motivation in briefly isolated rats

Authors: *Y. MATSUMOTO, M. TOYOSHIMA, R. TACHIHARA, M. SONOYAMA, A. CHIBA, K. YAMADA;
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Abstract: Previous studies have shown that acute social isolation enhances social motivation in rodents. This behavioral change has been attributed to the dopaminergic and serotonergic systems. On the other hand, the involvement of the central noradrenergic system in isolation-induced social motivation remains unclear. Therefore, this study aimed to investigate the effects of pharmacological inhibition of the central noradrenergic function on social motivation following short-term social isolation using DSP-4, a selective noradrenaline neurotoxin. A total of 27 male Sprague-Dawley rats (9 weeks old) were divided into three groups: a saline control

group (SAL), a low-dose DSP-4 group (LOW, 10 mg/kg), and a high-dose DSP-4 group (HIGH, 20 mg/kg). One week before the behavioral test, rats were intraperitoneally injected with either saline or DSP-4. Behavioral tests were conducted over five days, and consisted of arena habituation, social habituation, baseline measurement, a social motivation test, and an empty cylinder test. In the 10-minute baseline measurement, focal rats were allowed to freely explore a three-chambered box containing a cylinder with an age- and sex-matched conspecific. After the baseline measurement, the rats were individually placed in an isolation condition cage. In the social motivation test, the rats were re-exposed to cylinders containing conspecifics, and their sniffing behavior toward the cylinders was observed for 10 minutes. Data analysis is still ongoing. Based on our results, potential roles of central noradrenergic system in isolation-induced social motivation will be discussed.

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Support: NIMH R01 MH131807
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Title: Phenotype and projections of Vasopressin 1a receptor-expressing neurons in the ventral tegmental area

Authors: *M. SADEGHI ALIABADI¹, B. PATEL², B. D. ROOD³;

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Abstract: Social behavior is fundamental for survival and well-being in most species, including humans. Although social behavior is fundamentally innate, it is modulated by learning and memory. Social behavior can be prosocial, including affiliative behaviors such as huddling and allogrooming, and antisocial, including different forms of aggression, and both patterns of behavior can be reinforced through rewarding outcomes. To demonstrate appropriate behavior, the social behavior network and the mesocorticolimbic reward pathway work together to form a social decision-making network. However, the neuronal mechanisms that drive the motivational aspect of social behavior remain poorly understood. Vasopressin (Avp) is a neuropeptide produced in the bed nucleus of the stria terminalis (BNST) and medial amygdala (MeA), which has been implicated in both prosocial and antisocial behaviors. Anatomical studies in mice determined that the ventral tegmental area (VTA) receives Avp-immunoreactive (Avp-ir) fibers from the sexually dimorphic Avp-producing cells in the MeA and BNST, and Avpr1a cells exist

in the VTA, a brain region best known for its dopaminergic (DA) neurons involved in reward processing. Although the VTA is considered a main source of dopamine neurons, half of its neurons are non-dopaminergic. In the literature, it has been found that DA VTA neurons play a role in responding to both social and nonsocial reward. The heterogeneity within the VTA makes it likely that individual subtypes of neurons in the VTA may function differently in encoding social and nonsocial reward, and the phenotype and function of Avpr1a cells in the VTA have not been examined. Previous studies using electrophysiology and in-situ hybridization indicated that AVP indirectly excites serotonin neurons in the Dorsal Raphe (DR) through putative glutamatergic Avpr1a neurons. We predict a similar functional role in that VTA Avpr1a cells are non-dopamine neurons that form local circuits regulating VTA dopamine neurons. Using RNAscope fluorescent in-situ hybridization in adult C57BL/J6 male and female mice, we co-labeled Avpr1a mRNA with markers for dopamine (tyrosine hydroxylase, TH), vesicular glutamate transporters (vGlut1 or 2), and vesicular GABA transporters (VGAT) to determine neurotransmitter phenotypes. Using a combination of Cre-dependent and non-Cre dependent fluorophore encoding AAVs, we examined the differential projections of Avpr1a and surrounding neurons. Our data identify phenotypes and projection patterns of Avpr1a neurons in a critical node in the mammalian reward pathway.

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Poster

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Topic: I.06. Social Cognition

Support: CIHR

Title: Crh^{PVN} neurons evaluate social threat and distress in conspecifics

Authors: *M. PARDASANI^{1,2}, I. D. AKINRINADE³, T.-L. STERLEY⁴, T. FUZESI⁴, J. S. BAINS²;

¹MCDB, Univ. of Colorado, Boulder, CO; ²Hotchkiss Brain Inst., ³Hotchkiss brain institute, ⁴Univ. of Calgary, Calgary, AB, Canada

Abstract: Our understanding of how animals detect and respond to threat rely on a framework of predator-prey interactions. However, conspecific interactions represent a critical source of social threat and distress, necessitating distinct neural mechanisms. The specificity of social threat-induced behavioral responses towards unfamiliar conspecifics and the role of their underlying neural circuitry remains poorly understood. Work from Bains lab has identified Corticotrophin releasing hormone neurons of Paraventricular nucleus of Hypothalamus (CRH^{PVN}) as central orchestrators of threat responses: encoding both escape response to looming visual threat and undergoing physiological adaptations during social transmission of stress. We examined CRH^{PVN}

neural dynamics in resident mice during resident-intruder interactions using synchronized fiber photometry and behavioral tracking. CRH^{PVN} activity increased during social approach to unfamiliar intruders, with a significantly larger response compared to familiar intruders. This differential response correlated with heightened chemosensory investigative behaviors. Optogenetic perturbation of CRH^{PVN} neurons disrupted investigative behaviors towards an unfamiliar intruder, suggestive of their role in coordinating appropriate behavioral responses. Notably, CRH^{PVN} neurons exhibited state-dependent encoding, specifically responding to the social distress of familiar conspecifics. These familiarity- and state-dependent responses reflect the specific role of CRH^{PVN} neurons in guiding appropriate social investigative behaviors.

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Poster

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Title: Competition-induced dopamine dynamics in the medial prefrontal cortex shape social hierarchy in mice

Authors: *M. SIM, H. PARK, C. CHUNG;
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Abstract: Social animals, including humans, naturally establish social hierarchies to optimize resource allocation and minimize conflict. While numerous studies have explored the neural basis of social dominance and competitive behavior, the mechanisms underlying the formation of social hierarchies remain unclear. To examine how competition shapes social hierarchy, we employed the tube test (TT), which evaluates social rank by inducing a competitive situation where animals express their motivation to lead. We found that social ranks were initially unstable but stabilized following the TT, showing significant correlations in rankings derived from the TT. These results highlight the role of competitive interaction in establishing social hierarchy. Given that the medial prefrontal cortex (mPFC) is a key region involved in regulating competitive behavior, and that dopamine receptor-expressing neurons in the mPFC exhibit neuronal properties dependent on social rank, we hypothesized that competition-driven hierarchy formation is mediated by dopamine dynamics in the mPFC. Pharmacological blockade of D1- or D2-type dopamine receptors in the mPFC during the TT disrupted the stabilization of social ranks. Notably, distinct temporal dynamics of dopamine release between losers and winners were

observed using fiber photometry with a dopamine sensor during the TT. Dopamine dynamics varied according to the competitive result, suggesting differentiated dopaminergic signaling during competition. Overall, these findings suggest that competition-induced dopamine release in the mPFC is a key mechanism for the formation and stabilization of social hierarchies.

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: U01

Title: Global and Modular Acetylcholine Dynamics to Movement, Sound and Reinforcement

Authors: *B. S. COHEN;
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Abstract: The neuromodulator and neurotransmitter acetylcholine (ACh) is necessary for normal cognition. However, the functional organization of the cortical cholinergic system remains elusive. Cortical ACh largely originates from subcortical projections in the basal forebrain which innervate the entire cortex with a modular architecture. Whether this intricate anatomy translates into modular ACh release during task-related behavior remains unknown. We used whole-brain expression of a next-generation G-protein-coupled receptor-activation-based ACh sensor (GRAB-ACh4m) and mesoscopic imaging to record ACh dynamics across the entire dorsal cortex during conditioning to reward and punishment. Our preliminary findings suggest that the cortical cholinergic system responds in a remarkably global fashion to activity and stimuli, while simultaneously organizing into distinct modules with unique response properties. This work advances our understanding of the degree of spatial and temporal flexibility of the cholinergic system and its potential role in modifying cognitive processes.

Disclosures: B.S. Cohen: None.

Poster

PSTR191: Learning and Memory in Subcortical Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR191.01/QQ4

Topic: I.08. Learning and Memory

Support: 5U19NS113201-05

Title: Dual mechanism of value learning underlying stability and flexibility tradeoff

Authors: *J. LEE¹, J. A. HENNIG⁴, S. J. GERSHMAN², N. UCHIDA³;

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Abstract: Value computation is a fundamental to the survival of animals. Classical models suggest value is stored in the synaptic weights. More recent theories propose that recurrent network dynamics can encode and update value through recurrent dynamics, independent of synaptic change. Although these two mechanisms are not mutually exclusive, the conditions under which each dominates remain unclear. Here, we show that environmental stability determines the neural mechanism underlying value learning. In stable environments, mice relied on synaptic plasticity in the basolateral amygdala (BLA), supporting stable value representations lasting over a week. In contrast, in volatile environments, mice transitioned to a dynamics-based strategy, with value signals degrading over minutes. A recurrent neural network with both online synaptic weight update and recurrent dynamics recapitulated this shift, displaying both plasticity- and dynamics-driven value learning. Pharmacological blockade of plasticity selectively impaired value updating in stable but not dynamic environments. Furthermore, inactivating OFC in mice trained on the dynamic task caused a deficit in the ability to infer value based on structural knowledge. Overall, our results demonstrate that environmental volatility governs the balance between synaptic and dynamic mechanisms, suggesting an important tradeoff between stability and flexibility in value computation.

Disclosures: J. Lee: None. J.A. Hennig: None. S.J. Gershman: None. N. Uchida: None.

Poster

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Program #/Poster #: PSTR191.02/QQ5

Topic: I.08. Learning and Memory

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NIH/NIDA 1R01DA059751
NIH/NINDS 1R01NS116753
NIH/NINDS 5U19NS113201
Simonds Foundation / Simons Collaboration on Global Brain

Title: The core neural circuit underlying temporal difference learning

Authors: *M. G. CAMPBELL¹, S. XU⁵, S. MATIAS², M. H. BURRELL³, M. WATABE-UCHIDA⁴, N. UCHIDA²;

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Abstract: Phasic dopamine (DA) release plays a major role in learning by assigning incentive value to associated stimuli. A leading theory proposes that this process is analogous to a reinforcement learning algorithm called temporal difference (TD) learning, and that DA acts analogously to the reward prediction error term within the TD algorithm, called the TD error. TD learning assigns reward predictions (values) to states by learning not only from rewards but also when its internal value estimates change. Although many studies have demonstrated similarities between DA activity and TD errors, including this core derivative-like property, the mechanistic basis for dopaminergic TD learning remains unknown. Here, we demonstrate that the circuitry bidirectionally connecting D1 DA receptor-expressing medium spiny neurons (D1-MSNs) in the lateral nucleus accumbens (INAc) to INAc-projecting DA neurons in the ventral tegmental area (VTA) accomplishes key components of TD learning. Specifically, pairing optogenetic stimulation of INAc DA axons with a preceding odor cue (“opto-conditioning”) potentiated the odor-evoked activity of INAc D1-MSNs (n = 7 mice), but not D2-MSNs (n = 6 mice), and generated signatures of TD error in DA activity (n = 5 mice, n = 43 optotagged dopamine neurons). In turn, optogenetic stimulation of INAc D1-MSNs with diverse temporal patterns drove INAc DA release and spiking of INAc-projecting VTA DA neurons according to the TD error of the stimulation pattern (n = 13 mice). This TD error-like transformation was well-approximated as a linear time invariant (LTI) system, which can be used to extract TD parameters at the level of single neurons. To establish necessity in a more natural context, we show that pharmacological inactivation of INAc altered DA signaling by specifically reducing the reward expectation (value) associated with conditioned odors (n = 5 mice) in a Pavlovian task associating an odor with water reward. Thus, the bidirectional circuit connecting INAc D1-MSNs and INAc-projecting DA neurons constitutes a minimal TD learning loop. A TD error-like response was also observed in dorsal striatal dopamine release following stimulation of dorsal striatal D1 MSNs (n = 11 mice), suggesting that diverse mesostriatal systems may perform analogous learning algorithms in parallel. These parallel circuits, employing a shared learning motif, may be flexibly recruited in specialized task contexts depending on the relevant state spaces, timescales, or behavioral demands.

Disclosures: M.G. Campbell: None. S. Xu: None. S. Matias: None. M.H. Burrell: None. M. Watabe-Uchida: None. N. Uchida: None.

Poster

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Program #/Poster #: PSTR191.03/QQ6

Topic: I.08. Learning and Memory

Title: Cortical configuration of integrator dynamics for context-dependent foraging decisions

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Abstract: For most animals, survival depends on the ability to forage for resources that are distributed throughout the environment. This involves making decisions about when to harvest from a "patch" of food/water, and when to leave in search of other opportunities - the classical "patch-leaving problem" studied in behavioral ecology. Across different environments, animals use knowledge of resource statistics to flexibly adjust foraging strategies. This capacity to adapt behavior to context is a core feature of animal cognition, yet while there is some understanding of how the brain instantiates decision processes, it remains unclear how neural circuits for cognition are contextually configured to tune their functionality. Foraging provides a natural window into the underlying neural circuit mechanisms that enable cognitive and behavioral flexibility. Here, we developed structurally equivalent virtual and free-moving foraging tasks to investigate flexible decision-making in mice. Animals navigate different environments to find patches that give water rewards - while deterministic patches yield a fixed reward sequence, stochastic patches give diminishing probabilistic rewards. Mice can toggle between decision strategies in different contexts, and using theoretical models, we find that this can be explained as a reconfiguration of integrator dynamics that instantiate an evidence-accumulation process for foraging decisions. Neural recordings in head-fixed and freely moving mice reveal distinct brain-wide activity modes that are recruited in different environments, and which drive coding of context-specific decision variables in the dorsal frontal cortex. Muscimol silencing experiments demonstrate causal necessity of this cortical circuitry for context-dependent, flexible decision-making.

Disclosures: L. Kingsbury: None. N. Uchida: None.

Poster

PSTR191: Learning and Memory in Subcortical Circuits

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Program #/Poster #: PSTR191.04/QQ7

Topic: I.08. Learning and Memory

Support: Howard Hughes Medical Institute
NIH R35

Title: Synaptic sign switching mediates online dopamine update

Authors: *S. LI, W. WANG, G. KNIPE, E. JERNG, P. CAPELLI, C. ZHOU, E. BILSEL, B. L. SABATINI;

Neurobio., Harvard Med. Sch., Boston, MA

Abstract: Excitatory and inhibitory synapses in the brain are generally thought as distinct entities with fixed synaptic signs. Unlike neurons in artificial neural networks, well-characterized biological synaptic plasticity rules only exert changes in synaptic weights but not signs. Here, we showed evidence of sign switching at synapses formed between glutamate and GABA co-releasing neurons in the entopeduncular nucleus (EP) and lateral habenula (LHb). Pairing of reward or punishment with optogenetic activation of EP co-release neurons makes EP-LHb synapses becoming net inhibitory or excitatory, respectively. This synaptic sign switch results in increase or decrease of downstream dopamine release and strongly correlates with recent DA updates. These data unveil a previously unknown plasticity at the EP-LHb synapse that alters both the synaptic sign and weight to rapidly update dopamine release and drive subsequent learning.

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Poster

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Program #/Poster #: PSTR191.05/QQ8

Topic: I.08. Learning and Memory

Title: Sevoflurane anesthesia selectively drives cognitive deficits in mice with high or low anxiety levels - Closing the bridge between pre-anesthetic anxiety and post-anesthetic neurocognitive dysfunction

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Abstract: Introduction Preoperative anxiety (POA) frequently correlates with postoperative delirium (POD), a significant clinical picture with outcomes from mild cognitive impairment to chronic deficits. Yet, their neurophysiological interplay is unclear. This study characterized how murine pre-anesthetic anxiety levels modulate post-sevoflurane behavioral/cognitive responses via fine-grained Water-Cross Maze (WCM) behavioral analysis. Methods 25 C57BL/6N male mice had EEG/EMG implants. Post-recovery, fear conditioning/retrieval freezing behavior was k-medoids clustered for Low Anxiety (LA; n=12) and High Anxiety (HA; n=13) groups. WCM spatial learning involved 5 training days (6 trials/day), then a Test day (10 trials). Post-Test, mice received 1hr sevoflurane (2.0%vol target, EEG-guided adjustments for burst suppression/anesthesia depth). A WCM Re-Test (10 trials) followed 1-day post-anesthesia. DeepLabCut tracked key body parts. Keypoint MoSeq identified behavioral syllables. Syllable frequency, duration, velocity changes (Test vs. Re-Test) were compared between LA/HA groups.

Results Gross WCM metrics (latency, accuracy) showed no LA/HA group differences post-anesthesia. However, syllable analysis revealed distinct, potential anxiety-dependent behavioral changes. During "Confusion" (repetitive/aimless swim) states, HA mice markedly decreased velocity (HA: -4.07%, LA: +25.94%; $p < 0.001$) and spent more time in "Confusion" (HA: -1.8%, LA: -37.1%; $p = 0.0014$). For "Wall" (boundary interaction/decision-making) syllables, HA mice increased duration (HA: +5.6%, LA: -14.5%; $p = 0.024$) and had a smaller velocity increase (HA: +5.87%, LA: +21.77%; $p < 0.001$). For "Swim" syllables, HA mice increased duration (mean change HA: +6.1% vs LA: -17.7%; $p < 0.001$) and had a smaller velocity increase (HA: +7.14% vs LA: +16.28%; $p < 0.001$). Discussion Fine-grained automated behavioral analysis revealed subtle but significant anxiety-dependent alterations in post-anesthetic behavioral strategies and motor control in the WCM, which were not captured by traditional cognitive measures. HA mice displayed a distinct post-anesthetic behavioral phenotype consistent with impaired cognitive processing (e.g., indecision, prolonged confusion with motor slowing) and inefficient motor patterns. These findings support our mouse model for investigating POA-POD interactions and identify objective behavioral markers for post-anesthetic cognitive dysfunction, modulated by individual anxiety traits.

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Poster

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Topic: I.08. Learning and Memory

Support: National Research Foundation of Korea (NRF) Grant RS-2025-00557395

Title: Analysis of functional circuits based on time-dependent brain activity in cortical and subcortical areas in response to CaMKII-specific stimulation reflecting microtubule structure

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Abstract: In Parkinson's patients, electric extradural motor cortex stimulation improves motor symptoms and verbal episodic memory-related cognition. Memory formation involves CaMKII activation via Ca^{2+} influx, with CaMKII's structure matching microtubules, suggesting their role in neural encoding. Microtubules exhibit piezoelectric and flexoelectric properties, indicating potential for direct stimulation via focused ultrasound. As a preliminary study, we used optogenetics to selectively stimulate CaMKII, consistent with microtubule structure, and tracked brain activity over time to decipher the neural circuitry activated by this targeted stimulation. In

this study, Sprague Dawley rats (n = 18) were injected with AAV5-CaMKII α -ChR2(H134R)-eYFP (1 μ l) in the motor cortex, and viral constructs were expressed. After implantation of an optical ferrule in the same region, 30-minute dynamic PET data were obtained simultaneously with injection of [18F] FDG (100 mCi / 100 g). The next day, a similar PET scan was performed with 30 minutes of optogenetic motor cortex stimulation. The entire PET scan was divided into 30 time frames. Each time frame from the two separate scans was compared to statistically examine differences in regional glucose metabolism. Furthermore, statistical tests on the static PET incorporating all time frames were also compared to the metabolic maps derived from the dynamic PET. Paired t-tests were performed using AFNI software. Brain regions with significant FDG changes in the stimulation group were calculated based on a P value of less than 0.05 and a cluster size of 12 or more contiguous voxels. Plotting normalized mean activity as a region of significance over the entire time allowed us to observe time-dependent fluctuations in long-range signaling. The motor cortex had higher metabolism than the sham group throughout the stimulation time. The striatum was active at the beginning of the stimulation and gradually decreased. Activity in the internal capsule and thalamus was significant at the beginning (< 10 min) and end (> 20 min) of the stimulation, with the middle being less active than the sham group. In conclusion, the neural circuit responding to temporal stimulation of the motor cortex showed fluctuations in activity during the response time. This is thought to be closely related to the electromagnetic oscillation of microtubules, which is expected to contribute to brain functions including memory in response to repetitive stimulation of the cortical and subcortical areas. This study is expected to be able to predict time-dependent neural circuits induced by microtubule-specific neuromodulation using focused ultrasound.

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Poster

PSTR191: Learning and Memory in Subcortical Circuits

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Topic: I.08. Learning and Memory

Support: NIH Grant R01NS118440
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Title: Engram neuron activity across amygdala, hippocampus, entorhinal cortex and medial prefrontal cortex during contextual fear memory processing stages

Authors: *L. VAN BOEKHOLDT¹, K. MCDONALD¹, V. BALENDRAN², S. J. ATON³;
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Abstract: Memory processing is often divided into three stages: encoding, consolidation and retrieval. During fear memory consolidation, encoded memories are reorganized and stabilized,

which is thought to involve a shift of the memory trace from the hippocampus (HPC) to neocortical regions. Other prominent regions with a role in fear memory processing include the entorhinal cortex (EC), amygdala and medial prefrontal cortex (mPFC). However, the exact mechanisms through which these structures support the memory process throughout the different stages remains elusive. In the current study, we aim to gain further insights into the role of the HPC, EC, amygdala, and mPFC throughout the memory process by looking at the activation of context-encoding engram neurons in these regions and their subregions at different timepoints in contextual fear memory (CFM- processing). To this end, *cfos-CRE^{ER}::tdTomato* mice underwent engram neuron labeling during exposure to the CFM context, using targeted recombination in activated populations (TRAP). Activation patterns of context-encoding neurons were subsequently quantified during and after single-trial contextual fear conditioning (CFC) in the same context. Cfos expression within tdTomato+ neurons was measured at four different times, as a measure of neuronal activity: immediately after CFC (CFM encoding), 2 hours post CFC (early consolidation), 4 hours post CFC (late consolidation), and 24 hours post CFC, following context re-exposure (CFM retrieval). Four groups of control animals were euthanized at the same four timepoints but were not fear conditioned. Preliminary data show overall trend of increased activation of context-encoding engram neurons in HPC, EC, amygdala and mPFC at all four timepoints compared to control animals. Interestingly, this increase is not present in all brain regions measured, and pronounced differences in activity were observed in these subregions at different stages of CFM processing. Characterization of engram reactivation in various brain regions will clarify their mechanistic contribution to the different stages of memory processing.

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Poster

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Topic: I.08. Learning and Memory

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Title: Scn vip neurons mediate light-induced transient forgetting

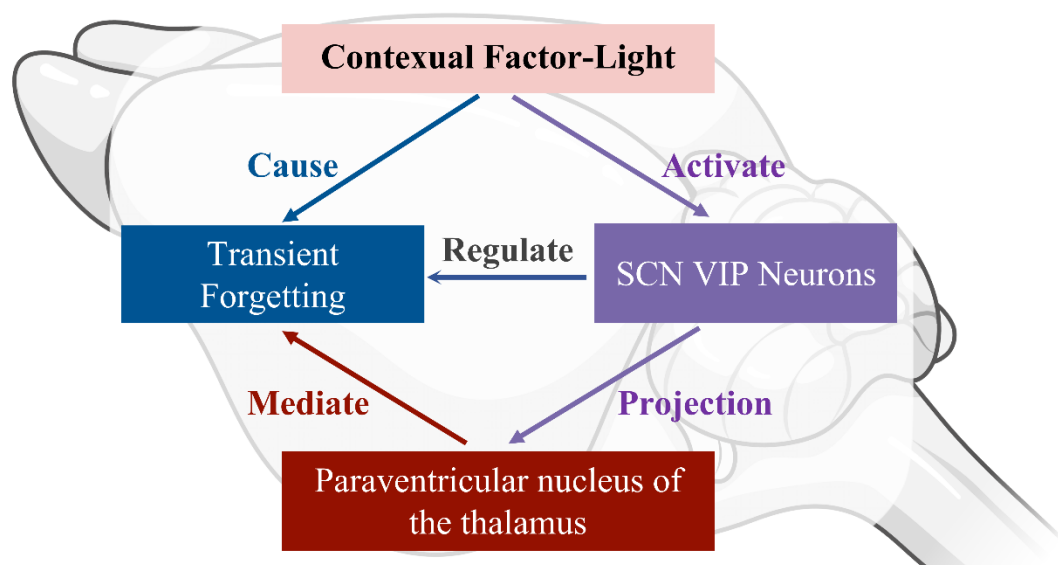
Authors: *X. SU¹, Y. LIU³, Y. ZHONG²;

¹Tsinghua Univ., Beijing, China; ²Tsinghua Univ., Beijing City, China; ³Sch. of Life Sciences, Tsinghua Univ., Beijing City, China

Abstract: While the suprachiasmatic nucleus (SCN) is well established as the master circadian clock in mammals, emerging evidence suggests that its influence extends beyond timekeeping functions. Our research uncovers a previously unrecognized role of vasoactive intestinal peptide

(VIP)-expressing neurons in the SCN in modulating memory accessibility in response to environmental light cues. We demonstrate that acute exposure to bright light leads to a selective and transient impairment of trace fear memory in mice. This light-induced forgetting is mediated by the activation of SCN VIP neurons, as indicated by increased c-Fos expression and elevated calcium activity. Through targeted optogenetic and chemogenetic manipulations, we show that artificial activation of SCN VIP neurons mimics the memory impairment caused by light, whereas their inhibition effectively blocks this effect. Importantly, we identify a functional SCN→PVT (paraventricular nucleus of the thalamus) VIP neuronal circuit that is both necessary and sufficient for this light-dependent modulation of memory. These findings significantly expand the known functions of SCN VIP neurons beyond their classical role in circadian rhythm regulation, revealing a novel mechanism by which light can dynamically influence cognitive states. By linking environmental light exposure to changes in memory retrieval, our study provides new insight into how sensory stimuli impact memory processes and suggests a potential neural basis for light-induced transient forgetting.

Model of Light-induced Transient Forgetting



Disclosures: X. Su: None. Y. Liu: None. Y. Zhong: None.

Poster

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UA High Performance Computing clusters

Title: Characterizing Sex Differences in the Domestic Ferret on Cognitive and Naturalistic Tasks

Authors: ***J. MENDOZA**¹, A. CRUZ PEREZ², L. ASGHARZADEH FALBINAN², R. CARLSON², L. DIECKHAUS², E. B. HUTCHINSON²;
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Abstract: Biological sex affects development, behavior, and age-related changes in the brain, which influence the risk of developing neurodegenerative diseases such as Alzheimer's Disease (AD). For example, females are disproportionately affected by AD, making up two-thirds of diagnosed cases (Moutinho, 2025). This sexual dimorphism has been documented across various animal models, from rodents to non-human primates. We assessed sex differences in a cohort of age-matched (6-12 months) males (n=4) and females (n=4) by measuring brain volume and cognitive behavior. Males exhibited ~25% larger brain volumes compared to females. This motivated us to explore whether these physiological differences impacted behavioral performance. Previous studies in ferrets have shown that males are more exploratory and social than females; based on these findings, we hypothesized that male ferrets would engage more with cognitive tasks than females (Talbot, 2021). To assess cognitive differences between male and female ferrets, we employed a NOR task, which has been previously used to evaluate TBI in ferrets (Schwerin, 2022). Due to ferrets being heavily motivated by scent (Fisher, 2006), and to build upon the high variability observed in the NOR task in ferrets, we expanded the cognitive tasks to also include a task that has been previously used in rodents (NoDoR) to the ferret. We developed a novel odor recognition (NOdoR) paradigm to assess whether ferrets of different sexes could identify new smells following a variable delay (60 minutes). To quantify cognitive task performance, we used DeepLabCut (Mathis, 2018) to label two points on the ferret: the nose and the back of the head. We classified interaction as any frame where the angle between the vector running through the ferret's two points and the object point was less than 30 degrees. We calculated the amount of time the ferret spent interacting with object A and object B. By analyzing sex differences in the brain volumes between males and females we found that males had greater brain volume than females with a volume difference of 25.73% (p<0.001). Despite these anatomical differences, there were no significant sex differences in cognitive performance on either cognitive task. Unexpectedly, male ferrets spent more time interacting with either object in both the NoDoR and NOR tasks compared to females. This suggests that males exhibit greater exploratory behavior or task engagement than female ferrets and underscores the importance of sex-specific baseline engagement level for the interpretation of cognitive task performance.

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Poster

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Topic: I.08. Learning and Memory

Support: KAKENHI JP: 23K27478
KAKENHI JP: 23K14683

Title: Spontaneous histaminergic neuronal activity in priming memory accessibility

Authors: *Y. MORISHITA¹, Y. TAKAMURA¹, K. NISHIMURA², Y. YOKOI¹, R. IZUTSU¹, N. HITORA-IMAMURA³, M. MINAMI², H. NOMURA¹;

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Abstract: Memory expression is influenced by fluctuating psychological and physiological states, rather than being a direct reflection of memory traces. Even with identical cues, memory expression varies, suggesting that pre-cue brain states may prime neural circuits to either enhance or hinder memory accessibility. However, the pre-cue neuronal mechanisms influencing cue-triggered activity and underlying fluctuations in memory accessibility remain poorly understood. One potential system constituting these brain states is the histaminergic system, which originates in the tuberomammillary nucleus within the hypothalamus. Histamine acts as a modulatory neurotransmitter, influencing neuronal excitability and neurotransmitter release across a wide range of brain regions, including memory-related regions such as the cerebral cortex, hippocampus, and amygdala. Here, we show that in mice, the pre-cue spontaneous activity of histamine neurons, which exhibits a slow oscillation, is critical for fluctuations in the accessibility of associative memory. Using fiber photometry with closed-loop stimulation, we found that cues presented during high histaminergic states evoke stronger memory expression. Pre-cue optogenetic manipulation of these neurons bidirectionally controls memory expression. Furthermore, using simultaneous calcium imaging and optogenetics, we showed that pre-cue histaminergic neuronal activity regulates cue-excited neurons in the basolateral amygdala, maintaining the ensemble activity patterns associated with memory expression. Our findings demonstrate that pre-cue spontaneous activity in histaminergic neurons shapes cue-evoked neuronal ensemble activity and memory accessibility, suggesting that this activity represents a priming state that prepares the brain for memory expression in response to cues and highlighting the need to understand the precise mechanisms through which the timing and dynamics of histaminergic activity influence memory expression.

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Poster

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Topic: I.08. Learning and Memory

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National Natural Science Foundation of China grant 32471089

Title: Adaptive reward representations integrate expected uncertainty signals in orbitofrontal cortex

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Abstract: Incorporating expected uncertainty into reward evaluation is critical for adaptive learning and behavior. The orbitofrontal cortex (OFC) represents reward attributes, such as delay and magnitude, alongside expected uncertainties about upcoming rewards, serving its established role in both value- and risk-based behaviors. However, the cellular basis of how reward and uncertainty interact remains unclear. To investigate, we trained rats on a task where odor cues predicted sucrose rewards with varying uncertainties in delay or magnitude. Single-unit recordings revealed that many OFC neurons encoded expected uncertainties related to reward delay or magnitude. Population-level analysis showed distinct neural codes for delay and magnitude uncertainties, separate from those for reward delay and magnitude. Importantly, signals for each reward attribute and associated uncertainty converged onto the same neurons, reducing the sensitivity of delay and magnitude encoding as uncertainty increased. These findings suggest a cellular-level computation in OFC neurons, whereby uncertainty signals are integrated into attribute-specific reward representations, potentially supporting flexible learning and risk control.

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Poster

PSTR191: Learning and Memory in Subcortical Circuits

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Topic: I.08. Learning and Memory

Support: Stanford School of Medicine Dean's Postdoctoral Fellowship

Title: Circuit dynamics underlying inter-hemispheric learning in premotor cortex

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Abstract: Planning and execution of goal directed action depends upon neural computations distributed across brain regions. During planning of directional tongue movements in mice, activity distributed across the two hemispheres of anterior lateral motor cortex (ALM) support robust neural computations: corruption of task encoding activity in one hemisphere can be rapidly rescued by uncorrupted activity in the other (Li, Daie et al. 2016, Chen, Kang et al. 2021). Achieving robustness requires a remarkable balance in inter-regional coupling: coding for task variables (instructed stimulus, choice) must be shared across brain areas, while simultaneously gating out task irrelevant noise. As animals learn to perform goal directed actions, how are learning-related changes in neural computation coordinated across multi-regional networks?

We investigate this question in mice learning to perform a short term memory task. Mice learned to discriminate the position of a tactile stimulus, maintain the location of this stimulus in memory over a delay period (3s), and report the stimulus location during a cued response period for water reward. We recorded ALM activity using longitudinal two-photon calcium imaging in single hemispheres, or bilateral Neuropixels probe recordings at different stages of learning. Intermittently throughout learning, we used optogenetics to silence activity in one ALM hemisphere and analyzed consequences to neural activity.

Animals learned the task over a period of weeks, measured as an increase in behavioral accuracy from 50% (naive) to above 70% (expert). We used probabilistic graphical models to infer cross-learning changes in the structure of neural activity within and across hemispheres. Neurons initially formed subpopulations which were co-active in the same task conditions, but with distinct subpopulations active on disjoint subsets of trials. Notably, recruitment of subpopulations was coordinated across ALM hemispheres, whereby activity of subpopulations in one hemisphere could be predicted from the other. As animals achieved expert level performance, these subpopulations merged, stabilizing coding of task variables. Video analysis indicated that these activity changes cannot be explained by uninstructed movements. Simultaneously, in the expert stage, coding for task related variables became robust to perturbations of the contralateral hemisphere.

Our results suggest a coordinated learning process across ALM hemispheres, marked by synchronized recruitment of subpopulations encoding task variables. Subsequent refinement of these subpopulations gives rise to robustness between larger multi-regional networks.

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Poster

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Topic: I.08. Learning and Memory

Support: 2019FYA0709504

Title: Opposing roles of projections from OFC and AIC to BLA in learning and memory

Authors: *J. ZHANG¹, C. QI², C. T. LI³;

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Abstract: How cortical inputs from various regions are integrated in subcortical areas to control behavior is an essential question in systems neuroscience. Here we addressed the question focusing on cortical inputs to the basolateral amygdala (BLA), which is critical for working memory and reward learning. BLA receives inputs from the orbitofrontal cortex (IOFC) and agranular insular cortex (AIC), however, it is not clear how the projections from these two regions to BLA contribute to learning and memory. Anterograde tracing showed that the BLA neurons receiving projections from IOFC distributed more anterior and dorsal than those from AIC. We then trained head-fixed mice to perform olfactory-based working-memory task. Optogenetically suppression of delay-period activity of the IOFC-BLA projections in the learning phase improved task performance, whereas suppression that of the AIC-BLA projection impaired task performance. To examine neuronal encoding of learning and memory related information by these two pathways, we conducted two-photon calcium imaging of BLA neurons receiving projections from either IOFC or AIC. We found stronger encoding of working-memory related information in the BLA neurons receiving AIC projections than that receiving IOFC projections. Thus, the projections from the IOFC and AIC to BLA exert opposing roles in learning of working-memory task, through distinct neuronal populations.

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Poster

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Topic: I.08. Learning and Memory

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Title: Substantia nigra pars reticulata modulation of the prefrontal cortex via the ventral medial thalamus

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Abstract: Functional connections between higher-order (non-sensory) thalamus and the medial prefrontal cortex (mPFC) are implicated in executive functioning and arousal. The ventromedial thalamus (VM) is a higher -order thalamic nucleus that has been shown to play a critical role in

movement initiation, sleep-wake transitions, and regulation of attention. We previously showed that thalamocortical (TC) cells in VM project to the most superficial layers of mPFC, where they contact specific populations of inhibitory and excitatory cells. Similar to TC cells studied in sensory systems, VM is modulated by robust feedback from the cortex, representing a feed-back loop. However, unlike first-order thalamic nuclei, VM receives no inputs from the periphery, and instead is influenced by subcortical inputs. In motor systems, VM receives a major subcortical input from the substantia nigra pars reticulata (SNr), which potently inhibits TC cells. However, it remains unknown how SNr and other subcortical inputs influence the parts of VM that project to more cognitive areas like mPFC. Here, we use viral tracing, optogenetics, and in-vivo whole cell patch clamp electrophysiology to elucidate how SubCtx impacts VM to shape mPFC activity.

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Poster

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Title: Calcium signaling in distinct cortical cell types during visual discrimination

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Abstract: The role and functional mechanisms of distinct cortical cell types in the representation of external world context-dependent variability of sensory input remain largely unexplored as of yet. To investigate the occurrence and interaction between visual cue representation and reinforcement feedback during learning, we developed a behavioral task where controlled water-access mice were trained to discriminate between two types of drifting grating visual stimuli, one followed by a drop of water as a reward while the other was unrewarded. Learning progression was assessed on the ratio of anticipatory lick rates during stimulation. We conducted these measurements in the early stages of learning, when the mice were familiar with the visual discrimination task, but discrimination between the rewarded and non-rewarded stimuli was not yet significant. We repeated the measurements once the mice were able to reliably discriminate between the two types of stimuli. We used in-vivo 3D two-photon laser scanning microscopy with acousto-optical deflectors to examine calcium activity in the in pyramidal cells and VIP- and SOM-expressing interneurons in the V1 region of the awake, behaving mice. Here we

present findings about the differences in the recruitment of pyramidal neurons, VIP-INs and SOM-INs by visual stimulation and reward delivery, and possible explanations of their function based on microcircuitry connections.

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FRM FELLOWSHIP

Title: Beyond classes: distinct parvalbumin interneuron types in aversive states

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Abstract: The survival of animals is determined by their ability to cope with danger. As such, mechanisms regulating emotions such as fear and anxiety are crucial. The basolateral amygdala (BLA) plays a central role in regulating these emotional processes. Within the BLA, excitatory principal neurons encode and relay emotionally relevant information to other brain regions, while GABAergic interneurons provide precise regulation of their activity. Among these interneurons, parvalbumin-expressing (PV) interneurons are critical for the control of anxiety- and fear-related behaviors. PV interneurons in the BLA consist primarily of two subtypes: basket cells (BCs) and axo-axonic cells (AACs). Their distinct postsynaptic targets, along with previous studies in anesthetized rodents, suggest that BCs and AACs may have specialized roles in controlling fear-related behaviors. To investigate this, we developed a novel transgenic mouse line enabling the selective genetic targeting of AACs and BCs in the BLA, allowing us to record and manipulate these interneurons during behavior. Our recordings revealed that AACs and BCs are differentially engaged during fear- and anxiety-related behaviors. Furthermore, their selective inhibition demonstrated that these distinct PV interneuron subtypes play complementary roles in regulating BLA network activity. We postulate that AAC are essential during aversive emotional states transitions while BC appear crucial in their maintenance. This work provides the first evidence that specific GABAergic cell types, beyond broader interneuron classes, contribute to the encoding of emotional processes.

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Poster

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Title: Harnessing mechanisms of learning-induced neuroplasticity to enhance signal-in-noise detection in auditory cortex and behavior

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Abstract: Auditory associative learning induces sound-specific changes in the auditory cortex (ACx) (Schreiner and Polley 2014; Weinberger 2015). Does neurophysiological plasticity offers a signal processing advantage for learned signals under subsequently challenging listening conditions? Learning mechanisms may selectively promote listening for a remembered sound signal in noisy backgrounds via signal-specific ACx plasticity to facilitate signal-cued behaviors. To test if learning-induced ACx changes improves signal processing in noisy backgrounds, adult male rats ($n = 11$) were shaped to press a lever to receive a water reward. Training followed in “Quiet” on a simple tone-reward associative task (5.0 kHz, 60 dB SPL). Daily sessions required for >80% correct presses to tones were used to identify rapid (< 10 days) vs. slower (> 10 days) learners. After reaching the same high levels of asymptotic performance, a behavioral memory test confirmed response specificity for acoustic frequency (5.0 kHz (trained tone), vs. 4.2 kHz, 5.9 kHz) in “Quiet” vs. “Noise” under different signal-to-noise ratios (SNR). *In vivo* ACx multiunit recordings followed all behavioral assessments in a single acute anesthetized recording session in two parts: (1) pure tones (25ms, 0.525-47.7 kHz, 10-60 dB SPL) were in “Quiet” to identify ACx multiunit activity based on short-latency, frequency-tuned, tonotopic evoked responses; (2) the same tones (25ms) embedded in Gaussian white noise trials (275-415ms after noise onset) under varying SNRs. Remarkably, responses to the remembered tone frequency in noise differed in rapid- ($n = 6$) vs. slower- ($n = 5$) learning rats, even though testing was done when all rats performed the task (in Quiet) equally well. Only rapid learning changed sound-evoked ACx activity ($n_{\text{rapid}} = 99$ vs. $n_{\text{slower}} = 67$ sites relative to naive: $n = 7$ rats, 94 sites) as: (i) signal-specific significantly increased evoked activity for the behaviorally relevant tone and (ii) significantly decreased evoked activity during steady state noise. Statistically significant differences emerged with higher noise conditions and were most pronounced in rapid vs. slower learners. Surprisingly, behavioral responses generalized across acoustic frequency in both groups during quiet and the lowest levels of background noise—signal-specificity only emerged for rapid learners with higher levels of background noise before failing again under the noisiest conditions. This work highlights the impact of learning experiences on enhancing signal

detection via a non-linear auditory cortical decoding mechanism that is established early during the acquisition of novel auditory associations.

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Title: Learning an association is limited by changes to the dynamics, not geometry, of posterior parietal cortex representations

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Abstract: When an animal learns a novel cued choice task, several types of neural plasticity are required. The animal must learn sensory representations to distinguish the stimuli, motor representations to produce the correct actions, and finally must form the correct associations between sensory and motor representations. Even when stimuli and actions are easily distinguishable, mice require tens of hours to learn an association that is stable over seconds of working memory. We hypothesize that in such cases, the limiting factor for task performance is not learning sensory or motor representations, but rather the formation and stabilization of an association between them through changes to the dynamical landscape of neuronal activity in association cortex. To test this, we trained mice on two related two-alternative choice tasks in a virtual T-maze. The first task requires first simply perceiving a visual cue on the left or right side of the maze and turning in the same direction at the end. The second task requires remembering the same type of cue for a variable distance before turning. During hour-long sessions over 4-6 weeks of training, we recorded activity from neurons in the posterior parietal cortex (PPC) expressing jGCaMP8f using two-photon calcium imaging. We extracted activity from matching neurons across all sessions and time warped activity based on location in the maze. Finally, we identified components of activity in each session associated with cue and choice using demixed principal components analysis (dPCA). Despite observing abrupt improvements in both perceptual and memory task performance midway through training, PPC activity can be linearly separated based on both cue and choice identity even in early sessions in both tasks. Furthermore, the dPCA components that best separate cue and choice are non-orthogonal, and the angle between them does not significantly change over the course of learning for either task. Thus, learning does not reflect changes to representational geometry in the PPC. However, over

the course of learning, trajectories elongate along the choice axis, such that the neuronal activity patterns for left and right turns become more distinct. This sharpening or deepening of attractor wells likely helps to maintain a committed choice for longer without being corrupted by noise, particularly for the memory task. After elongation, performance is still limited for several sessions, as the association between cue and trajectory is still inaccurate. Eventual improvements are likely associated with changes to the dynamical landscape such that the existing cue representations reliably map to the correct choice attractors.

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Poster

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Topic: I.08. Learning and Memory

Title: Cortical mechanism underlying associative learning process

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Abstract: Associative learning refers to the ability to learn and remember the relationship between two initially unrelated pieces of information, a fundamental cognitive function in biological intelligence. The cerebral cortex, as the high-order center of the neural system, contains neuronal ensembles capable of encoding various types of information, and plays a critical role in processing information and facilitating associative learning. In this study, we trained mice to learning a sensorimotor association task and recorded the simultaneous activity of up to 16,000 neurons across dorsal cortical areas throughout the learning process. Functional neuronal groups were identified based on principles of sensorimotor association and task structure. During learning, the functional connectivity and activity causality among these groups exhibited a backward-propagated strengthening pattern in primary sensory and motor areas, reflecting the transformation of strong relationships between reward and motor into preparatory temporal activity and motor. Through cortex-wide analyses of functional activity and connectivity changes, we identified dynamic alterations in functional cortical pathways during learning and highlighted the unique role of the posterior parietal cortex (PPC) in associating temporal gap at early learning stages. Combining our imaging technique and optogenetic inhibition, we further confirmed that the PPC regulate sensory-motor area activity and co-fluctuation in specific communication subspace, and is crucial for driving associative learning. Cortical global disinhibition microcircuits might contribute to temporal gap activity generalization from PPC to sensory-motor areas in the initial learning stage. In summary, our findings identified a potential teaching signal in PPC at acquisition learning stage, and revealed a systematic functional connectivity change for sensorimotor association expression.

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Title: Sensory-evoked acetylcholine release across cortical regions is modulated by stimulus modality, complexity and valence

Authors: *E. Y. KIMCHI¹, A. R. CHAMBERS^{2,3}, T. L. CHAKOMA³, D. KRANZ⁴, D. B. POLLEY^{3,2};

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Abstract: Acetylcholine release in the cortex, primarily originating from cholinergic basal forebrain (BF) neurons, is a mediator of plasticity, learning and stimulus salience. Recent evidence highlights the diverse temporal and spatial scales, as well as the sensory contexts, over which cholinergic BF neurons act to shape the plasticity of cortical neurons. We and others have observed sensory-evoked neural activity in BF neurons that varied according to the recording location within BF, sensory modality, and whether sensory cues predicted reward, punishment, or had no behavioral relevance. These findings question whether acetylcholine release in cortical regions targeted by BF neurons displays a similar degree of topographic and functional heterogeneity. We measured local acetylcholine release in response to sensory stimuli in the visual, auditory and prefrontal cortices of awake, head-fixed mice with fiber photometry mediated by the fluorescent sensor GRAB_{ACh}3.0. Slow acetylcholine release exhibited a similar degree of coherence with pupil-indexed arousal across sensory and non-sensory cortical regions. For phasic release, however, we found that spatial topography and amplitude are modulated by the modality, complexity, and valence of the stimulus. ACh release to visual gratings elicited weak responses only at high contrast, while auditory gratings (ripples) elicited rapid and sustained ACh release across cortical regions. Highlighting the modality dependence of ACh release, even the simplest auditory stimuli, pure tones, elicited more robust ACh release in auditory and visual cortex than visual gratings. We then compared sound-evoked phasic ACh release to classic elicitors of neuromodulatory activity—appetitive and aversive reinforcement—and found them comparable in scale. Finally, combining sound with reward did not impact the magnitude of the already robust sound-evoked ACh release in the passive case. These results point to a potentially privileged role for the auditory modality, which is unique in its importance

for signaling threats across brain and behavioral states, for recruiting widespread and robust acetylcholine release in the cortex.

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Title: Generalization and abstraction: primate hippocampus and prefrontal cortex in learning set formation

Authors: *M. GARZA¹, A. ORLYANCHIK¹, V. SHIRHATTI², S. LUPKIN⁴, R. COOLEY¹, B. PEYSAKHOVICH⁵, E. A. BUFFALO⁶, D. J. FREEDMAN³;

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Abstract: Primates are remarkably efficient at learning from experience: we rely on knowledge structures to organize regularities in our environments and apply this information to new scenarios. A learning set is a cognitive structure which enables us to solve tasks increasingly more efficiently by developing a generalizable strategy: 'learning how to learn'. Hippocampus (HPC) and prefrontal cortex (PFC) are each implicated in rapid learning, yet how their neuronal encoding changes with experience to guide the long-term learning process remains unknown. We trained one female, and are preparing two male rhesus macaques, to learn 24 sequential problems of a visual association task. In each problem, monkeys learn to associate two novel, arbitrary stimulus images with two conserved targets, responding with a saccade to obtain a fluid reward. A problem is considered 'learned' upon reaching 85% accuracy on 100 consecutive trials. Monkey 1 'learned how to learn' with an exponential decrease ($R^2 = 0.788$) in trials-to-criterion. We used semi-chronic electrode arrays to record from PFC (Brodmann Areas 9/46, 21-26 multiunit channels / session) and HPC (mainly CA3, 14-25 / session) during learning in Monkey 1, and are using Diagnostic Biochips' Deep Array 128-channel probes in each area in Monkeys 2-3. All sessions include both a familiar and a novel problem, to assess changes in cross-problem generalizability of neural representations across learning. By randomizing target location, we dissociate saccade planning from image-target association and evaluate neural encoding of these variables independently. Preliminary analyses of neurophysiological data from Monkey 1 indicate that HPC and dlPFC neuronal populations represent learned associations and saccadic response direction in a problem-general manner, as assessed by problem-general Support Vector

Machine decoding and projections onto low-dimensional feature axes. Our results suggest this generalizability of response direction, and association during early stimulus viewing, increases from early to late problems in each brain area. We also assessed stimulus-independent abstraction as the performance of decoders on problems held out from training. Both areas trend toward representing learned associations in an abstract format during stimulus viewing in later problems. Interestingly, our data suggest both areas may also represent response direction increasingly abstractly as animals form a learning set. Taken together, our results support a neural basis of increasing efficiency in “learning how to learn” an association task in both HPC and PFC: abstracting and generalizing the commonalities across problems.

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Title: Emergence of learned abstract and context dependent encoding in primate oculomotor areas and hippocampus during foraging

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Abstract: Rapid learning and generalization across sequentially learned experiences are key to behavior in humans and other animals. To study the neural basis of rapid learning in non-human primates we developed a naturalistic foraging-based associative learning paradigm under which monkeys rapidly learned novel stimulus-reward associations in single sessions. In the saccade foraging task (SFT) they freely explored arrays of visual stimuli to harvest chosen targets for rewards, and successfully learned hierarchies based on stimulus features (e.g. color, spatial location, category) to maximize their rewards. Monkeys were able to solve 2-3 such problems on each day allowing us to compare their behavior and neural responses across multiple oculomotor

(frontal eye field (FEF), lateral intraparietal area (LIP), and superior colliculus (SC)) and reward-based learning and memory related (orbitofrontal cortex (OFC) and hippocampus) brain regions throughout learning. To understand the various strategies used by the monkeys to learn new problems we adapted a modified Bayesian approach, based on dynamically decaying evidence, to update their probabilities depending on ongoing choices, and infer underlying behavioral strategies at the level of individual harvests. Furthermore, we introduced the idea of a contextual update-magnitude that depends on the surprisal of an event. These methodical approaches lend greater flexibility to the evolution of probabilities associated with different strategies, reflecting dynamic switches in behavioral patterns and performance during learning of problem sets. These behavioral analyses revealed emergence and evolution of different problem-specific and monkey-specific strategies across learning. Abstract encoding of the reward value and the preferred feature which generalized across successively learned problems were observed strongly in FEF and SC, to a lesser degree in LIP, and weakly in hippocampus. Encoding in hippocampus was context specific, exhibiting rapid discrimination between stimuli within a problem set during learning, with no generalization across sequentially learned problems. Shared representations in these areas across successive problems depended on the state of learning, choice preferences and the behavioral strategy in use. These results suggest complementary roles for these areas during learning of problem sets, wherein the oculomotor areas develop and maintain abstract schema representations which generalize across contexts, while the hippocampus forms context specific cognitive maps that may facilitate rapid learning of novel problems within a context.

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Title: How do neural representations in area LIP during categorization depend on category structure?

Authors: *R. COOLEY¹, P. MOGHIMI³, D. J. FREEDMAN²;
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Abstract: Categorization is a cognitive process by which stimuli are assigned to behaviorally relevant groups. Categorization allows knowledge about structure in the world to be organized in

a generalizable format, and is a key computation underlying the robustness of complex behavior. Previous work has revealed category learning-induced changes in neural representations across a variety of brain regions implicated in supporting categorical decisions. The lateral intraparietal area (LIP), in particular, contains generalized representations of visual stimuli during categorization. This has led to the theory that LIP plays a role in mapping stimuli to categorical outcomes. However, these studies generally used tasks in which a single stimulus dimension determines category membership. In contrast, real-world objects have multiple visual features which can be shared across stimuli that must be treated differently. In this case, the visual features of an object must be integrated so that it may be correctly acted upon. In this study, we trained two monkeys to categorize stimuli defined in a multidimensional color and motion-direction space where the category rule requires integration of the two features. We recorded neural activity in area LIP during 51 sessions (28 sessions Monkey D, 23 sessions Monkey M), obtaining 831 LIP units (379 Monkey D, 452 Monkey M). We observed motion direction and color selectivity at the unit level in both monkeys; in Monkey D, 62/379 units were selective at the $p < 0.05$ level for motion direction and 75/379 for color using n-way ANOVA. In Monkey M, 122/452 units were selective for motion direction and 80/452 for color. Selectivity for both stimulus features permitted above-chance linear category decoding ($73 \pm 5\%$ Monkey D, $78 \pm 5\%$ Monkey M, 50% chance); however, abstract category encoding was absent in LIP at both the single-unit (mean ROC-based category tuning index for Monkey D: 0.0004 ± 0.04 , $p = 0.9$ via one-sample t-test; mean rCTI for Monkey M: 0.0035 ± 0.04 , $p = 0.3$) and population level (cross-condition generalization decoders were at chance for both monkeys). We believe this finding could suggest general constraints on when and why LIP shows explicit categorical encoding; specifically, that category structure with respect to stimulus dimensions may be a factor determining how LIP is recruited during categorization. Current work focuses on identifying the nature of these constraints through modeling of animals' behavior, constructing circuit models of category learning, and deeper analysis of LIP neural representations at the single-unit (linear encoding models) and population (representational similarity analysis) level.

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Title: Anatomical and functional dissociation of flexible and stable value processing in the primate subthalamic nucleus

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Abstract: Deep brain stimulation (DBS) of the subthalamic nucleus (STN) is a therapy for alleviating motor impairments in Parkinson's disease (PD). Accordingly, research on the STN has predominantly focused on motor control. However, previous studies have provided evidence that the STN is also involved in cognitive functions. Clinical studies have reported that STN-DBS worsens value-based decision-making deficits in PD patients (Saint-Cyr et al., 2000, Brain). Furthermore, recent anatomical studies have shown that the STN receives inputs from value-processing structures involved in goal-directed and habitual behaviors, including the substantia nigra pars compacta and the globus pallidus externa (Kim & Hikosaka, 2015, Cell; Kim et al., 2017, Neuron). These therapeutic and anatomical findings suggest a potential role for the STN in value-guided behaviors. However, it remains unclear how the STN processes object values for goal-directed and habitual behaviors. To examine this, we recorded STN neuronal activity in monkeys performing a reversal learning task with visual objects to assess flexible value for goal-directed behavior, and a passive-viewing task to assess stable value for habitual behavior. In both reversal learning and visual habit tasks, monkeys more frequently gazed at good objects, confirming value-based behaviors. Among 149 object-responsive neurons, 73 neurons (49%) encoded flexible value, and 48 neurons (32%) encoded stable value. Notably, we found that the STN processes flexible and stable values differently, both anatomically and functionally: Flexible value neurons were distributed throughout the STN, whereas stable value neurons were concentrated in the caudal STN (cSTN). In addition, on average, while flexible value neurons showed no bias in their response to good or bad objects, stable value neurons responded more strongly to bad objects. This negative value coding in the cSTN suggests a mechanism for suppressing habitual gaze toward bad objects. To examine whether the cSTN plays a crucial role in visual habit, we inactivated the cSTN by Muscimol injection. Interestingly, cSTN inactivation led to automatic saccades toward stable bad objects, but did not affect goal-directed behavior, indicating selective impairment of habitual behavior. In contrast, inactivation of the rostral STN had no effect on visual habit, likely due to the restricted distribution of stable value neurons in the cSTN. Overall, our findings suggest that excitatory responses of cSTN neurons to bad objects enhance downstream activity in the substantia nigra pars reticulata, thereby suppressing automatic gazes toward bad objects during habitual behavior.

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Title: Uncovering Lifespan-Consistent Brain Representations in Cognitive Function via Task Decoding

Authors: *X. SUN^{1,2,4}, C. CHANG¹, H. HE³, A. MITTAL¹, C. G. HABECK³, Y. STERN³, P. SAJDA¹;

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Abstract: Understanding how cognitive functions are represented in the brain across the lifespan is essential for mapping normative and pathological development. Changes in cognitive function across the lifespan can be captured by four core reference abilities (RA): episodic memory (MEM), fluid reasoning (FLUID), perceptual speed (SPEED), and vocabulary (VOCAB). Stern et al. collected fMRI data across tasks targeting these reference abilities and found no significant age-related differences in Reference Ability Neural Networks (RANNs) across age groups (20-80 years). Efforts to distinguish these networks with linear-indicator regression, resulting in an average accuracy of 77% (MEM: 76%; FLUID: 82%; SPEED: 79%; VOCAB: 71%). Here, we consider a non-linear approach based on metric learning, which constructs latent spaces from the same high-dimensional fMRI data and is interpretable via sampling. Our metric learning approach substantially improved classification accuracy across all four reference abilities (87%) by acquiring the latent embeddings that reduce the intra-class variability while maximizing the inter-class variability. On pairwise classification, we achieved an even higher average accuracy of 96% across the six binary task comparisons. We also compared our results with advanced linear methods such as Principal Component Analysis (PCA) and ElasticNet, and found that our approach significantly outperformed these techniques, highlighting the effectiveness of metric learning in uncovering meaningful brain representations. Furthermore, the latent embeddings derived from metric learning enabled us to extract robust and interpretable spatial activation patterns. The resulting activation maps reveal precise, task-specific networks that align with known cognitive systems and remain stable across the lifespan. We identified key functional substrates associated with cognitive control, memory, and reasoning. The age-related changes observed in these networks offer valuable insights into trajectories of cognitive decline and may serve as early indicators for clinical intervention. Additionally, our findings support the existence of stable neural representations of cognitive function and demonstrate the potential of decoding-based approaches in advancing lifespan cognitive neuroscience.

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Poster

PSTR191: Learning and Memory in Subcortical Circuits

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR191.26/RR9

Topic: I.08. Learning and Memory

Support: R00

Title: The effects of reactivation during sleep on neural representations of episodic memory in humans.

Authors: *S. AQUINO ARGUETA¹, M. CHO¹, C. TAYLOR¹, F. YAO¹, A. THOMAS¹, E. SCHECHTMAN²;

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Abstract: Sleep has been shown to play an active role in consolidating memories by reactivating their memory traces. In this project, we directly examined the effects of reactivation on the neural representation of episodic memories. Participants formed stories linking four objects (e.g., a ball) to a coherent narrative (e.g., a birthday party). We measured object-context binding using a multivariate pattern analysis with functional MRI (fMRI) before and after sleep. Selectively targeting memories for reactivation by unobtrusively presenting memory-related sounds during sleep - a technique termed targeted memory reactivation - promoted the specificity of episodic memories. The overlap in neural representation among memories that were contextually linked together was reduced when these memories were reactivated, leading to their decontextualization. This study was complemented by another study examining the neural correlates of endogenous memory reactivation across multiple sleep stages using both fMRI and EEG. This study examines whether reactivation during sleep leads to decontextualization. Taken together, these studies inform our understanding of how memory reactivation of objects in their context plays out during undisturbed sleep.

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Poster

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Topic: I.08. Learning and Memory

Support: Army Research Office AWD-7776145

Title: From System 2 to System 1: Neural mechanisms of deep concept learning in the brain

Authors: *L. CHANG¹, N. STEINBERG^{2,1}, J. LIN¹, F. A. MARTINEZ ADDIEGO¹, T. MORGAN³, L. HUBER³, P. BANDETTINI³, M. RIESENHUBER¹;

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Abstract: Object categorization is a crucial cognitive operation and fundamental to mapping sensory stimuli to semantic knowledge. Prior work has shown a central role of the prefrontal cortex (PFC) in learning object categories. Yet, the PFC is not the brain area associated with the storage of semantic information and concept representations in the brain. Rather, recent research has shown that while PFC is a flexible control area central to the execution and learning of diverse tasks, the *storage* of semantic information is mediated by another brain area (that provides input to the PFC)—namely the anterior temporal lobe, ATL. Influential theories of semantic cognition have proposed a key role for the ATL in representing concepts. Yet, it is not well understood how concept representations come to reside in the ATL. We hypothesize that slower, more effortful learning first occurs in the PFC (System 2, in Kahneman’s terminology), using its ability to flexibly learn new tasks. We have developed a biologically plausible computational model to show how, once category circuits have been learned in the PFC, top-down, re-entrant signals from PFC to ATL can mediate transfer learning of these category circuits to ATL (System 1) to allow fast, automatic categorization, freeing up frontal cortex. To test this hypothesis, we trained typical adults (N=11) on a visual concept learning task on morphed stimuli and performed high-density (128 channel) EEG while individuals learned the task in blocks of 320 trials. Participants demonstrated significant learning early on between the first two blocks ($T(10)=4.9$, $P<0.001$), with performance saturating within the second block (performance in 1st half vs. 2nd half of block 2: $P=0.47$). Source estimation revealed initial engagement of the left frontal cortex in the first block that was reduced in the second block. In contrast, activation in left mid-anterior temporal cortex increased from the first to the second block. Compatible with the source-space analyses, SVM analyses in sensor space showed a decrease in category information over left frontal channels from block 1 to block 2 and an increase in category information in left temporal channels. Preliminary Granger causality (GC) analyses indicate a decrease in GC from frontal to temporal channels from block 1 to 2, and an increase from temporal to frontal channels, compatible with a decreasing role of frontal cortex and an increasing role of temporal cortex in categorization. Taken together, these results provide preliminary support for the System 2→System 1 transfer hypothesis, with the frontal cortex (System 2) involved in initial category learning, followed by transfer to temporal cortex (System 1).

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Poster

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Program #/Poster #: PSTR191.28/RR11

Topic: I.08. Learning and Memory

Support: This study is supported by NIH grant 5R37HD094623-09 awarded to Dr. Vinod Menon

Title: Categorical vs. graded mapping between numerical systems in the developing brain

Authors: *L. ADAMS¹, R. LIU¹, V. MENON²;

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Abstract: The integration of different numerical representations—non-symbolic (dots) and symbolic (Arabic numerals)—constitutes a fundamental cognitive process underpinning mathematical development. Yet, the neural architecture supporting this integration remains inadequately characterized, particularly in developing brains. In this study, we employed a comprehensive experimental paradigm comprising three distinct numerical comparison tasks (dot, symbolic, and mixed-format) with systematically varied numerical ratios (1.125 to 6) to elucidate format-specific and integrative numerical processing mechanisms. School-aged children (n=26, 11 females; mean age=9.4±1.6 years) performed these tasks during functional MRI scanning. Our analyses revealed a pronounced right-hemispheric engagement during high-difficulty comparisons across all tasks, with significant activation in the right intraparietal sulcus (IPS), angular gyrus (AG), motor cortex, and dorsolateral frontal cortex. Critically, representational similarity analysis (RSA)—a powerful multivariate technique that captures fine-grained neural representation patterns—demonstrated dissociable representational structures in these key numerical processing regions. The IPS maintained graded ratio representations for both dot and symbolic comparisons, but notably lacked such encoding during cross-format integration. In contrast, the right AG exhibited format-integration sensitivity, showing categorical (dichotomous) encoding during mixed-format comparisons but graded encoding during pure symbolic comparisons. These novel findings provide compelling evidence that children's brains employ qualitatively different representational strategies when processing within versus across numerical formats. The categorical nature of cross-format numerical integration suggests a surprise result: the child brain is not sensitive to refined ratio information when integrating numerical information across the non-symbolic and symbolic formats. This insight advances our understanding of numerical cognition development and has significant implications for educational approaches and interventions for children with mathematical learning difficulties. Future longitudinal research should examine how these representational structures mature throughout development and whether atypical integration patterns characterize mathematical learning disorders.

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Poster

PSTR191: Learning and Memory in Subcortical Circuits

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR191.29/RR12

Topic: I.07. Long-Term Memory

Title: Learning general structure from old and new experiences through replay-guided learning

Authors: *M. NATRAJAN¹, A. SAXE², J. E. FITZGERALD³;

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Abstract: To navigate novel situations, animals extract common structure across old and new experiences, enabling generalization. In the standard model of systems consolidation, the hippocampus initially stores memories, which are later transferred to the neocortex. A recent theory, Generalization-Optimized Complementary Learning Systems (Go-CLS) proposed that the hippocampus replays memories to train the neocortex only until it captures predictable relationships, halting before it overfits to noise and harms generalization. While insightful, Go-CLS models the neocortex as a feedforward network learning fixed input-output mappings. In reality, the neocortex has many layers with feedback connections and no fixed input or output neurons. Representations are shaped by ongoing synaptic changes, meaning the same stimulus may be encoded differently over time. This raises a key question. How can such a system acquire generalizable representations through replay-guided learning? We addressed this by studying a simple three-layer network model of the neocortex. While all layers receive feedback connections, two layers are also directly activated by the environment. The hippocampus was modeled implicitly by storing neocortical activity during experience and reactivating specific layers during replay. The system encountered novel experiences in a continual learning paradigm, with hippocampal replay interleaved to drive neocortical learning. Using a local plasticity rule during replay, the network successfully learned to reconstruct the activity of the entire network when one of the externally driven layers was reactivated. However, reactivation of the intermediate layer—whose activity was shaped indirectly and evolved over time—failed to regenerate the network state. While these representational changes significantly influenced the activity of other layers, they could remain modest in magnitude, so the errors for outdated representations weren't large enough to disrupt new learning. Introducing noise during encoding showed that generalization error decreased as more memories were added, except near the memory capacity limit—where error rose consistent with the double descent phenomenon. Interestingly, while input noise acts as a regularizer when learning outputs from inputs, in our setting with multi-directional mappings, generalization error still increased near the memory capacity limit. These findings highlight the unique challenges of replay-driven learning in networks with feedback and evolving representations—offering insights into how biological networks may generalize across experiences in continual learning settings.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR192.01/RR13

Topic: B.07. Network Interactions

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Simons Collaboration on Plasticity and the Aging Brain Fellows-to-Faculty Award
American Epilepsy Society Postdoctoral Fellowship
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Title: Interneuron theta phase locking controls seizure susceptibility

Authors: *Z. CHRISTENSON WICK, P. A. PHILIPSBERG, C. KOHLER, S. I. LAMSIFER, E. KATANOV, K. GORDON, G. DONNELLY, Y. FENG, L. M. VETERE, D. J. CAI, T. SHUMAN;
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Abstract: Network-wide oscillations, such as theta, orchestrate and organize the spiking of individual neurons. This leads many neurons, particularly interneurons, to be active at specific phases of ongoing oscillations, a phenomenon known as phase locking. This precise temporal organization of spiking is thought to be critically important for maintaining excitatory-inhibitory homeostasis and network function. This is illustrated in a variety of contexts and circuits, with spike timing altered in addiction, schizophrenia, depression, autism, Alzheimer's disease, and epilepsy. Indeed, we've recently found altered theta phase locking of inhibitory neurons in the dentate gyrus of epileptic mice. This strongly suggests that disruptions to theta phase-locked spiking may underly network dysfunction broadly, though the causal influence of this phenomenon has never been determined. Thus, here we 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. We then applied our closed-loop system to directly control the phase locking of these dentate interneurons to their preferred or non-preferred phase of theta while measuring latency to seize after a systemic kainic acid injection. In control mice, both PV+ and SOM+ interneurons in the dentate gyrus are primarily active at the trough of CA1 theta oscillations, while in epileptic mice, PV+ interneurons have disrupted phase locking. We found that mis-aligning PV+ interneuron spiking to the peak of theta increased seizure susceptibility in otherwise healthy, control mice and that re-aligning PV+ spiking to the trough of theta diminished seizure susceptibility in epileptic mice. On the other hand, manipulating SOM+ interneuron phase locking did not impact seizure susceptibility in either control or epileptic animals. These data suggest that theta phase locking of PV+ interneuron spiking plays an important and causal role in seizure susceptibility. Gaining deeper insights into the impacts of inhibitory theta phase locking will reveal the potential of oscillation-driven stimulation as an effective epilepsy therapeutic, and the direct influence that specific interneurons' theta phase locking holds over network-wide activity.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

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Program #/Poster #: PSTR192.02/RR14

Topic: I.08. Learning and Memory

Support: R01 NS123424
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Title: Opposing responses of hippocampal theta oscillations to running and a forelimb-dominated sensorimotor behavior

Authors: G. HOLGUIN¹, K. JORGENSEN², A. TAPIA², G. A. JORDAN², A. VISHWANATH⁴, C. A. BARNES³, *S. L. COWEN²;

¹Psychology, ³Evelyn F. McKnight Brain Inst., ²Univ. of Arizona, Tucson, AZ; ⁴Psychology, The Univ. of Arizona, Tucson, AZ

Abstract: Hippocampal theta oscillations (6 - 12 Hz) regulate the timing of neurons to support navigation, memory formation, and sensorimotor integration. Theta is modulated by running speed, breathing, whisking, and jumping and increases during memory encoding or retrieval. The positive relationship between theta frequency and running speed is believed to stabilize representations of space amid movement variability. Here, we incorporated a novel string-pulling task to determine if relationships between movement and theta hold when progress to reward is determined by the length of string pulled. This task eliminates many speed-associated inputs, such as vestibular, visual, and hindlimb information, and allows unprecedented precision in the analysis of paw movement. Even so, given that animals move forward in 'string space' to acquire reward, we predicted that the relationship between theta frequency and speed would be positive. **Approach:** Five Sprague Dawley rats (4 mo.) were trained to pull a string 208 cm using an automated string-pulling system and run on a track for food reward. Local-field data was acquired from dorsal CA1. **Results:** Relationships between theta and speed (running or string-pulling speed) were distinct during pulling and running. While theta was robust in both conditions, frequency was reduced during string-pulling and showed no speed-frequency coupling. This difference could result from the conflict between hindlimb and forelimb signals, with only forelimb movement signaling advancement during string pulling. Fine-grained analysis of paw movements during string-pulling revealed that theta power and frequency peaked during the contralateral paw's downward push despite paw speed being low. This suggests that under these conditions theta frequency and power respond to effort rather than kinematic information. Notably, running-associated theta may similarly reflect speed and effort as most locomotor tasks

conflate these variables. Finally, theta phase aligned from one reach-pull cycle to the next during the pull movement, the first action that advances the string forward. Since phase-locking has been associated with sensorimotor gating, synchrony during the pull could reflect gating of inputs most relevant for reaching the reward, potentially facilitating integration of action-outcome signals for memory encoding and navigation. Taken together, these data support a dual view of hippocampal processing where macroscale theta activity requires suprathreshold sensory, vestibular, and proprioceptive drive and microscale theta is sensitive to subsecond limb movements.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR192.03/RR15

Topic: I.08. Learning and Memory

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Title: Modulation of hippocampal rhythms by median raphe glutamatergic neurons

Authors: *J. FORTIN-HOUDE¹, G. DUCHARME², B. AMILHON¹;

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Abstract: The median raphe region (MRR) contains diverse neuronal populations including hippocampus-projecting glutamatergic neurons expressing the vesicular glutamate transporter type 3 (VGLUT3). The MRR is a powerful modulator of hippocampal rhythms including sharp-wave ripples (SWR, ~50 ms, 150-250 Hz) occurring predominantly during NREM sleep and theta rhythm (5 to 12 Hz) occurring during both wake and REM sleep. Both rhythms are essential for memory consolidation. Yet, the specific contribution of MRR-VGLUT3+ neurons to hippocampal rhythms is still unclear. In this study, we aim to 1) measure MRR-VGLUT3+ neuronal population activity across vigilance states and in relation to hippocampal rhythms, and 2) evaluate the effects of manipulating MRR-VGLUT3+ neurons activity on SWR and theta rhythm. To target MRR-VGLUT3+ neurons, we injected Cre-dependent viral vectors in the MRR of VGLUT3-Cre mice allowing for specific expression of a calcium sensor or optogenetics tools. First, we assessed MRR-VGLUT3+ population activity in relation to sleep-wake cycles. We recorded local field potential and units in the hippocampus while simultaneously recording MRR-VGLUT3+ neurons activity using fiber photometry. MRR-VGLUT3+ neurons were highly active during wake and REM sleep and their activity covaried with theta frequency and power. During NREM sleep, they were active in short bursts which were anticorrelated with SWR rate. Second, we optogenetically activated or inhibited MRR-VGLUT3+ neurons during different vigilance states. Activation during non-REM sleep powerfully suppressed SWR. During

REM sleep, optogenetic manipulations of MRR-VGLUT3+ neurons activity disrupted theta rhythm. Taken together, our results highlight contrasted activity patterns of MRR-VGLUT3+ neurons across vigilance states and reveal a powerful modulation of hippocampal SWR and theta rhythm. These results suggest an important contribution of MRR-VGLUT3+ neurons to hippocampal functions such as memory consolidation.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

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Topic: H.01. Fear and Aversive Learning and Memory

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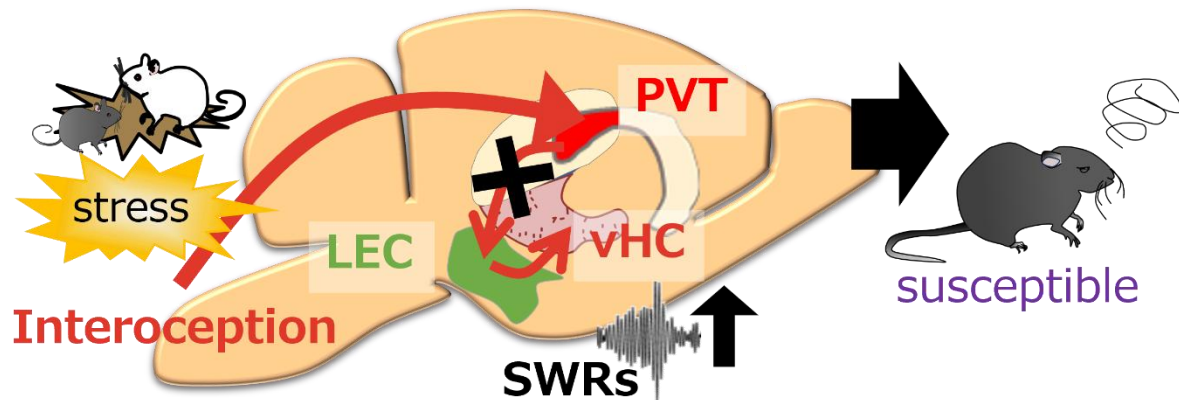
Title: Interoceptive signals modulate sharp wave ripples in the ventral hippocampus

Authors: *H. SHIOZAKI¹, T. SASAKI^{1,2}, N. KUGA^{1,3};

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Abstract: The ventral hippocampus (vHC) is critical for integrating exteroceptive sensory stimuli with emotional experiences and storing them as emotional memories. Recent findings suggest that the hippocampus may also process interoceptive signals, implying a potential role for interoception in shaping emotional memory formation in the vHC. To investigate this, we examined neural activity in the vHC of mice subjected to peripheral inflammation induced by lipopolysaccharide (LPS). We observed a significant reduction in the frequency of sharp-wave ripples (SWRs), high-frequency oscillations that are essential for memory consolidation. This result suggests that interoceptive input may modulate memory consolidation within the vHC. To identify the neural pathway through which interoceptive information reaches the vHC, we focused on the paraventricular thalamic nucleus (PVT), a midline thalamic structure adjacent to the third ventricle that is well-positioned to receive peripheral signals. Using AAV-mediated anterograde transsynaptic labeling, we found that the PVT projects to the vHC indirectly via the lateral entorhinal cortex (LEC). Building on our previous findings that mice displaying more frequent SWRs in the vHC following social defeat stress exhibit higher stress susceptibility, we tested the role of the PVT-LEC-vHC pathway in this process. Chemogenetic inhibition of the PVT-LEC pathway led to a further increase in SWR activity after stress exposure. This suggests that interoceptive signals transmitted via the PVT-LEC-vHC circuit exert an inhibitory influence on stress-induced SWRs, thereby suppressing the consolidation of negative emotional memories. In summary, our study reveals a novel interoceptive pathway that modulates emotional memory

consolidation in the vHC, providing insights into how internal physiological states can influence susceptibility to stress-related memory formation.



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Poster

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Program #/Poster #: PSTR192.05/RR17

Topic: I.08. Learning and Memory

Support: JST ERATO (JPMJER1801)
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Title: Differential coupling of hippocampal sharp-wave ripples with prefrontal and retrosplenial slow waves

Authors: *H. YAMADA, H. MIZUNO, Y. IKEGAYA, N. MATSUMOTO;
Grad. Sch. of Pharmaceut. Sci., The Univ. of Tokyo, Tokyo, Japan

Abstract: Memory consolidation, the process by which short-term memories are transformed into long-term ones, occurs during non-REM sleep. Hippocampal sharp-wave ripples (SWRs) play a crucial role in forming and transferring memories to the neocortex. Neocortical slow waves also contribute to this process, and there is a relationship whereby SWRs tend to occur at

specific phases of slow waves. Although neocortical slow waves are often synchronized across widespread areas, regional phase differences sometimes occur. Consequently, the possibility of specific interactions between neocortical slow waves and hippocampal SWRs during periods of slow-wave desynchronization remains poorly understood. To investigate this relationship, we examined simultaneous recordings of hippocampal ripples and slow waves from the prefrontal cortex (PFC) and retrosplenial cortex (RSC) in urethane-anesthetized mice, a model exhibiting neural activity similar to non-REM sleep. We recorded local field potentials (LFPs) from the hippocampus to identify ripples and from the PFC and RSC to detect slow waves. These cortical areas are known for their strong connectivity with the hippocampus and their distinct roles in cognition and memory. We examined the phase of slow waves in these regions relative to ripple occurrence to identify region-specific patterns of interaction. Our results revealed a significant difference in temporal coupling: Ripples tend to occur at more specific phases with PFC slow waves than with RSC slow waves, despite the RSC's closer anatomical proximity to the hippocampus. This suggests that proximity alone does not determine the strength of interaction. Ripples also tend to occur at an earlier phase in the PFC than in the RSC, which may reflect information transfer from the RSC to the PFC. However, we failed to find any correlation between ripple characteristics (e.g., amplitude, frequency, asymmetry) and slow wave states in either region. Ripple duration varied with neocortical activity. It was shorter during periods of neuronal inactivity (down states) in one cortical region. These results imply that the RSC and PFC may communicate with the hippocampus independently during memory consolidation. Differences in temporal coupling imply that hippocampal information may be processed or routed differently depending on the neocortical target. Furthermore, region-specific modulation of ripple duration by cortical down states highlights the complexity and specificity of interregional interactions during brain states conducive to memory consolidation.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

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Topic: I.08. Learning and Memory

Support: DBI2 Grant

Title: Real-time detection and closed-loop perturbation of hippocampal sharp-wave ripples using Bonsai-rx and Onix

Authors: *C. URAN^{1,2}, C. GASCO GALVEZ¹, A. ZORDAN¹, J. J. BOS¹, M. VINCK^{1,2}, F. P. BATTAGLIA^{3,1};

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Abstract: Sharp-wave ripples (SWRs) are synchronous bursts in hippocampal CA1 that are hypothesized to coordinate memory consolidation, yet causal tests demand sub-cycle (< 10 ms) closed-loop control. We therefore built an open-source pipeline that pairs the Open Ephys ONIX acquisition system with a lightweight temporal-convolutional network (TCN) as a plug-and-play Bonsai-RX package. We trained the network using publicly available, expert-annotated CA1 data. We have also recorded local-field potentials with 32-channel Atlas laminar probes spanning the CA1 pyramidal layer in awake, freely moving mice. Off-line, the TCN achieved state-of-the-art ripple detection, outperforming conventional thresholded ripple-band power detection on both public and in-house datasets. On-line, continuous LFPs were fed directly to the TCN model for inference which produced a ripple-probability trace that triggered electrical stimulation via ONIX with hardware-to-pulse latencies below 5 ms— within a few ripple cycles from event onset. On-line accuracy in freely moving animals matched off-line performance, demonstrating robust generalization across datasets and platforms. This openly distributed Bonsai-RX package thus provides millisecond-scale, state-of-the-art SWR detection, enabling new closed-loop experiments to dissect the causal role of ripples during sleep and memory processing. The same framework can readily be adapted to other neural events and closed-loop neuromodulation paradigms to investigate and/or to control neural circuits in real-time, expanding its utility across basic and translational neuroscience applications.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

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Topic: I.08. Learning and Memory

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Title: Exploring effects of electrical closed-loop stimulation at hippocampal sharp-wave ripple times in rat visual cortex.

Authors: *O. J. RAUHALA, J. GELINAS, D. KHODAGHOLY;
Univ. of California, Irvine, Irvine, CA

Abstract: Several oscillatory biomarkers in the hippocampal (HC) and neocortical local-field potential (LFP), as well as in their cross-regional interactions have been causally implicated in long-term memory consolidation processes via closed-loop electrical manipulation of these

markers. By disrupting or enhancing individual oscillations, or by altering their temporal coupling patterns, many studies have demonstrated modulation of behavioral outcomes in animal models, thus linking these markers with learning and memory functions of the brain. One such hippocampal biomarker is the sharp-wave ripple (SWR), a quiescence- and non-REM sleep-specific fast oscillation that mediates information transfer from local, short-term circuits in the HC to a stable, long-term storage in the neocortex. The role of SWRs in episodic memory consolidation is clear and causal, but more exploration of their interactions with cortical regions is needed for a comprehensive understanding of these neural mechanisms. In this work, we aim to characterize the interactions between SWRs and the visual cortex (VIS), including V1 and V2, in a rat model utilizing closed-loop manipulation of the visual areas at SWR times. By recording LFP in HC and VIS using high-density silicon probes, we characterize the broadband LFP and spike responses in VIS to direct electrical stimulation during SWRs and compare those to standard visually evoked potentials (VEPs) through a flashing light stimulus. The key focus of this manipulation is to explore whether SWR-coupled stimulus delivery to VIS regions can result in stable patterns of coupling between the HC and VIS that last beyond the stimulation protocol. In addition, we perform a light flash-cued reward search task with freely moving rats and observe differences in learning performance between closed-loop stimulated and control animals. By modulating the association between SWRs and VIS, we aim to produce insights into the dynamics of memory formation and recall in primary sensory systems. As many of the previous demonstrations of closed-loop manipulation of HC-neocortex interactions have focused on higher order association and executive regions of the neocortex, this exploration adds to a more complete picture of the neural dynamics of episodic memory consolidation.

Disclosures: O.J. Rauhala: None. J. Gelinas: None. D. Khodagholy: None.

Poster

PSTR192: Hippocampal Oscillations and Synchrony

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR192.08/SS2

Topic: I.08. Learning and Memory

Support: NIH Grant FG27374

Title: Developmental emergence and functional maturation of oscillatory coupling in the hippocampal-neocortical network

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Abstract: Mature hippocampal-neocortical networks are central to multiple cognitive processes, such as learning and memory. Expression and coupling of hippocampal sharp-wave ripples (SWRs) and cortical oscillations facilitate and further differentiate different memory stages.

However, neither precisely coordinated oscillatory activity nor spatial memory capacity are innate properties of nascent neural networks. We hypothesized that hippocampal and cortical oscillations require early developmental interactions to accompany emergence of spatial memory maturation. To test this hypothesis, we performed recordings simultaneously from hippocampus and neocortex of unanesthetized mouse pups during early development, using soft, conformable and implantable interface devices. We used an open-field spatial location memory task to assess the functional maturation of the developing hippocampal-neocortical networks. We found that ripple-band oscillations emerged concurrently in hippocampus and cortex. These oscillations robustly recruited local neural firing, and developed temporal coupling patterns. These results suggest the importance of hippocampal-cortical communication in the maturation of neural networks, with implications for memory processes.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

Location: SDCC Halls B-H

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Topic: I.08. Learning and Memory

Support: NINDS Grant 1RF1NS127128-01
NEI (P30 EY008126)
Whitehall Foundation Grant 100001391

Title: Coordinated dynamics of Dentate Spikes and ripples in the hippocampus of sleeping macaques

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Abstract: Sharp-wave ripples (SWRs) and dentate spikes (DSs) are prominent hippocampal local field potential events that mark brief epochs of highly synchronous neuronal firing. Both phenomena signal local and long-range changes to network states, and both often accompany the reactivations of waking cell assembly patterns during sleep (replay), though in distinct epochs of time. Whereas SWRs have been described across mammalian species, DSs have only been reported in rodents, leaving open the question of whether this influential dentate-gyrus phenomenon exists in the primate hippocampus. We implanted adult female macaques with 4 or 5 indwelling, movable, high-density linear probes targeting anterior and posterior hippocampus, ventromedial prefrontal cortex, and posteromedial cortex. We recorded 512 channels wirelessly during a task in which monkeys learned to infer object category membership using spatial context rules, and we continued recording during subsequent overnight sleep. Using established methods for the detection of DS events, we observed that the dentate gyrus probe had negative deflections flipping to positive in the ascending layers, with complementary sink-source pairs in

current-source-density maps, validating the laminar identity of DSs. We identified 5901 Dentate Spikes and 20,771 SWR events across 18 hours of sleep recordings. Aligning every SWR to its nearest DS revealed a biphasic coupling: in the 200 ms *preceding* DS peak, there was a decrease in SWR rate, whereas *following* the DS the probability of a SWR increased by 42 % compared to baseline rate (binomial test, $p = 7.8 \times 10^{-16}$). Thus, during post-learning sleep, dentate spikes punctuate SWR expression: arising during SWR-suppressed states and then potentially facilitating SWR activity, indicating that DSs could play a role in gating information flow through a rapid inhibitory-excitatory sequence. These data provide the first evidence of dentate spikes in the primate hippocampus and show that DSs are part of a biphasic network modulation of SWR activity. Previous findings showed that DSs were important for subsequent recognition memory, and for task-related reactivation during sleep. Together, this suggests that in primate sleep following learning, DSs could act as temporal gates that modulate hippocampo-neocortical replay, though this has yet to be measured. Future work should disambiguate the independent role of DSs in memory, and in regulating hippocampo-neocortical coupling, from their influence via their interactions with SWRs.

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Poster

PSTR192: Hippocampal Oscillations and Synchrony

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Topic: I.08. Learning and Memory

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NEI (P30 EY008126)
Whitehall Foundation Grant 100001391

Title: Organization of hippocampal and medial prefrontal activity during spatial-inference category learning in freely moving rhesus macaques

Authors: *N. E. WILLHITE, A. ALJISHI, S. S. COOPER, K. L. HOFFMAN;
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Abstract: Natural cognition in humans and other primates relies on inferring rules of the environment to inform perceptual and conceptual groups that guide behavior. The prefrontal cortex and hippocampus are considered important for such contextual inference, though the nature of their contributions and their interactions remains unclear. To address this, we implanted two female rhesus macaques with probes targeting medial prefrontal cortex (mPFC), posterior medial cortex and hippocampus (anterior/posterior, CA1, DG/CA3). We recorded 512 channels while monkeys learned to use each of four touchscreen locations to select the one of four object families assigned to that touchscreen. Families were created by placing boundaries in the stimulus space across evenly spaced exemplars defined by their similarity in multidimensional

feature space. The task requires location rule use to infer which exemplars to integrate across and which to segregate. Using a state-space model to estimate learning, we found that monkeys learned categories and used the rule to infer category membership, generalizing to new exemplars. We then stratified trials into “early”, “mid”, or “late” learning from model estimates. The analyzed epochs included the choice epoch and the post-selection period. CA3, DG, and mPFC were characterized by sustained beta oscillations, but peak frequencies (~18-22 Hz vs. ~15-25 Hz) and modulation differed between hippocampal and cortical sites. In DG, decreased gamma band power (40 - 80 Hz) predicted array appearance with learning (one-way ANOVA, $p < 0.05$), while beta oscillations maintained power after array selection. In contrast, mPFC dynamics showed drops in beta power that scaled with learning in the same epoch. To understand the interactions across areas, we measured fluctuations in mPFC and DG beta strength, but found that they decorrelated during and around the choice epoch with learning (Pearson's r , $p < .05$). This, with past work on cell-type specific spike coupling to hippocampal beta oscillations, suggests local generation and potential homology with rodent dentate gamma oscillations, not direct coupling with prefrontal beta sources. Further, as categories are learned the prominent oscillatory modes of one area may suppress the other. These results underscore the importance of treating oscillatory motifs in accordance with their local instantiation and not as a general marker of cognition, and suggest specific states or motifs that may regulate information flow across regions in response to category learning.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR193.01/SS5

Topic: I.09. Spatial Navigation

Support: NSF-IOS 2137023
NIMH-R01MH132018-01A1

Title: Region-specific chemogenetic modulation of hippocampal activity by il and pvn glutamatergic projections under stress conditions

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Abstract: The hippocampus (HPC) is a region of the brain associated with a wide array of functions, including but not limited to spatial memory, memory consolidation and value encoding. It is believed that the functions of the hippocampus have a distinct spatial organization. Recent studies have shown that dorso-ventral organization of the hippocampus is related to conditioned stimulus and value encoding. There is a gap in literature pertaining to the

glutamatergic projections from the infralimbic cortex (IL) and paraventricular nucleus (PVN) of the hypothalamus with relation to this hippocampal axis. The relationship between stress and memory in rodent models is contradictory, some studies claim stress aids in learning whilst others find that stress hampers spatial memory and learning. To understand the spatial relationships between the HPC and the IL/PVN we decided to employ chemogenetic behavioral modulation after stressing rodents. Specifically, retrograde excitatory/inhibitory AAVs (HM3Dq/HMD4i) were injected in the IL or PVN and a cannula was inserted in the CA1 of the HPC of 12-16-week-old VGlut2IRES^{Cre} male mice. After at least 18 days post cannulation DREADD agonist *compound 21* (C21) was injected at 0.5 µg/kg intracranially (i.c.) into the ventral CA1 of the hippocampus using the guide cannula. The animal was allowed to rest in its home cage for 15 minutes after the i.c. C21 injection. The animals were stressed with a stressor from one of the 3 modalities: (i) unconditioned non-adaptive stress, (ii) unconditioned adaptive stress and (iii) conditioned stimuli stress. After the appropriate stressor was applied the animal placed in a clean cage for 10 minutes to allow for rest. After this washout period the animal was allowed to explore in an open field test for 5 minutes. The animal was then returned to its home cage; this test was done for 4 days. On the 4th day the animal was sacrificed immediately after the task was performed, and whole-head was placed in 4% PFA-PBS. One week later the brain was removed and placed in 30% Surose-4%PFA-PBS. Brain was sectioned and immunofluorescent staining was done for c-Fos antibodies with the HPC mounted in a dorsal to ventral manner. c-Fos is used as a marker for how neuronal activity is altered during stress because of a short half-life. Exploratory behavior of the rodents was altered in a region of injection specific and AAV dependent manner. The distribution of c-Fos molecules was seen to be specific to the spatial organization of the hippocampus.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Title: Retrograde Tracing of Neuronal Pathways to Dorsal CA1 Reveals Novel Circuitries Underlying Memory Processing

Authors: *Y. CHUNG¹, J. IP²;

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Abstract: Background: The trisynaptic pathway—comprising the entorhinal cortex, dentate gyrus, CA3, and CA1—is a foundational model for understanding memory mechanisms. However, it does not fully capture the complexity of memory processing. Recent studies suggest that multiple cortical regions also play critical roles. This study aims to comprehensively map neuronal inputs to the hippocampal CA1 region to better understand the broader circuitry involved in memory coordination. **Methods:** We employed rabies viral vectors to retrogradely trace excitatory neurons projecting to CA1. Brain tissues were sectioned and imaged to identify input regions. Quantification of labeled neurons was performed using QuPath and ABBA software, with attention to laminar specificity and anterior-posterior (AP) coordinates. **Results:** Over 50% of neuronal inputs to CA1 originated locally from within the hippocampus, particularly from CA1, CA3, and the dentate gyrus. Significant long-range projections were also observed from cortical areas, including both medial and lateral entorhinal cortices, each showing distinct connectivity patterns. Additional inputs were identified from the retrosplenial and perirhinal cortices, primarily ipsilateral. To further explore upstream connectivity, we applied the same tracing strategy to the perirhinal cortex, revealing disynaptic inputs from diverse sensory association areas, including olfactory, visual, and auditory cortices. **Conclusion:** This study provides a quantitative map of CA1 input sources and identifies specific laminar layers potentially involved in spatial learning and memory. Future work will investigate how these upstream regions contribute to distinct memory processes, using single-cell transcriptomics to examine molecular changes during memory tasks and in disease states.

Disclosures: Y. Chung: None. J. Ip: None.

Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

Location: SDCC Halls B-H

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Program #/Poster #: PSTR193.03/SS7

Topic: I.09. Spatial Navigation

Support: NIH grant EY01234

Title: A Novel Role of New Dentate Gyrus Neurons in Long-Term Pattern Separation Memory

Authors: *T. X. PHAN¹, P. KUMAR², O. LAZAROV³;

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Abstract: Memory is a temporally dynamic process involving distinct phases such as encoding, consolidation, and retrieval. The dentate gyrus (DG) of the hippocampus plays a critical role in

pattern separation—a process that allows for the discrimination of similar contexts. New neurons in the DG are known to integrate into existing circuits over several weeks and may differentially contribute to specific phases of memory processing. However, the functional role of these new neurons in temporally specific memory retrieval remains underexplored. This study investigates the causal role of newly mature neurons in the DG in remote contextual discrimination memory. Using chemogenetic inhibition to temporally manipulate these neurons, we demonstrate that their activity is essential for memory retrieval at remote time points, but not required during encoding or the consolidation period. In addition, in vivo calcium imaging reveals a potential novel mechanism of engram involved in contextual discrimination.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Topic: I.09. Spatial Navigation

Support: PICT 2020/00360
FOCEM-Mercosur (COF 03/11)
SNSF SPIRIT 216044
PICT 20220/01536

Title: Reorganization of neural codes in the Dentate Gyrus and CA3 during odor-spatial learning

Authors: *M. RAMOS, S. A. ROMANO, J. PONCE, F. MONTIEL, A. MARIN-BURGIN, N. FEDERMAN;

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Abstract: The hippocampus is a brain region that plays a major role in memory and spatial navigation, particularly forming and retrieving episodic memories. During exploration of new environments, animals form internal representations of space by integrating external and internal cues, a process that depends on the hippocampus. The dentate gyrus (DG), the initial processing stage of the hippocampus, contains cells responsive to distinct variables such as position, speed, sensory cues, and reward. Information processed in the DG is conveyed via mossy fibers to CA3 pyramidal cells, where it is integrated into a dense recurrent collateral network. CA3 also contains place cells and speed-tuned neurons, and its extensive recurrent circuitry is thought to underlie its capacity to perform pattern completion. Yet, how these two connected hippocampal fields encode information within the same task and how each restructures its coding with experience remain poorly understood. In our study, we trained head-fixed mice in a virtual reality environment to perform a discrimination task based on olfactory and visual context cues.

Using in-vivo electrophysiology, we compared DG and CA3 responses at different learning stages, in first-session and expert animals. We analyzed the data using a Poisson Generalized Linear Model (GLM), quantifying the contribution of various sensory, behavioral, and cognitive variables such as inhalation, licking, position, speed, and reward to neuronal activity. We observed that in the DG, the capacity of single neurons to respond to multiple variables simultaneously, known as mixed-selectivity, increases with learning. Moreover, DG encoding of task-relevant factors such as position, speed, and reward is strengthened, revealing an experience-dependent reorganization process. In contrast, CA3 exhibits mixed-selectivity even before learning, indicating an intrinsic predisposition to integrate multiple signals. However, these modulations are insufficient to decode some variables in first-session animals, suggesting that information is refined after learning, particularly regarding spatial context and odors, while reward representation remains limited. Together, these findings suggest that learning differentially reorganizes representations in DG and CA3, enabling a richer and more specific encoding of key task elements. The DG builds its codes from experience, whereas CA3 refines and selects relevant signals on a preexisting framework.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Program #/Poster #: PSTR193.05/SS9

Topic: I.09. Spatial Navigation

Support: NIH Grant R01 ES006189
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Title: Relationship between thigmotaxic behavior and hippocampal sharp-wave ripples in rats

Authors: *C. L. STEDMAN¹, N. W. SCHULTHEISS^{1,3}, A. T. MATTFELD¹, T. A. ALLEN^{1,2}; ¹Psychology, ²Envrn. Hlth. Sci., Florida Intl. Univ., Miami, FL; ³Brain Institute, Nicklaus Children's Hosp., Miami, FL

Abstract: Anxiety is a potent memory modulator, but the underlying neurophysiological mechanisms are poorly understood. One possibility is that anxiety modulates sharp-wave ripples (SWRs), which then drives anxiety-induced memory modifications. SWRs, high-frequency bursts of activity in the CA1 region of the hippocampus, correspond to an increase in structured spiking activity and reflect experiences in memory (Buzsáki, 2015). Specifically, spiking in SWRs contains information about past and future events in a time-compressed manner and is thought to provide a rapid retrieval mechanism that contributes to real-time decision-making or feedback in the cortex. If and how SWRs are affected by anxiety is unknown. To begin to

explore this, we asked if thigmotaxis, a proxy for anxiety, influences SWRs. Here we recorded LFPs and single units in the rat hippocampus ($n = 6$) during open-field exploration. We developed a custom SWR detection algorithm that classified events as SWRs based on their frequency, amplitude, number of cycles, and duration. We found that spiking activity increases following the onset of detected SWRs ($z = -18.407$, $p < 0.001$), helping to validate the algorithm. Next, we examined SWR characteristics while rats were in the outer (thigmotaxis) compared to the inner (no thigmotaxis) zones of an open field. We found evidence that thigmotaxis modulates SWR characteristics. First, SWR amplitude was greater while in the outer zone of the field compared to the inner zone ($F_{(1,43)} = 5.598$, $p = 0.023$) during the first session. Second, we examined SWR rate as a function of zone and time across early and late sessions, and we observed a significant main effect of thigmotactic zone on SWR rate ($F_{(1,15)} = 5.045$, $p = 0.040$). In this second analysis, there was no effect of zone on amplitude or duration. The observed changes in SWR amplitude and rate within the thigmotactic zone provide preliminary evidence that thigmotaxis, a proxy for anxiety, affects SWR characteristics in ways that may modify memory.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Topic: I.09. Spatial Navigation

Support: ARDRAF 224657
1R21MH135232-01

Title: Maturation of Network Activity in Hippocampal Area CA1 Viewed Through in-vivo Electrophysiological Recording of Local Field Potentials during Spatial Learning and Memory Phases of Barnes Maze Testing

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²Interdisciplinary Neurosci. Phd Program, ⁴Psychology, ³George Mason Univ., Fairfax, VA

Abstract: The hippocampus is a forebrain structure that enables spatial learning and memory. In rodents, spatial learning and memory develops late in the postnatal period, near the end of the third postnatal week. Prior work implicates changes in activity dependent synaptic plasticity at excitatory synapses largely driven by changes in the composition of AMPA and NMDA receptor that enable proper encoding and retrieval of spatial information. Alterations in synaptic transmission likely produce changes in network functions that support spatial memory encoding

and retrieval. Prior developmental studies focused on random foraging. Changes in hippocampal network activity in relation to maturation of spatial learning and memory in juveniles has not been investigated. We addressed this question by implanting recording electrodes into area CA1 of juvenile rats to record local field potentials (LFPs) during testing on the Barnes maze at just under (Younger) or over three weeks of age (Older). Tethered juvenile rats learn the Barnes maze task in a similar fashion to published reports of untethered juveniles. Implanted Older animals displayed reduced escape latencies and path lengths compared to Younger animals across training blocks. During probe trials immediately after training, Older animals displayed fewer search errors and shorter path lengths to the goal relative to Younger animals. During the long-term memory probe, neither group showed memory for the goal location. When analyzing LFP oscillations for entire training trials, we found no effect of training block or age on power or event rate for theta (4-12 Hz) or slow gamma (20-55 Hz). During long-term memory probe epochs just prior to first movement, we found older animals had an increased theta event rate compared to younger animals. There was no age effect on theta/slow gamma power or slow gamma event rate, though there was an inverse relationship between slow gamma power and latency to reach the goal location. These results indicate that, like adult subjects, slow gamma power is correlated with memory retrieval performance in juvenile rats. This suggests that deficits in spatial memory seen in juveniles prior to three weeks of age likely involves theta event rate and possibly theta-slow gamma coupling. Patients suffering from Alzheimer's and Schizophrenia also display a distinct impairment in spatial memory ability, decreased slow gamma power, and impaired theta-slow gamma coupling. Thus, greater knowledge of late postnatal developmental alterations in slow gamma and the maturation of spatial memory ability may translate to better understanding of memory deficits associated with disease in adulthood.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Topic: I.09. Spatial Navigation

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Title: Multidimensional coding and coordinate transformation in primate hippocampus during flexible decision-making

Authors: M. S. TU¹, *C. R. FETSCH²;

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Abstract: The hippocampus (HP) exhibits remarkable representational flexibility, with neurons displaying complex, multiplexed coding that encompasses both spatial and non-spatial variables. While human fMRI and rodent electrophysiology studies have provided valuable insights into HP function, our understanding of neural computations in the nonhuman primate HP remains limited. In particular, relatively little is known about how HP representations are extracted in real time to support flexible spatial decisions. To address this gap, we developed a 3D virtual maze task targeting an intermediate level of complexity between classic 2AFC decision tasks and full-blown VR navigation. Two adult rhesus macaques were trained to navigate a four-room linear maze via joystick control. Each room featured unique coloration with minimal extraneous visual cues to isolate spatial decision strategies. Initial starting position, heading angle, and goal location varied systematically across trials to limit the role of simple sensorimotor associations while maintaining high accuracy. HP ensemble recordings from one monkey revealed multiplexed encoding extending beyond simple spatial representation. Population decoding demonstrated that HP activity patterns could predict upcoming navigational errors before action execution, suggesting that the fidelity of hippocampal representations limits decision accuracy on a trial-by-trial basis. We trained separate decoders to predict upcoming directional choices in joystick (egocentric) vs. map-based (allocentric) coordinates, revealing dissociable neural representations with distinct temporal dynamics. Allocentric representation was prominent during cue presentation and re-emerged as animals approached goals, while egocentric representation peaked before movement initiation and quickly diminished post-choice. This temporal dissociation indicates the primate HP maintains abstract spatial representations along with immediate motor demands, potentially supporting the coordinate transformations required for flexible navigation. Analysis of goal encoding in visually identical scenes requiring opposite actions revealed anticorrelated patterns in HP population activity. We speculate that this feature allows the HP to minimize interference between conflicting goals while maintaining multiple potential action plans simultaneously. These findings provide preliminary constraints on theories for how multiplexed coding in the nonhuman primate HP supports dynamic integration of spatial context and goal information during adaptive decision-making.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Topic: I.09. Spatial Navigation

Support: Smith Family Foundation
Swartz Foundation

Title: Subicular plateau potentials signal reward proximity and locomotor dynamics during goal-directed behavior

Authors: *A. BHATIA, M. ADEL, C. GRIENBERGER;
Brandeis Univ., Waltham, MA

Abstract: The subiculum is a major output region of the dorsal hippocampal formation, receiving spatial and contextual information from CA1 and the entorhinal cortex. It has been implicated in a range of functions, including navigation, reward processing, and behavioral planning; however, how it processes these diverse synaptic inputs to generate an output signal in the form of action potentials (APs) during goal-directed behavior remains poorly understood. To address this question on the single-cell level, we performed in vivo whole-cell recordings in mice running on a treadmill with fixed spatial cues to collect a sucrose reward. Consistent with previous reports, subicular neurons exhibited significantly higher firing rates (14.4 ± 9.4 Hz during running, 12.6 ± 7.3 Hz during standing; mean $\pm$ std) compared to pyramidal neurons in other hippocampal subfields, such as CA1 and CA3. A striking feature of subicular activity in our recordings was the frequent occurrence of “plateau potentials” - high-frequency trains (100-250 Hz) of more than three action potentials of decreasing amplitude riding on a large depolarization (20-30 mV) with a duration of tens to hundreds of milliseconds. We find that these plateau potentials are of synaptic origin, as they require N-methyl-D-aspartate (NMDA) receptor activation, while blocking T-type voltage-gated calcium channels with Mibefradil (100uM) had no effect on their frequency and duration. Functionally, we found that plateau potentials clustered at two behavioral junctures: (1) they were significantly more likely to occur near reward locations compared to other locations matched for speed and acceleration, and (2) they were more prevalent at the peaks or troughs of speed or acceleration - specifically, at the peaks in neurons positively encoding speed or acceleration and the troughs in neurons negatively encoding these variables. Together, our findings reveal that plateau potentials represent a distinct and behaviorally selective mode of subicular activity. By selectively engaging at reward locations and during transitions in locomotor activity, these events may allow the subiculum to dynamically shape hippocampal output during goal-directed behavior.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Topic: I.09. Spatial Navigation

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Israel Science Foundation Grant # 2418/24

Title: Structured remapping in the subiculum: A shared latent code underlies spatial transformations across environments

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Abstract: How does the brain preserve a coherent sense of space across distinct environments? In this study, we investigated how neurons in the subiculum, a key output region of the hippocampal formation, encode spatial information as animals explore different rooms. Using large-scale Neuropixels recordings from freely moving mice, we observed that while individual neurons frequently shifted their firing locations, the population-level activity exhibited smooth, structured transformations of the spatial map. To probe the principles underlying this stability, we developed a data-driven model that decodes 2D position from subicular activity through a shared latent representation. Temporal dynamics are captured by a recurrent network (RNN), and environment-specific position estimates were produced through dedicated decoders. This structure allowed us to infer the transformation between spatial representations across environments by analyzing how the shared latent space was mapped onto position in each context. Despite its capacity to learn complex mappings, we observed that transformations between environments were often well-approximated by simple affine operations, such as rotations, scalings, and translations. These findings reveal that beneath the complexity of neural remapping lies a low-dimensional, structured transformation, suggesting that the brain maintains spatial coherence across contexts through flexible yet geometrically consistent coding strategies.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR193.10/TT2

Topic: I.09. Spatial Navigation

Title: Neurozoo: A tool for training recurrent neural network models on behavioral tasks

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Abstract: System neuroscientists regularly investigate cognitive functions by studying model rodents through various predefined experiments. These experiments reveal diverse neural mechanisms that subserve computation in rodents' brains. Recent advancements in artificial neural networks have enabled neuroscientists to expand these neural studies to silico models. To this end, computational neuroscientists regularly train recurrent neural networks (RNNs) on synthetically design cognitive tasks to gain mechanistic insights. However, even though recent work has shown that even the most trivial changes in task parameters lead to diverse neural circuits learned by RNNs, most existing silico tasks are coded without clear standardization. Moreover, there have been several distinct learning rules developed in the last decade to train RNNs, each of which can favor one neural mechanism over another. To investigate and standardize this process, we designed an extensive dataset for various cognitive model training purposes and benchmarked diverse RNN architectures trained on these tasks using several learning rules. We extracted the learned latent mechanisms in these diverse tasks and compared them across RNN architectures and learning paradigms. We also examined the persistence of learned mechanisms in RNNs trained to perform additional tasks. To facilitate future extensions of these benchmarks and support ongoing research in this field, we outline detailed methodologies for standardizing these tasks and provide them open-source. Our resource presents a standardized and principled approach for benchmarking various RNN models, paving the way for future comparative studies of neural computations in system neuroscience.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Program #/Poster #: PSTR193.11/TT3

Topic: I.09. Spatial Navigation

Support: DOE CRCNS REFRAME
NIH R00 NS119665

Title: Cross-regional cortical dynamics support predictive spatial learning during visual target pursuit

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Abstract: Successful pursuit behavior in dynamic environments, such as hunting prey or escaping predators, requires animals to predict future target locations based on internal representations of the environment. Rather than tracking current target positions, animals learn through experience to anticipate future states, optimizing pursuit efficiency. Prior studies demonstrate that repeated exposure to structured trajectories enables rodents to accelerate capture performance and develop shortcut strategies to intercept visual targets. While subcortical circuits are known to mediate motion-related sensory processing during predation, the mechanisms by which cortical circuits support the transition from reactive to predictive behavior during learning remain poorly understood. To investigate this, we trained mice in a novel reward-associated visual target pursuit task, where a visual target followed either pseudorandom (unpredictable) or structured (predictable) trajectories. The animal's position and the target trajectory were tracked in real-time using a deep learning model (DeepLabCut), and successful captures were paired with water rewards. This setup allowed for simultaneous tracking of movement trajectories and heading directions, enabling precise alignment of behavioral and neural data. Behaviorally, naive animals exhibited reactive pursuit guided by immediate visual feedback. With training under structured trajectories, they progressively adopted predictive strategies, initiating movement toward anticipated future target positions, suggesting the emergence of an internal model of target dynamics relative to their own motion. To formalize these changes, we fit behavioral data to reinforcement learning models, testing whether learning was characterized by a shift from model-free strategies, relying on direct reward contingencies, to model-based strategies leveraging learned environmental structure. We performed high-density electrophysiological recordings in the cingulate cortices and the hippocampal formation, regions implicated in spatial representation and value-driven action planning. We implemented a variety of single cell and neuronal population level analyses to test whether the emergence of predictive shortcuts corresponded to distinct patterns of cortical engagement. Together, these findings illuminate how cortical circuits orchestrate internal model construction to enable flexible, predictive pursuit, offering a mechanistic bridge between spatial navigation and goal-directed behavior.

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Poster

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Topic: I.09. Spatial Navigation

Support: DOE CRCNS REFRAME
NIH R00 NS119665

Title: Computations Supporting Predictive Pursuit in Recurrent Neural Networks

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Abstract: Predicting the future locations of others is necessary for success in collaborative and competitive environments. For instance, when pursuing prey, a predator must anticipate not only where the prey is, but also where the prey is going. The complex way in which environmental affordances (e.g., boundaries, burrows), movement statistics (e.g., range of typical speeds), and stereotyped actions (e.g., zigzagging, slowing and accelerating) inform this prediction makes pursuit a rich paradigm for studying the neural computations underlying model-based inference and predictive planning. Despite this, little is known about the neural basis of pursuit, partly because it is difficult to implement naturalistic pursuit tasks with repeatable trial structure in the laboratory. To address this challenge, we develop a recurrent neural network (RNN) framework for examining predictive behavior and computations that emerge during continuous pursuit of a moving target. We find that our RNN model is capable of quickly learning to pursue a target with high accuracy. By comparing the trajectories generated by the RNN on each trial with a non-predictive null model that minimizes distance at each time step, we demonstrate that the RNN generates internal predictions of the target's future locations. This predictivity increases when the RNN is exposed to stereotyped trajectories of the target, in-line with recent rodent experiments and indicative that prediction is bolstered by internal model formation over experience. Investigating the computations that underlie the RNN's ability to perform predictive pursuit, we find units that encode the relative position of the target to the RNN, a representation analogous to egocentric target neurons, a functional class of neurons that have been identified in neural recordings. In addition, the RNN develops coding of the target's distance to the boundary, a computation that links the affordances of the environment with the future actions of the target. Re-analyzing existing neurophysiological data from rodent pursuit experiments, we find evidence of similar neural computations. Our results demonstrate that our RNN framework is a valuable new tool for studying predictive pursuit and can be used to generate testable hypotheses on the underlying neural computations that support this important cognitive process.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

Location: SDCC Halls B-H

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Topic: I.09. Spatial Navigation

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Title: Cortico-thalamic coordination with the hippocampal formation during contextual learning and memory

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Abstract: The retrosplenial cortex (RSC) is heavily interconnected with sensorimotor cortices and subcortical regions including the hippocampal formation (HPC) and anterior thalamic nuclei (ATN). In addition to a role in spatial navigation, this limbic circuit is implicated in contextual and episodic learning and memory. Neurophysiological evidence suggests that ATN-RSC-HPC memory processing may be facilitated by theta oscillations (4-12 Hz). While HPC and sub-regions of ATN possess continuous theta modulation during spatial memory tasks, RSC and the anteroventral nucleus (AV) of the thalamus seemingly engage with theta rhythms in a more transient manner. We hypothesize that this transient theta engagement serves as a signature of memory processing; however, there has been minimal investigation of coordination across the AV-RSC circuit during the encoding, consolidation, and retrieval of spatial memories. Here, we develop a novel cheeseboard task for freely moving rats in which baited reward locations are cued by distinct visual stimuli that define context. Rats learn reward locations associated with each context across a 7-day period, and recall is examined during 2 test sessions following a break from the task. Preliminary data indicate that inactivation of RSC impairs task performance. We paired this behavior with simultaneous multi-site in vivo electrophysiological recordings in RSC, AV, and the extended hippocampal formation across learning, consolidation during sleep, and recall.

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Topic: I.09. Spatial Navigation

Support: NIH NINDS K99/R00 NS119665

Title: Projection-specific interdependence of egocentric boundary coding between retrosplenial and posterior parietal cortices

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Abstract: Sensitive to egocentric bearing and/or distance to environmental features, egocentric boundary cells (EBC) are critical for navigation and the construction of a cognitive map, capabilities that decline in neurodegenerative disorders such as Alzheimer's disease. In these disorders, the inability to form accurate spatial representations often leads to disorientation and memory impairment. EBCs have been documented across several cortical and subcortical regions including the dorsal striatum, and retrosplenial, parietal, secondary motor, lateral entorhinal, and postrhinal cortices. Many of these regions are known for their robust interconnectivity but it is unclear whether hierarchical processing mechanisms contribute to egocentric vector coding. Data from our lab indicate that EBCs found in the retrosplenial (RSC) and posterior parietal cortices (PPC) share similar tuning properties, such as tuning strength and field-distributions, yet differ in their stability over time and other features relating to the timing of boundary coding. These differences suggest that properties of egocentric spatial representations may be influenced by cross-regional interactions. To dissect the relative influence of RSC to PPC or PPC to RSC projections on this form of spatial tuning, we used high-density electrophysiology and neuroimaging methods to record neural activity from each region while disrupting afferent inputs in freely exploring mice. Preliminary data yield important insights regarding dependencies between regions critical for the egocentric sensation of the spatial world.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Topic: I.09. Spatial Navigation

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Title: Visual landmark coding in the retrosplenial cortex of freely moving mice

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Abstract: During navigation, path integration enables self-localization by tracking continuous self-motion signals over time. Path integration is an essential computation in the generation of

spatial representations, yet errors in position estimates accumulate over time. Sensory inputs such as visual environmental landmarks function as external anchors to correct path integration miscalculations. The retrosplenial cortex (RSC), exhibits reciprocal connectivity with multiple sensorimotor processing areas and the hippocampal formation, a region critical for spatial cognition and navigation. Thus, the RSC is well positioned to contribute to path integration-related computations. RSC is known to encode multiple forms of self-motion and the presence of visual landmarks in head-fixed mice. Interestingly, visual landmark coding in RSC is nonlinearly modulated by an animal's position in allocentric space, suggesting that path integration and landmark coding both contribute to RSC spatial representations. Here, we assess RSC-dependent landmark processing in freely-moving mice trained to run ballistically along a linear track featuring identical, equally-spaced visual cues. We paired this behavior with methods for head-mounted calcium imaging and high-density electrophysiology to further characterize landmark coding in the region. Our data identify new roles for the RSC in path integration and further characterize spatially-modulated gain modulation in a region that may be critical for spatial transformations.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Topic: I.09. Spatial Navigation

Support: BBSRC SWBio DTP PhD studentship

Title: Acetylcholine dynamics and spatial remapping in the retrosplenial cortex in uncertainty

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Abstract: Novel environmental changes introduce uncertainty into spatial representations, requiring neural systems to adapt for optimal behaviour. Acetylcholine (ACh), a key neuromodulator, is thought to support such adaptation by enhancing attention and promoting synaptic plasticity (Yu and Dayan, 2005, Hasselmo et al., 2011). The retrosplenial cortex (RSC), a hub for spatial memory and contextual integration (Vann, 2009), may contribute to resolving spatial uncertainty by modulating and relaying environmental information. However, how ACh signalling and spatial coding in the RSC respond to different forms of uncertainty remains unclear.

We developed a virtual reality paradigm to investigate how the RSC adapts to spatial uncertainty. Mice were injected with either GRAB-ACh3.5 (n = 12, 6 males, 6 females; 10-18

weeks old) to monitor ACh release, or GCaMP8m (n = 6, 3 males, 3 females, 10-18 weeks old) to track calcium activity in RSC neurons. Mice were trained to run along a linear track for a sucrose reward delivered at a fixed location. Uncertainty was introduced in two forms: unexpected, through novel environment switches or un-cued reward shifts; and expected, by broadening the possible reward zone. Two-photon imaging was used to record sensor signals, and pupillometry was collected to track attentional state (Keene, 2022).

Unexpected uncertainty elicited the largest and most sustained increases in ACh release, particularly during first exposure to novel environments. This corresponded to a complete remapping of position-tuned cells in the RSC. Subsequent environment switches led to attenuated ACh responses, reflecting a decrease in unexpected uncertainty and a shift toward expected uncertainty. Un-cued reward shifts produced a similar increase in ACh, but with only partial remapping, suggesting preserved spatial structure despite contextual change. In contrast, expected uncertainty drove a slower, sustained ACh rise and remapping that was localised to the reward zone. Across all conditions, pupil diameter tracked ACh dynamics, reinforcing a link between cholinergic signalling and cognitive state.

These findings demonstrate that both ACh release and spatial representations in the RSC are strongly modulated by the predictability and type of spatial uncertainty. The extent of remapping scales with ACh levels, suggesting that cholinergic signalling may facilitate adaptive updating of spatial codes in response to changes in environmental context.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Program #/Poster #: PSTR193.17/TT9

Topic: I.09. Spatial Navigation

Support: Stanford School of Medicine Dean's fellowship.

Title: Investigating the spatial and social feature coding in the hippocampus through a head-fixed setup.

Authors: *C. DONG¹, E. SAY¹, K. BATRA², L. M. GIOCOMO^{2,3};

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Abstract: Episodic memories are rich and diverse in features. For instance, recalling the memory of finding a new café on campus with a friend contains both spatial (the location of the café) and social features (the friend). The hippocampus is critical for these types of episodic memories and consists of different subregions (dentate gyrus, and the cornu ammonis regions: CA1, CA2, CA3) that have been theorized to participate in different memory processes. Specifically, CA3 is well known for spatial coding and CA2 is essential for social coding. How

their shared downstream region, CA1, integrates these two features remains unclear. We asked three questions: 1) Does social information in CA1 exhibit the same selectivity and remapping rules as those observed for spatial location? 2) Are there distinct spatial-dominant, social-dominant, or conjunctive neuronal sub-populations? 3) How are spatial and social cues combined when a single experience contains both? To address this, we designed a head-fixed setup that facilitates both virtual reality (VR) based spatial navigation and real-world social interaction. This design enables switches between purely spatial and social contexts while imaging the same group of neurons longitudinally with two-photon calcium imaging. A dual-camera system tracked the conspecific's location and relevant facial features of the recorded animal, such as snout movement and pupil size/ movement. We identified 'social-place cells' in CA1 during the interaction session. We also found that the interaction time increased in the novel conspecific interaction session. Both of these findings are consistent with freely moving studies^{1,2}. Ongoing work will determine whether CA1 contains discrete feature-biased subnetworks and whether specific facial features are predictive of neural dynamics during social interaction. This work will elucidate spatial and social coding dynamics in hippocampal CA1, providing new insight into how brain computations support complex episodic memories.

1. "Assessment of social interaction behaviors." Journal of visualized experiments: JoVE 48 (2011): 2473.

2. "Multiplexed representation of others in the hippocampal CA1 subfield of female mice." Nature Communications 15.1 (2024): 3702.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Title: Manipulating postsynaptic membrane fusion modifies hippocampal place code plasticity

Authors: M. H. PLITT^{1,2}, K. KAGANOVSKY^{3,4}, E. SAY², M. SOSA^{2,5}, T. C. SUDHOF^{3,6}, *L. M. GIOCOMO^{2,6};

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Abstract: Place cells in hippocampal area CA1 form fields rapidly in new environments and can flexibly update to incorporate novel spatial features or experiences. Such changes are hypothesized to arise from plasticity events operating on multiple timescales. Synaptic plasticity requires activity-dependent delivery of membrane proteins, such as AMPA receptors, to the synapse via membrane fusion. Disentangling the roles of synaptic plasticity from other neural mechanisms in CA1 place cell dynamics remains a challenge. In this work, we ask whether activity-dependent membrane fusion is necessary for generating the *in vivo* neural dynamics that support learning.

To address this question, we combined a conditional knockout (cKO) of the postsynaptic membrane fusion protein Syntaxin-3 (Stx3) with *in vivo* two-photon calcium imaging in CA1 neurons. We trained head-fixed male mice to perform a virtual reality novel-arm Y-maze task to examine the effects of novelty and reward on spatial representations. A dense, bilateral knockout of Stx3 in dorsal CA1 showed that Stx3 is not necessary for the formation of stable place cell representations. However, Stx3-cKO mice exhibit distinct reward-approach behavior suggesting a weakened reward-predictive code. Analyses revealed that Stx3 is necessary for several flexible features of the CA1 place code, including responses to environmental novelty, place field modifications consistent with behavioral timescale synaptic plasticity (BTSP) and offline consolidation, and hippocampal over-representation of reward.

In order to control for behavioral differences between the Stx3-KO and Stx3-WT animals, we devised an intersectional Cre/Flp viral strategy with dual-color calcium indicators to compare Stx3-cKO and Stx3-WT cell properties within the same animal. Stx3-WT place cells continued to exhibit plasticity-related features, but Stx3-cKO cells showed signs of altered place field properties and reward representation, pointing to a cell autonomous role of Stx3. Altogether, this work highlights the role of postsynaptic activity-dependent membrane trafficking in shaping and stabilizing the hippocampal spatial code.

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Poster

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Title: Parallel hippocampal coding of space and experience relative to reward

Authors: *M. SOSA^{1,2}, M. H. PLITT^{3,1}, L. M. GIOCOMO^{1,4};

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Abstract: To find reward in a spatial environment, the brain must create an internal map of space while specifically remembering the events leading up to and following reward. Hippocampal place cells have been shown to over-represent specific reward locations, but whether hippocampal activity encodes sequences of events relative to reward at greater distances is unclear. To test the hypothesis that hippocampal activity can anchor to reward across the entire environment, we used 2-photon calcium imaging in hippocampal area CA1 to monitor the same neuronal population across days as head-fixed mice navigated virtual environments with changing hidden reward locations, dissociating reward from sensory stimuli. We found that when the reward moved, a subpopulation of cells updated their preferred firing to the same relative position with respect to reward, including cells active far away from reward. More neurons were recruited to this reward-relative code over learning, while the spatial environment code was maintained in a parallel subpopulation. These populations were dynamic rather than dedicated cell classes: cells could change coding identity day to day, and coding properties were exhibited independently in individual place fields. We next examined the relationship of reward-relative activity to behavior and to environmental adaptations. We found that reward-relative cells exhibited mixed selectivity for multiple features of experience, that the organization of reward-relative fields correlated with the precision of behavior, and that updates in reward-relative activity often preceded behavioral changes. This work suggests that the hippocampus encodes a flexible representation of reward experience while preserving a stable memory of the spatial environment.

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Poster

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Title: Coordination of remote representations across days, environments, and the entorhinal-hippocampal network

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Abstract: Neurons can collectively represent the current sensory experience while an animal is exploring its environment or remote experiences while the animal is immobile. These remote representations can reflect learned associations and be required for learning. Recent work has identified that during immobility, neurons in the medial entorhinal cortex (MEC) frequently collectively represent 'non-local' positions far from the animal's current location. This non-local coding was pertinent to the task, as MEC preferentially represented remote task-relevant locations at appropriate times, while rarely representing task-irrelevant locations. Here, we extend this work through simultaneous recordings in MEC, CA1, and CA3 over multiple days and environments to characterize the dynamics of these remote representations. Non-local coding emerged rapidly over the course of an initial exposure to a novel environment and was stably present across multiple days. Remarkably, cells preferentially recruited to non-local coding were less likely to encode reward consumption, despite non-local coding overrepresenting rewarded locations. Ongoing work will characterize whether the same cells are recruited to non-local coding over multiple days, locations overrepresented in non-rewarded environments, and the activity of these recruited cells during offline rest sessions. Finally, CA1 activity was decoupled from MEC during non-local coding. Ongoing work will describe non-local coding in CA1 and CA3 and how this decoupling may be mediated by different subtypes of local inhibitory neurons. Together, this work will illuminate how remote representations flexibly adapt over time, space, and circuits to potentially support spatial memory.

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Poster

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Title: Dynamic Interfacing Between Allocentric and Egocentric Frames via the Parietal-Hippocampal Network During Spatial Navigation and Sleep

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Abstract: Effective navigation and memory formation are critical for survival and depend on dynamic transformations between allocentric (world-centered) and egocentric (self-centered) reference frames. These transformations—such as recalling a city layout (allocentric) and selecting a specific turn (egocentric)—are thought to rely on interactions within a parietal cortex (PC)-anterior thalamic-hippocampal (HPC) network (Bermudez-Contreras et al., 2020). Building on our recent work (Zheng et al., 2025), we examined how this circuit supports coordination between route-centered, allocentric place representation and egocentric action using a complex sequence task in rats. This task induced bidirectional functional interactions between HPC and PC, so we set out to look for similar bidirectional interactions during sleep. We found that PC multi-unit activity (MUA) exhibits a delta (~5 Hz) rhythmic firing pattern during both behavioral sessions in a single day. Remarkably, a similar delta pattern re-emerged during mid- and post-sleep—but not pre-sleep—suggesting a role in memory consolidation. Furthermore, during task performance, we observed that PC local field potentials (LFPs) displayed theta-band (~9 Hz) oscillations around HPC spike events, pointing to coordinated activity across these regions during behavior. Ongoing work investigates this coordination further using the “Map-to-Action Transformation Task” (MATT), where rats navigate under three reference frame conditions: allocentric, transformation, and egocentric. These findings aim to elucidate how PC-HPC interactions support flexible navigation and memory-guided behavior across waking and sleep states.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR193.22/TT14

Topic: I.09. Spatial Navigation

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FLDOH 20A09
NIH R56 MH133929 to AW
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NIH R01 NS072497
FLDOH 24A04 to SCG
NIH R01 GM131283

Title: Oral administration of dual orexin receptor antagonists (DORAs) in young 3xTg mice improves diminished delta and may promote efficient brain waste clearance to prevent the progression of AD pathogenesis

Authors: *I. I. COIDURAS¹, E. SALVADOR¹, K. HARDIN¹, J. RADOVICH¹, S. C. GRANT², W. MCCALL³, C. LEE¹, A. A. WILBER¹;

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Abstract: The brain, unlike other systems, has an unconventional lymphatic filtration system (Xie et al., 2013). Extracellular waste is cleared partly by cerebrospinal fluid (CSF) and astrocytes of the blood brain barrier. It is thought that circulating CSF flows into the brain along the perivascular space surrounding arteries (Iliff et al., 2013). Fluid moves through astrocytic water channels, gathering debris from the extracellular space. This waste exits the brain as interstitial fluid (ISF) along the space surrounding venules. While this ‘glymphatic’ system is thought always active, the oscillations generated by slow wave sleep (SWS) and vascular pumping during micro-arousals may provide an enhancing flow rate optimal environment for clearance (Benveniste et al., 2020; Mander et al., 2016). Alzheimer’s Disease (AD) is characterized by aggressive intra and extra -cellular protein aggregations with devastating effects (Mander et al., 2016). Best known for its effects on cognition (one of the earliest changes being problems with spatial navigation), many with AD also have sleep disturbances (Mander et al., 2016). Detecting sleep changes before significant disease progression and enhancing glymphatic function by improving sleep at this early time may protect against cognitive decline. We are treating sleep deficits by targeting the orexin pathway, an established regulator of the circadian cycle, which likely preserves critical sleep features like micro-arousals. Previously shown to enhance SWS, we hypothesize that administration of a dual orexin receptor antagonist (DORA) to improve sleep quality. We implanted an electrode into the parietal cortex and hippocampus and an EMG wire in the nuchal muscle. Sleep recordings were measured for 20h, and we used a linear spatial reorientation task (akin to conditions where pre-clinical patients get lost in new surroundings) to test for cognitive impairment in pre-plaque (intracellular aggregation only) 3xTg mice. After each daily task session and before light onset, mice received oral DORA. We are also assessing the impact of DORAs on glymphatic flow (using MRI, tracers, and fiber photometry) in 3xTg and NonTg mice. We identified a diminished delta power marker, present in TgF344-AD rats and 3xTg mice on hybrid or B16 background, and detectable with short (< 2h) or long (24h) sleep recordings. Delta power is also reduced early in APP/PS1 mice (Chen et al., 2023), and found that DORAs improved delta power during sleep. We are assessing the impact on cognition, glymphatic flow, and levels of intracellular aggregation. These findings support the use of DORA to hold protein aggregation in check by facilitating clearance during sleep.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

Location: SDCC Halls B-H

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Florida Department of Health (DOH) 20A09
Florida Department of Health (DOH) 21K12

Title: Disentangling Spatial Reference Frames in Rodent Navigation Using a Novel Behavioral and Neural Analysis Approach

Authors: *Y. CHEN¹, E. ESCOBAR², K. COSS¹, J. HURTADO³, Y. ZHENG⁵, B. J. CLARK⁷, A. A. FENTON⁴, A. A. WILBER⁶;

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Abstract: Understanding how rodents navigate space requires disentangling the use of different spatial reference frames, including allocentric (map-based) and egocentric (body-centered) strategies. While many brain regions are known to contribute to processing these frames of reference, determining which reference frame animals rely on in a given context remains challenging—particularly as rodents often integrate multiple cues and across reference frames to optimize navigation.

To address this, we introduce a novel behavioral paradigm designed to isolate and probe reference frames and transformations. Rats are first trained to use stable distal cues to locate a fixed goal arm in an eight-arm maze (a circular table with removable barriers to make 8 arms), the allocentric condition. Once rats reach performance criteria, they are trained on a transformation task: animals are briefly shown the environment, after which it is occluded with a black curtain while the rat is in a covered box. This is designed to force a switch from an allocentric to egocentric reference frame. Finally, rats are trained on an egocentric task, where distal cues are always blocked and animals must make the same action (e.g., take second right turn) regardless of starting position.

Potential confounds, particularly for the allocentric and transformation conditions, is that animals may still use unintended cues (e.g., local cues such as olfactory or tactile traces) or alternative strategies, such as path integration. We describe behavioral and neural approaches to disentangle

these possibilities. 1) We designed a rotating maze system to make local cues unreliable, and present data showing that trained rats can navigate without using local cues. 2) We developed and present a probe test, "levitation" probes: in darkness, rats are lifted slightly above the maze while the maze and/or distal cues are rotated. Although rats typically integrate both systems these manipulations dissociate the path integrator from external input. Finally, we present and approach for 1) analyzing population data to measure changes in population geometry reflecting different reference frames, and 2) assessing population data for egocentric, allocentric and potential transformation brain states to identify timepoints to analyze in depth for transformation neural processes. Thus, even if neural activity fails to show evidence of a transformation, this would not be due to our inability to disambiguate path integration and allothetic behavior. Our approach offers a more precise behavioral and neural assay for studying spatial computations and the neural mechanisms of reference frame transformation.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

Location: SDCC Halls B-H

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Topic: I.09. Spatial Navigation

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R01 AG070094
Florida DOH 20A09
NIA F31AG079619-01

Title: Rescuing impaired hippocampal-cortical interactions and spatial reorientation learning and memory during sleep in a mouse model of Alzheimer's Disease using hippocampal 40Hz stimulation

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Abstract: Alzheimer's Disease (AD) is the most common form of dementia affecting millions of patients and caretakers. In preclinical AD, spatial learning and memory is impaired (Allison et al., 2016). We reported similar impairments in 6-month 3xTg-AD mice on a virtual *spatial-reorientation task* (VM) that requires learning to use landmarks to navigate (Cushing et al., 2020). Memory replay during sleep is critical for learning related plasticity (Ego-Stengel & Wilson, 2009; Jadhav et al., 2012; Maingret et al., 2016), and hippocampal (HPC)-cortical

dysfunction is a potential mechanism for AD memory impairments (Gennaro et al., 2017; Khan et al., 2014). We previously found deficits in HPC-parietal cortex (PC) coordination during sleep coinciding with VM impairments (Cushing et al., 2020). Various 40Hz stimulation forms have cleared mouse AD pathology (Iaccarino et al., 2016; Martorell et al., 2019), and improve functional connectivity in preclinical AD patients (He et al., 2021; Paulson et al., 2024), though some papers found a lack of light only 40Hz improvement (e.g. Soula et al., 2023). We assessed HPC-PC coordination in 3xTg-AD/PV^{cre} mice with the VM to assess the impact of targeting HPC with optogenetically induced 40Hz. We implanted a 16-tetrode recording array targeting PC and HPC and an optical fiber targeting HPC. Daily recording sessions of rest-task-rest began as mice learned the VM, followed by HPC optogenetic stimulation, either 40Hz ipsilateral or contralateral, no stim or SHAM. We assessed sleep quality metrics, PC delta waves (DW), and HPC markers of memory replay (SWRs) during slow wave sleep. We also assessed intracellular density of pTau, and two conformation specific antibodies preferring A β 42. In SHAM stimulated mice SWR-DW cross-correlations were reduced, similar to 3xTg-AD mice (Cushing et al., 2020). In 40Hz stimulated mice, this phase-locking was rescued. Furthermore, both 40Hz stimulation groups restored VM performance compared to SHAM mice. However, contralateral 40Hz stimulation rescued HPC-PC coupling no longer predicted performance as in control animals. These final neural analyses are still underway in the ipsilateral 40Hz group. Both contralateral 40Hz and SHAM stimulation reduced hippocampal beta amyloid load, and 40Hz stimulation was only capable of reducing further reducing A β 42 in PC. Thus 40Hz stimulation of HPC rescued learning and memory related functional interactions in the HPC-PC network during sleep and impairments in spatial navigation. Furthermore, the observed effects seem to be mediated by direct 40Hz impacts on brain activity patterns or by A β 42 reductions in PC only (opposite our original hypothesis).

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Program #/Poster #: PSTR193.25/TT17

Topic: I.09. Spatial Navigation

Support: NIH MH112688
NIH T32 DA07234

Title: Decision dynamics in hippocampus, dorsolateral striatum, and medial prefrontal cortex in rats on the Left / Right / Alternation task

Authors: *C. M. GAGLIARDI¹, U. MUGAN¹, S. L. HOFFMAN², A. D. REDISH¹;
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Abstract: Decision-making includes both prospective (deliberative) systems, which imagine potential decisions before committing to an action, allowing for flexibility in variable environments, and retrospective (procedural) systems, which rely on established action chains to get reward in reliable environments. These systems are controlled by distinct neural circuits, including dorsal hippocampus (dHC), dorsolateral striatum (DLS), and medial prefrontal cortex (mPFC). 8 rats with silicon probes in dHC, mPFC, and DLS ran the left/right/alternation (LRA) task, running through a complex central path culminating in turning left (L), right (R), or alternating between left and right (A) for food rewards. Although rats run this task in a continuous loop, providing a reward-site at the beginning of the central track creates a start of maze (SOM) location in which rats often stop before initiating a new lap.

The creation of a SOM induces task-bracketing in DLS that were negatively correlated with vicarious trial and error (VTE) behavior at the choice point (CP) at the end of the central path. VTE can be measured with integrated angular velocity, IdPhi. Some SOM passes were more behaviorally variable than others, which can also be measured with IdPhi. Behavioral variability at SOM increased following a rule switch. The increased IdPhi at SOM was quantitatively smaller than that at CP, but occurred before IdPhi increases at CP.

Both dHC sharp wave ripple (SWR) events and DLS gamma 50 (g50) events were more prominent at SOM and at the feeders than in CP. SWR events were rare on the central track, but G50 events did occur at interesting points on the central track.

The rate of SWRs at SOM decreased following a rule switch. Consistent with previous studies, SWR rate at SOM was negatively correlated with VTE at CP. Interestingly, however, SWR rate at SOM was correlated with larger IdPhi at SOM. mPFC multi-unit activity (MUA) increased during SWR events at SOM, being diminished before. DLS showed lower MUA through the HC SWR event. These effects were not fully explained by speed changes at SOM. HC MUA during SWRs increased as a function of experience with a rule, consistent with suggestions that SWRs and replay are more related to consistent paths and automated behaviors than deliberative planning processes.

G50 events also occurred at SOM, particularly at the start and end of pass through SOM. Both DLS and dHC activity increased shortly before the g50 event, with mPFC activity decreased after. Consistent with previous studies, speed increased dramatically at the start of the g50 event, suggesting a role for g50 in initiation of motion.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Program #/Poster #: PSTR193.26/TT18

Topic: I.09. Spatial Navigation

Support: NIH MH112688
T32-DA037183
NSERC Postdoctoral Fellowship
UMN MnDrive Brain Conditions

Title: Running the gauntlet: dorsal hippocampal representations of predator threat

Authors: *C. C. DAMPHOUSSE, O. L. CALVIN, A. D. REDISH;
Neurosci., Univ. of Minnesota, Minneapolis, MN

Abstract: During approach-approach conflict, the dorsal hippocampus (dHC) sweeps through mental simulations of paths to goals. However, whether dHC similarly signals potential negatively-valenced outcomes to avoid is unknown. The predator-inhabited foraging task (colloquially known as the “robogator” task) has been used to investigate approach-avoid conflict. Recent studies found dHC changes in representation on discovery of a threatening robot and subsequent sweeps to the robot danger (cohort 1, 6 Brown Norway [BN] rats, 3M 3F, Calvin et al. PLoS Biology 2025). Rats were trained to alternate between reward sites on a linear track. A robot was then introduced that attacked from the side, forcing rats to run past the robot to get food. A second cohort (BN, 4M 4F) was trained similarly. Rats showed behavioral changes after being attacked indicative of prospective fear (fewer laps, slower excursions to the far feeder, hesitation at the nest, increased mid-track aborts (MTAs)), which vanished during extinction phases. Interestingly, they did not robustly return during re-exposure, when the robot could attack again. Calvin et al. reported that new place fields appeared in cohort 1 representing the robot’s location after the first attack. The fact that these new place fields encoded the robot’s location, not the position of the animal when attacked suggests that they are not simple indexed representations of an episodic memory of a specific event. Cohort 2 partially replicated these results, finding new place fields, but with a distribution more concentrated at the location when attacked. dHC representations during MTAs revealed increased decoding to the attack line and beyond in both cohorts. During Extinction, decoding to the position of the robot during MTAs was only maintained in cohort 2, possibly indicating a more robust fear memory due to subtle differences in the training sequence of the two cohorts. A third cohort (4M 4F) was trained on a U-shaped version, where the robot attacked at a location midway between two nests (at the base of the U), allowing for simpler task analyses. This third cohort replicated the main results of the first two cohorts, including an increase in fear-like behavior and new place fields appearing around the robot location following the attack. During MTAs, preliminary data from dorsal HC on this task revealed decoding around the robot. Taken together, these data suggest that on attack, the rodent hippocampus develops representations of potential threat locations that may be used to guide prospective avoidance behavior during approach-avoid conflicts.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Program #/Poster #: PSTR193.27/UU1

Topic: I.09. Spatial Navigation

Support: NIH MH112688
UMN UROP undergraduate support

Title: Impact of systemic diazepam on dorsal hippocampal CA1 neural activity

Authors: J. G. PETERSON, A. SHEEHAN, M. T. ERICKSON, C. C. DAMPHOUSSE, *A. D. REDISH;
Univ. of Minnesota, Minneapolis, MN

Abstract: Systemic diazepam is a benzodiazepine often prescribed for its anxiolytic effects, acting upon GABA_A receptors to increase inhibition. To test the pharmacological validity of the anxiety hypothesis of rat behavior in the predator-inhabited foraging “robogator” task, diazepam (2 mg/kg) or Tween-20 vehicle control was injected systemically (IP) into a cohort of 5 rats (3M, 2F) trained to run past a threatening robot to find food. In both this cohort and previous cohorts, we observed strong reductions in the anxiety-like behaviors under diazepam (Walters et al. Psychopharm 2019, Calvin et al. PLoS Biology 2025). In this cohort, we also observed a dramatic change in dorsal hippocampal (dHC) local field potentials (LFP) under diazepam, including reduced power in the sharp-wave ripple (SWR) band (150-250 Hz), a reduced incidence of SWR events, and changes in the theta cycle (Calvin et al 2025). We also observed changes in gamma power that differed across the hippocampal CA1 layers, consistent with GABA_A receptor distributions in CA1. Unfortunately, these data only included LFP signals, and thus effects of diazepam on dHC cellular activity remained unknown.

In order to identify effects of diazepam on dHC single unit activity and population representations, 4 rats (4F), implanted with silicon probes in CA1 and previously trained on other tasks, learned to run back and forth on a linear track for alternating food reward. Each day, prior to the rat performing the task, rats were injected systemically (IP) with saline, Tween-20, or diazepam (doses ranging from 1-3 mg/kg). LFP data replicated the changes seen in the first cohort. At all doses, rats resting in a flower pot showed highly relaxed muscle tone. However, once put on the track, rats ran laps normally, particularly at lower doses (1-2 mg/kg). At 3 mg/kg, rats ran fewer laps than controls. Neurophysiological effects showed large individual differences, however, particularly at doses higher than 1 mg/kg, cell firing was reduced while running. After running, fewer SWRs were observed in the post-running rest. To test representation properties, tuning curves were constructed and the represented position was decoded at 100 ms time bins. After normalizing for the number of cells in the recording, the entropy of the decoded representations was higher under diazepam than controls both while running and while at rest at the feeders. Similar results were found when decoding using theta time bins and when decoding on-track SWR events directly.

These data suggest that systemic diazepam administration may affect dorsal hippocampal function in ways that may be important for spatial navigation, memory, and consolidation.

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Poster

PSTR193: Cortical and Hippocampal Circuits for Learning, Memory, and Spatial Representations

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Program #/Poster #: PSTR193.28/UU2

Topic: I.09. Spatial Navigation

Support: Helen Hay Whitney Postdoctoral Fellowship
HHMI

Title: A high resolution spatial map in the primary visual cortex of freely behaving rats

Authors: *K. LEE¹, P. ADENEKAN³, F. GAO⁴, D. M. MORALES-RODRIGUEZ², J. ZHOU⁵, A. M. YORITA⁶, R.-U. HAQUE⁷, U. EDEN⁸, M. SCANZIANI⁹, L. M. FRANK¹⁰;

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Abstract: The brain constructs internal models of the world from experience. For instance, it integrates current and recently experienced sensory input to build a cognitive map of the environment, as exemplified by the spatial representations in the hippocampus and related areas. But whether such internal models can be used to influence subsequent sensory processing is not well understood. Previous work has shown that feedback signals carrying information about attention, arousal, and stimulus history can influence sensory processing. In addition, neurons in the primary visual cortex (V1) respond differently to the same stimuli presented at different virtual locations. To probe the effect of the internal model on visual processing, we have recorded hundreds of neurons with flexible polymer probes bilaterally in both V1 and hippocampus CA1 in freely moving rats performing a memory-dependent spatial alternation task in a visually enriched environment. Using Bayesian decoding, we found that the V1 encodes spatial information at a very high-resolution (median decoding error: ~ 1 cm) comparable to CA1, even though the animal could move its head and eyes freely. Furthermore, this spatial information is largely maintained when the animal performs the task under very low light levels (< 100 R*/rod/s). These observations suggest that feedback signals from brain areas that implement the internal model may be present in V1 independent of feedforward visual input. Furthermore, we find single neurons in V1 that resemble highly cognitive representations that have been reported in the parahippocampal regions, such as generalized spatial tuning to different paths. These neurons maintain their tuning in darkness and serve as further evidence of

feedback from the internal model in V1. Future work will examine how such cognitive representations can be integrated with feedforward processing of visual input to guide behavior.

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Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR194.01/UU3

Topic: I.10. Human Learning and Cognition

Support: Kavli Institute for Brain Science

Title: The role of causal structure in organizing episodic memory

Authors: *I. GEFEN¹, D. SHOHAMY², C. BALDASSANO¹;

¹Columbia Univ., New York City, NY; ²Zuckerman Inst., Columbia Univ., New York, NY

Abstract: Causal structures have been shown to influence decision-making, learning, and inference, yet their role in organizing episodic memory remains underexplored. This study investigates whether causal judgment shapes memory recall independently of temporal sequence or semantic similarity. Participants viewed image sequences categorized as either causal (depicting a structured event progression) or semantic (thematically related but non-causal), presented in either correct or randomized order. They then completed immediate and delayed free recall tasks. Complementary experiments assessed participants' causal judgments (pairwise causality ratings) and perceived event order (image sorting tasks). To examine how different types of structure influenced recall, we modeled the transitions between recalled items based on causal, temporal, and semantic relationships among the events. Comparing these models revealed that when participants perceived causal structure in a sequence, their recall transitions more closely reflected the underlying causal links than the original presentation order. These findings support the hypothesis that causal judgment serves as a distinct organizing principle in episodic memory, enhancing both recall structure and retention over time. These results also provide a behavioral foundation for future research into the neural mechanisms underlying causal structures in memory.

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Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR194.02/UU4

Topic: I.10. Human Learning and Cognition

Support: TWCF-2021- 20639
DOD ONR MURI Co-PI Self- Learning Perception

Title: Understand Intrinsic Motivation in Causal Learning Through Intrinsically Motivated Exploration

Authors: *F. DAI, A. GOPNIK;
Univ. of California, Berkeley, Berkeley, CA

Abstract: Active exploration is essential to human causal learning, yet the intrinsic drives underpinning such exploratory behavior remain poorly understood. Drawing on principles from information and control theory, we examined how three candidate metrics—entropy reduction, information gain (IG), and empowerment (controllability of interventions over outcomes)—influence the selection of interventions and subsequent causal inference. Across two behavioral experiments (N = 40 each), we tested how these metrics influence the discovery of causal structures. In Experiment 1, participants engaged in an “alchemy” task in which they selected elements to uncover hidden causal chains linking inputs to outputs. Using mixed-effects logistic regression, we found that trial-level choice probabilities increased with predicted reductions in entropy (OR = 1.32, 95% CI [1.20, 1.46], $p < .001$), expected IG (OR = 1.39, 95% CI [1.29, 1.50], $p < .001$), and empowerment (OR = 1.51, 95% CI [1.34, 1.69], $p < .001$). Critically, only empowerment computed over potential interventions predicted individual differences in post-exploration causal-prediction accuracy (OR = 1.41, 95% CI [1.08, 1.85], $p = .012$), suggesting that learners who favored actions granting greater instrumental control formed more accurate causal models. In Experiment 2, we extended these findings to a probabilistic “blicket” detector paradigm wherein blocks had probabilistic activation of a machine. Regression analyses revealed strong positive influences of IG (OR = 1.36, 95% CI [1.28, 1.44], $p < 2 \times 10^{-16}$) and empowerment (OR = 1.56, 95% CI [1.45, 1.68], $p < 2 \times 10^{-16}$) on action selection, alongside a negative relationship with high initial entropy (OR = 0.87, 95% CI [0.83, 0.91], $p < 2 \times 10^{-16}$). Importantly, in subsequent feature-level inference tasks, both IG (OR = 1.66, 95% CI [1.50, 1.84], $p < 2 \times 10^{-16}$) and empowerment (OR = 2.10, 95% CI [1.65, 2.67], $p < 5 \times 10^{-6}$) robustly predicted the accuracy of judgments about causal links, whereas entropy reduction showed no significant predictive power (OR = 1.05, 95% CI [0.98, 1.12], $p = .18$). Collectively, these results demonstrate that human learners do not engage in undirected sampling; rather, they strategically favor interventions that both reduce uncertainty and afford high levels of instrumental control.

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Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR194.03/UU5

Topic: I.10. Human Learning and Cognition

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UKRI Frontier Research Grant to DB (EP/X023060/1)

Title: Human Hippocampal Theta-Gamma Coupling Coordinates Sequential Planning During Navigation

Authors: Z. HUANG¹, J. A. BISBY², N. BURGESS³, *D. BUSH¹;

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Abstract: Human behaviour often relies on executing a specific sequence of actions to achieve a desired outcome. However, the neural mechanisms underlying the dynamic construction and maintenance of such sequences during goal-directed behaviour are not yet clear. Empirical and theoretical studies of working memory function suggest that sequential information may be encoded in neural circuits by bursts of gamma activity occurring at consecutive theta phases. Here, we asked whether similar coding schemes might support sequential planning during goal-directed navigation. Using non-invasive magnetoencephalography and an abstract navigation task, we found that hippocampal theta power during both planning and subsequent navigation decreased with proximity to the current goal, only during accurate navigation. At the same time, theta-gamma phase-amplitude coupling increased with goal proximity, consistent with sequences of upcoming locations being represented by gamma bursts occurring at successive theta phases. Importantly, entorhinal high gamma and hippocampal low gamma dominated while traversing novel and previously experienced paths, respectively, consistent with previous rodent studies. These findings suggest that hippocampal theta-gamma phase amplitude coupling flexibly and dynamically coordinates sequences of actions during goal-directed behaviour across mammalian species, using different gamma bands for mnemonic and prospective planning.

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Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

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CAPES 88886.71450/2022-00, 88887.511156/2020-00

Title: The structure of the sequence of events retrieved from EEG signals correlates with performance during the Goalkeeper Game

Authors: *P. CABRAL PASSOS¹, P. AZEVEDO², V. MORAES³, A. DUARTE¹, C. VARGAS⁴;

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Abstract: We used the Goalkeeper Game (game.numec.prp.usp.br) to investigate the conjecture that the brain performs statistical inference to retrieve the temporal structure of probabilistic sequences. A sequence of kicker's choices was generated by a Probabilistic Context Tree. As a goalkeeper, the participant was asked to predict each kicker's choice across a sequence of 1500 penalties by pressing a button, which triggered an animation of the outcome. The Context Algorithm associated with a Projective Method was used to retrieve Context Trees estimated from EEG segments recorded 300 ms before the goalkeeper's button press. The kicker's context tree was compared to the one retrieved from the goalkeeper using a distance measure (Balding et al., 2008). This distance was correlated to the success rates of the participants. Twenty-six right-handed subjects (12 F, 24 ± 6.61 years) from two facilities with identical set-up participated in the study. In each trial, the goalkeeper was asked to choose left (0), center (1) or right (2) while his/her EEG was recorded. Raw EEGs (32 elec., avg ref., ActiHamp, 2.5kHz) were filtered at 1Hz for artifact removal using IClab. The resulting EEG was low-passed in 45 Hz and then downsampled to 256 Hz. For tree estimation, trials were divided in sliding windows of 300 trials with 50 trials displacement. For each window/electrode/participant the tree estimation was done using the EEG segments time-locked to the button press (-300ms to 0ms). A measure of distance from the kicker's tree was calculated for each retrieved tree. For each electrode, median-based centroids were then calculated for the set of participants' distances and paired with the mean success rates for the respective window. A Linear Mixed Effects model showed an inverse relationship between success rate and the distances for the electrodes Fp2($r=0.59$, $p<1\%$), F7($r=0.53$, $p<1\%$), F4($r=0.61$, $p<1\%$), FC1 ($r=0.38$, $p<5\%$), Cz($r=0.47$, $p<1\%$), C4 ($r=0.45$, $p<5\%$), CP2 ($r=0.68$, $p<1\%$), TP9($r=0.42$, $p<5\%$), P7($r=0.43$, $p<5\%$), P3($r=0.71$, $p<1\%$), Pz($r=0.48$, $p<1\%$) and Oz ($r=0.61$, $p<1\%$). This inverse relationship suggests that these brain regions participate in the process of learning the structure of the probabilistic sequence.

Disclosures: P. Cabral Passos: None. P. Azevedo: None. V. Moraes: None. A. Duarte: None. C. Vargas: None.

Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR194.05/UU7

Topic: I.10. Human Learning and Cognition

Support: NINDS Grant R01NS119468 (PI: ER Chrastil)
George E. Hewitt Foundation for Medical Research

Title: Contingency-dependent state augmentation as a normative learning rule for non-Markovian tasks

Authors: *J. YOO, A. GOESCHEL, D. ZHOU, A. BORNSTEIN;
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Abstract: Agents efficiently organize episodic memory sequences by their latent structure into representations such as cognitive maps. A prevalent assumption is that once the abstract structures have been extracted from individual episodes, the trajectory-specific history no longer influences behavior -- in other words, we assume that agents are learning a *Markovian* state space. Although state spaces in realistic tasks could be history-dependent, structure learning in non-Markovian environments has been underexplored. A key capability supporting structure learning in non-Markovian environments is *augmentation*, or “splitting” of perceptually aliased states dependent on the agents’ history. Here, we propose a new algorithm, Contingency-Dependent State-Space Augmentation (CoDA), which automatically discovers context-dependent contingencies and adjusts them. Specifically, we use two types of contingency -- prospective and retrospective -- to identify when augmented states should be created and disposed of. This method depends critically on the use of *contextual eligibility traces* that preserve trajectory-specific information, alongside predictive representations. We show that our model correctly identifies history-dependent contingencies of trajectories in non-Markovian tasks, outperforming other contingency or state-space learning algorithms. Critically, we also show that many canonical non-spatial associative learning experiments reduce to a spatial non Markovian task, and that our approach to these tasks explains widely observed conditioning phenomena such as blocking, latent inhibition, devaluation, and cue discovery, that were previously explained using bespoke, and sometimes conflicting, variants of associative learning rules.

Disclosures: J. Yoo: None. A. Goeschel: None. D. Zhou: None. A. Bornstein: None.

Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR194.06/UU8

Topic: I.10. Human Learning and Cognition

Support: ONR MURI N00014-17-1-2961

Title: Behavioral and neural effects of causal structure bridging across experiences

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Abstract: While recounting experiences, one can transition between events via several forms of structure, including nearby events in time (temporal), similar events (semantic), or events influenced by the current event (causal). I will present data from two experiments aimed at disentangling the influence and neural mechanisms underlying these factors. In a first experiment, participants watched the non-linear narrative, *Memento*, under different task instructions. For each scene, we separately computed semantic and causal networks, from which we contrasted the evidence for temporal, semantic, or causal strategies during recall. Critically, there was stronger evidence for the causal strategy than semantic or temporal strategies - even when we asked participants to recall the film in the presented order. In a second, fMRI experiment, participants watched and recalled a two-part episode of *Friends*, which featured five temporally interleaved storylines. Behaviorally, causal structure again significantly influenced recall organization. Neurally, pattern similarity analyses revealed that the angular gyrus and other default mode regions were more similar for scenes within versus across storylines while controlling for time. Moreover, they reflected (graded) causal structure better than merely considering the (binary) storyline or other explanatory models. In sum, these findings highlight the importance of accounting for complex, causal networks - and their underlying neural substrates - in scaffolding knowledge building and organizing recall.

Disclosures: J.W. Antony: None. K.A. Bennion: None. C. Ranganath: None.

Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR194.07/UU9

Topic: I.10. Human Learning and Cognition

Support: R01 DA055259

Title: Uncertainty resolution during hypotheses testing engages lateral prefrontal cortex to support memory encoding.

Authors: *V. P. MURTY¹, X. SHEN², D. V. SMITH³;

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Abstract: The relationship between uncertainty and memory is not one-to-one; rather, motivation to learn is greatest during moderate levels of uncertainty. However, research has yet to explore how dynamic changes in uncertainty resolution influence memory when individuals are updating their priors during goal-directed search. We ran two studies that utilized a hypothesis testing paradigm, in which participants learn rules to unlock treasure chests to reveal trial-unique memoranda. In study 1, we showed an inverted U-shape relationship between decision uncertainty and memory, such that memory was best at moderate levels of uncertainty during hypothesis testing. In study 2, we replicated our behavioral findings during collection of fMRI, and revealed that decision uncertainty and memory success were represented in the ventral striatum and hippocampus, respectively. Furthermore, the lateral prefrontal cortex represented an integration of decision uncertainty and memory success, highlighting this region as a key node in guiding incidental memory encoding in the context of uncertainty resolution. Together, these findings provide greater insight into how hypothesis testing primes mesolimbic-hippocampal interactions in service of storing features of the environment related to uncertainty resolution.

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Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR194.08/UU10

Topic: I.10. Human Learning and Cognition

Support: McDonnell Foundation

Title: Key-value memory model retrieves causally related past events during narrative comprehension

Authors: *H. SONG¹, Q. LU⁴, T. NGUYEN², J. CHEN⁵, Y. LEONG⁶, M. D. ROSENBERG⁶, S. CHING³, J. ZACKS²;

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Abstract: Comprehending ongoing narrative events entails retrieving causally related past events (Suh & Trabasso, 1993), indicating a process of causal inference during event comprehension (Graesser et al., 1994). However, the exact process by which this causal

inference occurs remains elusive. This study uses a neural network model that simulates cortico-hippocampal interactions to understand memory-guided causal inference. The model was trained to predict upcoming scenes in a TV episode, where prediction required integrating past events with the current event. We asked if the model, like humans (Song et al., 2025), selectively retrieves causally related past events to inform ongoing comprehension. Eighteen episodes of This Is Us Season 1 were segmented into ~4-second scenes based on shot changes and transformed into OpenAI's CLIP embeddings as inputs. The model was trained on all episodes but one and tested on the held-out episode presented in scrambled orders, matching stimuli used in Song et al. (2025). The model is based on a gated recurrent unit (GRU) recurrent neural network (RNN) architecture, where the input is transformed into a hidden layer activation pattern. These hidden states correspond to “values”, representing memory contents and are encoded in an episodic memory (EM) buffer at every time step. Inputs are also transformed into “keys” that represent memory addresses and are encoded in the EM, and “queries” that survey the keys to calculate self-attention and retrieve values stored in the EM (Gershman et al., 2025). The model uses an average of the current hidden state and retrieved memory to predict the CLIP embedding of the next scene. We found that the GRU RNN model with the EM buffer (hereby called EM-GRU) retrieved similar memories for event pairs that were causally related to one another. Memories retrieved by the model were similar to memories retrieved by humans ($\rho = .388$, $p < .00001$), while neither the EM-GRU with random selection of memories ($\rho = .073$) nor the EM-GRU with fixed input-to-key and input-to-query mappings ($\rho = .043$) resembled humans' memory retrieval. This suggests that the key-value memory system, which distinguishes representations used for encoding and retrieval and simulates cortico-hippocampal function in the brain, has successfully learned to assign higher attention weights to past memories that are causally related to the ongoing event. This suggests that causal inference emerges from the strategic use of episodic memory encoding and retrieval during event comprehension.

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Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

Location: SDCC Halls B-H

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Program #/Poster #: PSTR194.09/UU11

Topic: I.10. Human Learning and Cognition

Support: NIH/NEI EY024056
NSF SL-CN1640914

Title: Art and the deep brain: Probing cerebellar architecture and cerebro-cerebellar dynamics through creative cognition

Authors: *L. T. LIKOVA¹, C. W. TYLER², K. MINEFF¹;

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Abstract: Introduction: Once viewed primarily as a center for motor coordination, the cerebellum is now increasingly implicated in a wide range of cognitive functions. Yet, its precise roles—and its dynamic interactions with the cerebrum—remain elusive, particularly in relation to visual cognition. This study addresses this gap using *memory-guided drawing*, a multifaceted task that activates the full perception-cognition-action loop (Likova, 2013), offering a novel lens for dissecting cerebellar contributions to higher-order brain function. **Methods:** Participants underwent whole-brain fMRI (Prisma 3T) while performing four tasks designed to deconstruct memory-guided drawing into its key functional components: 1) **Drawing from visual memory** - Reconstructing complex images from recent visual memory; 2) **Visual-memory recall** - Mentally visualizing the images without drawing, isolating memory and imagery; 3) **Drawing from haptic memory** - Blindfolded drawing of tactilely explored shapes, isolating haptic memory and motor coordination, while excluding visual mechanisms; 4) **Blind scribbling** - Drawing random lines while blindfolded, isolating motor output without visual or memory input. Granger Causal Connectivity Analysis (GCA) was employed to characterize functional interactions both within the cerebellum and between cerebellar and cerebral networks. **Results:** The memory-guided drawing task evoked the broadest and most robust activation across both cerebellar and cerebral regions, with significant engagement of all cerebellar lobules, which include a broad range of non-motor territories. Each of the component tasks revealed distinct network patterns, providing a functional map of the cognitive architecture of the cerebellum. GCA uncovered causal intracerebellar interactions, as well as bidirectional causal cerebro-cerebellar connectivity, in the form of both facilitatory and inhibitory dynamics. Especially salient were interactions with the Default Mode Network and other large-scale cortical networks. **Conclusions:** Together, these findings offer compelling evidence for and provide a deeper understanding of the cerebellum's integrative role in the orchestration of complex cognitive processes, extending its influence well beyond traditional motor coordination domains into the realms of perception, memory, and cognition involved in the memory-guided drawing of complex images.

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Poster

PSTR194: Causal Structure as a Cognitive Scaffold: The Role of Causality in Learning and Memory

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Program #/Poster #: PSTR194.10/UU12

Topic: I.10. Human Learning and Cognition

Support: NIH Grant MH133732

Title: Agency personalizes episodic memories

Authors: *X. LI¹, N. K. NI¹, S. J. BORN², R. J. GUALANO³, I. LEE¹, B. BELLANA⁴, J. CHEN¹;

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Abstract: In daily life, we make choices that shape the flow of events and influence what we remember—yet most narrative memory studies do not allow such agency. We examined how agency affects memory using two interactive “choose-your-own-adventure” stories (Adventure, N=116; Romance, N=208). Participants were divided into three conditions: ‘Free’ (made influential choices), ‘Yoked’ (made choices but some were denied), or ‘Passive’ (made no choices), while reading the same stories. Agency increased inter-individual variability in recall: Free participants were less similar in what they remembered than Passive participants, suggesting that agency personalized memory composition. Agency also weakened the influence of semantic centrality—the degree to which an event is semantically related to others—on recall (Adventure: $F(2,113)=3.04$, $p=.052$; Romance: $F(2,123)=11.46$, $p<.001$), possibly due to a shift from normative to idiosyncratic semantic space. In contrast, causal centrality—how causally interconnected an event is—remained a robust predictor of recall across all conditions. To examine whether memory draws on causal structure in an individualized way, we introduce personalized causal centrality, where each event’s causal centrality score is recalculated after restricting the analysis to only the events an individual recalled. This measure predicted recall better than standard causal centrality (all $ps<.05$), with stronger effects under agency. In contrast, personalized semantic centrality effects was not consistently different from the standard semantic centrality effects, and were reduced by agency (network type $\times$ agency interaction: Romance: $F(2,123)=11.0$, $p<.001$; Adventure: $F(2,113)=2.39$, $p=.096$), suggesting that agency promotes individualized use of causal—but not semantic—structure. To support future studies of narrative causality, we developed a GPT-4 agent to automatically identify causal links between events. GPT-based causal centrality closely matched human ratings (all $ps<.05$) and predicted human memory on par with human-based values ($p>.1$). Together, our results reveal that agency drives idiosyncratic memory formation, yet causally structured relationships—especially when tailored to each individual’s recall—serve as a reliable predictor that organizes memories; moreover, our GPT-4 agent provides a scalable tool to map narrative causal structure for future research.

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Poster

PSTR195: Biochemical and Molecular Techniques I

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Program #/Poster #: PSTR195.01/UU13

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 1R35GM156968
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Title: Bioluminescent Kinase Sensors for the detection of growth factor signaling

Authors: ***M. P. CHATTERTON**¹, E. D. PETERSEN², J. BAKKE³, J. ROSSIGNOL⁴, O. DUBEY⁵, K. TAYLOR⁶;

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Abstract: Growth factor signaling is a crucial component of numerous cellular processes, including metabolism, differentiation, proliferation, neural plasticity, and migration. When growth factor signaling is altered, it can lead to pathologies like cancer cells forming and proliferating within the body, such as glioblastoma (GB). In this study, we focus on investigating and proposing novel tools to monitor growth factor signaling and use for therapeutic approaches utilizing genetically encoded Bioluminescent Kinase Sensors (BlinKS) to respond to growth factor signaling via kinases in the epidermal growth factor receptor (EGFR) signaling pathway. Specifically, this study is targeting the kinases within the MEK, RAS, and RAF signaling pathways. We developed a rational library of BlinKS variants with altered phospho-amino acid binding domains (PAABDs) as well as varying kinase substrate peptides and permutations of the linker regions, either flexible or rigid at the protein fusion sites. We tested our BlinKS constructs in U87 glioblastoma cells expressing our candidate sensor variants, treated the cells with epidermal growth factor (EGF), and measured the response of the BlinKS sensors through light emitted by the sensor. Bioluminescence readings were conducted on a plate reader, and it was found that the cells treated with EGF produced more luminescence than those not treated with EGF. We also paired our BlinKS constructs with a light-sensitive transcription factor to create a growth factor dependent genetic circuit, in this case driving expression of a fluorescent reporter. We found that those treated with EGF produced higher relative fluorescent units than those not treated with EGF. We aim to test these sensors in a variety of neuroscience applications. This includes reporting glioblastoma tumor growth factor signaling and using the sensors to control transcription of therapeutic protein that will inhibit growth to rein in unregulated tumor growth.

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Poster

PSTR195: Biochemical and Molecular Techniques I

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

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Topic: J.01. Molecular, Biochemical, and Genetic Techniques

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Title: Labeling opioid-sensitive neurons in the nucleus accumbens using mu opioid receptor iTango2

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MD

Abstract: Recent studies have shown the existence of the μ -opioid receptor genes (OPRM1) and four different subtypes of D1 and D2 medium spiny neurons (MSNs) within the islands of the ventral striatum and the nucleus accumbens (NAc) shell of Rhesus primates. The activations of such MSNs influence emotional decision making as well as value-based learning. However, the presence of such an island within the NAc shell of mice and rats have yet to be confirmed, and drug-seeking behavior (such as positive reinforcement and withdrawal) in these species in relation to the presence of such islands is less thoroughly explored. To establish a positive control, we first injected dopamine iTango2 (DRD2-iTango2) bilaterally into the NAc shell, core, and dorsal striatum of 1-4 month old DAT-cre mice, with a channelrhodopsin (ChR2) expressing virus simultaneously injected into the ventral tegmental area (VTA). After approximately 2 weeks, the mice were subjected to a 4 day lever press training and labeling schedule. Successful mice showed positive reinforcement behavior, and the number of lever presses were increased along the trial days. Imaging of ex-vivo brain slices revealed that labeling was more pronounced in the NAc. To identify the opioid-sensitive neural population in the NAc, we injected a newly developed μ -opioid receptor-based iTango2, named OPRM1-iTango2, bilaterally into the NAc shell and core of DAT-cre mice. In another set of mice, we injected ST-Cal-light into the NAc shell and core of DAT-cre mice, along with the ChR2 virus in the VTA. Using the same protocol with DRD2-iTango2, we were able to confirm both successful lever pressing behavior and the presence of an OPRM1-iTango2 labeled neurons near the mouse NAc core and shell with a fluorescent reporter GFP. We also observed a behavioral difference during the behavior protocol in male mice versus female mice, where females took a longer time (on average >1 day) in learning positive reinforcement. Withdrawal experiments using the ST-Cal-light in combination with a halorhodopsin expressing reporter and 561 nm light are also being undertaken, and we expect these to successfully reverse the reinforced lever pressing behavior. These experiments elucidate the presence of opioid-sensitive neuronal ensembles near the NAc core of mice, and their causal roles in opioid addiction.

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Poster

PSTR195: Biochemical and Molecular Techniques I

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Program #/Poster #: PSTR195.03/UU15

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Antibody Characterization through Open Science Enables Amyotrophic Lateral Sclerosis Research

Authors: *R. AYOUBI;

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Abstract: Understanding Amyotrophic lateral sclerosis (ALS) etiology requires a comprehensive molecular and biological investigation of the estimated 51 genes/proteins linked to ALS risk. However, most ALS research focuses on four genes, C9orf72, SOD1, TARDBP, and FUS, which receive 80% of all ALS-related PubMed hits. This highlights the need for a broader exploration of ALS risk factors. A major challenge is the limited availability of selective and renewable antibodies for studying these proteins. Antibody Characterization through Open Science (YCharOS) is an international, public-good initiative that unites academics, funding agencies, leading antibody manufacturers and knockout cell line providers to evaluate antibody performance (*Ayoubi et al., Nature Protocols, 2024*). Using knockouts as isogenic controls, antibodies from multiple manufacturers are tested side-by-side in western blot, immunoprecipitation and immunofluorescence. Data is openly disseminated on ZENODO, and selected studies are published on F1000. The ALS Reproducible Antibody Platform (ALS-RAP) focuses on identifying high-quality tools for ALS targets, enabling the success of future drug discovery. Together with antibody manufacturers and ALS charities, YCharOS characterized 441 antibodies targeting 35 community-prioritized ALS targets. Well-performing antibodies were identified for 95% of proteins in western blot, 80% in immunoprecipitation and 60% in immunofluorescence. Our findings revealed that selective and renewable antibodies, many of which are newly generated and rarely used in published studies, were available for 70% of these ALS targets. ALS associated proteins are assumed to be primarily expressed in motor neurons; however, C9orf72 has been shown to be highly expressed in microglia (*Laflamme et al., elife, 2019*). To systematically assess the expression of ALS-linked proteins across neurological cell types, we generated iPSC-derived neurological cell lines and performed western blotting using knockout-validated antibodies. Contrary to prevailing assumptions, we found that most ALS-associated proteins are ubiquitously expressed across neuronal and glial populations. Importantly, we identified a subset of seven proteins with predominant expression in microglia. Notably, inflammatory and anti-inflammatory stimuli modulated the expression levels of four of these microglia-enriched proteins. These findings provide new insight into the cellular context of ALS protein function, highlight underappreciated therapeutic pathways, and inform the selection of more biologically relevant cell models for future mechanistic and translational studies.

Disclosures: R. Ayoubi: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

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Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH R01MH122971
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NIH 1U01NS120820
HHMI
Lisa Yang
Ashar Aziz

Title: Spatial multiplexing of fluorescent reporters for in vivo imaging in the visual cortex

Authors: *N. SHMOEL DAVID¹, K. R. JENKS², E. RUESCH², K. R. TSIMRING², C. ZHENG³, C. LINGHU⁴, R. DESIMONE¹, M. SUR², E. S. BOYDEN^{1,5};
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Abstract: Molecular signaling is crucial for normal cellular function, enabling cells to convert inputs into outputs through intricate signaling networks that govern neural computation and behavior. Dysregulation of these pathways is implicated in neurological disorders, making it essential to understand how these networks operate in living brain circuits. For many years, bioengineers have utilized fluorescent indicators to study signaling relationships within living cells. However, multiplexing different reporters remains fundamentally limited by the number of colors that can be distinguished on conventional microscopes. This prevents researchers from simultaneously monitoring multiple pathways within individual cells, making it difficult to decode how different signals interact in brain circuits. Recently, we developed a novel approach called spatially multiplexed imaging (SMI) that allows more signals to be monitored than what is currently feasible with traditional multicolor imaging. By localizing distinct fluorescent reporters at stable but random locations throughout a cell, one can simultaneously monitor multiple signals (even those of the same color) within single living neurons. To implement SMI, we developed signaling reporter islands (SiRIs) using self-assembling peptide strategies that cluster reporters at stable but spatially distinct points throughout cells. Each SiRI serves as an independent detection node, enabling parallel readout of multiple signals using standard imaging approaches. We initially demonstrated this approach *in vitro* with four neuronal signaling pathways. Here, we have successfully adapted SiRIs for *in vivo* use in awake mice. We established comprehensive methods combining virus delivery, two-photon imaging, and post-imaging analysis to identify which signals come from which SiRI clusters. Critical to this approach is our ability to register SiRI locations across different imaging methods, allowing reliable mapping of live brain activity to specific molecular reporters. We applied this framework to monitor three key signaling molecules: Ca²⁺, PKA, and cAMP using SiRI-based indicators in visual cortex neurons. Through chronic imaging, we found that SiRIs remain stable and respond reproducibly to visual stimuli

across multiple sessions. By combining live brain recordings with detailed post-imaging analysis, we successfully mapped each signal to its specific molecular identity within individual neurons. This represents the first demonstration of fully spatially multiplexed imaging of three converging signaling pathways in the living brain at subcellular resolution.

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Poster

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Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.05/UU17

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Revolutionizing multiplex immunofluorescence with FlexAble: a novel technique for labeling primary antibodies

Authors: *D. CALLAHAN¹, L. WU¹, L. YURLOVA², P. BECKER², X. WANG³, C. LINKE-WINNEBECK², A. BUCHFELLNER², L. LIAN³, D. SHANKAR¹, J. LI¹;

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Abstract: Multiplex immunostaining, the simultaneous detection of multiple antigens within a single sample, has become a standard technique in neuroscience research. However, its scalability is limited by the host species of available primary antibodies. When using secondary antibodies for detection, this typically restricts multiplexing to 2-4 targets. One solution involves directly conjugating primary antibodies to fluorescent dyes, thereby bypassing the need for species-specific secondary antibodies. Unfortunately, commercially available fluorophore-conjugated primaries are limited, and in-house labeling via chemical methods requires large quantities of antibody in compatible buffers and carries the risk of damaging the antibody's paratope. To overcome this, we developed FlexAble, a rapid antibody labeling method that simplifies conjugation of primary antibodies to fluorophores, enabling efficient same-species multiplex immunofluorescence. This labeling approach encompasses a simple mixing and incubation process, requiring only 10 minutes, with no specialized equipment, buffer exchange, or chemical expertise needed. For developing FlexAble, we designed peptide-based multivalent "FlexLinkers" that bind to primary IgGs from rabbit, mouse, rat or human species with an apparent dissociation rate k_{off} (1/s) below 0.00001 and covalently conjugated them to different fluorophores. We observed strict specificity of the binding between the "FlexLinkers" and their target IgGs with BLI and confirmed the proposed molecular arrangement with X-ray crystallography. We validated FlexAble in IF, flow cytometry, and WB with >100 primary

antibodies. Among those, we confirmed FlexAble performance in immunostainings of mouse and rat brain FFPE sections for FUS/TLS, GAD67, GFAP, IBA1, MAP2, MBP, TDP-43, TUBB3, VGLUT-2, and Calbindin. Also, we show examples of FlexAble applied to live-cell time-lapse imaging, cyclic immunostaining, oligonucleotide-hybridization-based imaging, and Tyramide Signal Amplification (TSA). Using this technology, we are next expanding FlexAble to include reporter proteins, DNA oligonucleotides, and rare-earth metals to further expedite rapid labeling of primary antibodies and simplify experimental workflows.

Disclosures: **D. Callahan:** A. Employment/Salary (full or part-time): Proteintech. **L. Wu:** A. Employment/Salary (full or part-time): Proteintech. **L. Yurlova:** A. Employment/Salary (full or part-time): Proteintech. **P. Becker:** A. Employment/Salary (full or part-time): Proteintech. **X. Wang:** A. Employment/Salary (full or part-time): Proteintech. **C. Linke-Winnebeck:** A. Employment/Salary (full or part-time): Proteintech. **A. Buchfellner:** A. Employment/Salary (full or part-time): Proteintech. **L. Lian:** A. Employment/Salary (full or part-time): Proteintech. **D. Shankar:** A. Employment/Salary (full or part-time): Proteintech. **J. Li:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Proteintech.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.06/UU18

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: National Institutes of Health (NIH) Director's New Innovator Award (1DP2MH140133)
Chan Zuckerberg Initiative Collaborative Pairs Pilot Project Award
Glenn Foundation for Medical Research and American Federation for Aging Research Grant Award for Junior Faculty
Whitehall Foundation

Title: Multiplexed, scalable analog recording of gene regulation dynamics over weeks using intracellular protein tapes

Authors: ***L. ZHENG**¹, **D. SHI**¹, **Y. YAN**¹, **Y. HOU**¹, **B. AN**², **D. J. CAI**⁴, **E. S. BOYDEN**³, **D. WEI**⁵, **C. LINGHU**¹;

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Abstract: Gene expression is constantly regulated by gene regulatory networks that consist of multiple regulatory components to mediate cellular functions. An ideal tool for analyzing gene regulation processes would provide simultaneous measurements of the dynamics of many

components in the gene regulatory network, but existing methodologies fall short of simultaneously tracking the dynamics of components over long periods of time. Here, we present CytoTape—a genetically encoded, modular, and scalable analog recorder for continuous, multiplexed in situ recording of gene regulation dynamics over multiple days and weeks at single-cell resolution. CytoTape consists of a flexible, thread-like, elongating intracellular protein self-assembly engineered via AI-guided rational design. Gene regulation dynamics, together with timestamps for reconstruction of the continuous time axis, are directly encoded via distinct molecular tags distributed along single CytoTape assemblies in live cells, to be readout at scale after fixation via standard immunofluorescence imaging. CytoTape recorders are modularly designed to record gene expression driven by a variety of activity-dependent promoters. We demonstrated the utility of CytoTape in mammalian embryonic kidney cells, cancer cells, glial cells, and neurons, achieving simultaneous recording of five cell plasticity-associated transcription factor activities and immediate early gene expression levels, namely CREB, c-fos, Arc, Egr1, and Npas4 activities, within single cells in a spatiotemporally scalable manner. CytoTape revealed complex waveforms and nonlinear temporal couplings among these cellular activities, enabling investigations of how gene regulation histories and intrinsic signaling states shape transcriptional logics. We envision CytoTape to have broad applications in both basic and disease-related cell biology research.

Disclosures: L. Zheng: None. Y. Yan: None. D.J. Cai: None. E.S. Boyden: None. C. Linghu: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.07/UU19

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Comprehensive spatial metabolomics of developmental mouse brain

Authors: *L. XU¹, Y. HE²;

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Abstract: Mass spectrometry imaging (MSI) such as MALDI MSI and TOF-SIMS have become indispensable tools in biomedical research due to their unparalleled ability to spatially resolve individual molecules in complex biological systems in situ. Despite their transformative potential, the brain's metabolome—a dynamic network of small molecules governing neurodevelopment, aging, and disease—remains poorly characterized. Current MSI workflows often lack integration with complementary metabolomic profiling, creating a critical gap between spatially resolved molecular maps and their functional, systems-level interpretation. My research integrate MALDI MSI with metabolome to construct a comprehensive spatiotemporal developmental atlas of the mouse brain. Our work aims to bridge molecular scale imaging with

systems biology, paving the way for breakthroughs in treating developmental disorders and neurodegenerative diseases, including Alzheimer diseases, multiple sclerosis, brain tumor and spinal cord injury. My research addresses this gap by constructing the whole-brain, developmental metabolomic atlas of the mouse, integrating MALDI-MSI with LC-MS metabolomics to resolve spatial and temporal metabolite distributions across key neurodevelopmental milestones, provide foundation for future 3D mouse brain atlas.

Disclosures: L. Xu: None. Y. He: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR195.08/UU20

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

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the Sigrid Jusélius Foundation
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the Finnish Cultural Foundation
the Finnish Medical Foundation

Title: Dynamic investigation of the cerebrospinal fluid flow in the glymphatic system of rats with PET/CT using new albumin-based radiotracers

Authors: *M. PELTONIEMI^{1,2,3,4}, S. IMLIMTHAN⁴, S. JALONEN^{2,3}, N. PERSSON^{2,3}, T. J. LOHELA^{5,3}, T. O. LILIUS^{2,3,6}, M. SARPARANTA⁴;

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Abstract: The glymphatic system is a recently discovered cerebrospinal fluid (CSF) flow mediated waste clearance pathway in the brain. Research on the glymphatic system presents challenges due to the lack of tools to visualize the the glymphatic fluid flow in vivo in the whole body without disturbing its function. To explore the therapeutic potential of interventions such as enhancing the glymphatic flow in neurological diseases, novel imaging tools are needed. The use of dynamic positron emission tomography (PET) enables direct quantification of the whole-body tracer distribution, and due to its high sensitivity and clinical use, offers a compelling approach for future glymphatic research. In this study, we postulated that endogenous albumin-binding radiotracers would form macromolecular biological tracer in vivo and allow visualization of CSF flow with PET with high translational relevance. The albumin-binding tracers were synthesized

using two albumin-binding moieties 4-(p-iodophenyl)butyric acid and truncated Evans Blue that were conjugated with NODAGA-chelator and radiolabeled with gallium-68, achieving high radiochemical yields (>80%), purities (>95%), and acceptable molar activities ($A_m=1.7$ GBq/ μ mol). Additionally, we prepared an in vitro radiolabeled rat serum albumin (RSA) based tracer Al[^{18} F]F-RESCA-RSA ($A_m=3.4$ GBq/ μ mol) to serve as a macromolecule reference after intrathecal administration. Biological evaluation revealed high radiolabel stability and albumin-binding affinity in vitro and in vivo with the biological half-life in female Swiss mice after intravenous administration corresponding to serum albumin (>18 hours). Dynamic PET imaging (Molecubes, Ghent, Belgium) in female Sprague Dawley rats (n=6/group) under ketamine/dexmedetomidine anesthesia after lumbar and intracisternal infusion showed tracer distribution towards intracranial space and along the spinal canal from the infusion site. However, despite the high affinity to albumin, the albumin-binders did not behave identically to the reference. For instance, the cervical lymph nodes were only visualized after the latter one, characteristic for macromolecular tracers. These findings indicate that the relatively low molar activity of the gallium-68-NODAGA complex led to administered tracer concentrations (0.7-0.9 nmol) that exceeded the physiological albumin concentration in the CSF (0.012-0.024 nmol) and resulted in residual unbound tracer that distributes according to its own physiochemical properties. Nevertheless, the tracers show high promise for tracking CSF flow with PET, constituting the first tailored radiotracers for this application.

Disclosures: **M. Peltoniemi:** None. **S. Imlimthan:** None. **S. Jalonen:** None. **N. Persson:** None. **T.J. Lohela:** 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 GLYMPHATICDELIVERY BY MANIPULATING PLASMA OSMOLARITY Patent Application (Application #20220280423).. **M. Sarparanta:** None.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.09/UU21

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Competitive SimpleStep® ELISA: A 90-minute, one-wash assay for the quantification of small molecules, PTMs, and peptides

Authors: ***E. M. SWANSON**, A. H. HEUBERGER, J. N. HEATH, M. MOHAMMADI, D. L. DAVIS, A. C. GOERING, J. S. MONETTE;
Abcam, Eugene, OR

Abstract: The SimpleStep® ELISA platform utilizes Abcam's CaptSure™ technology to streamline the sandwich ELISA workflow into a 90-minute, one-wash assay. This format requires two antibodies binding different epitopes on the target of interest however, and small molecules such as neurotransmitters, hormones, and post-translational modifications (PTMs) are

too small to bind multiple antibodies. To quantify targets such as these, competitive ELISA can be used instead. Competitive ELISA utilizes a fixed concentration of the small molecule of interest, often conjugated to a carrier protein, to compete with the sample analyte for binding to a target-specific antibody. While effective for the quantification of these targets, assays in this format can present several issues. Antibody cross-reactivity among molecules of the same class is common due to similarities in their molecular structure. Batch-to-batch variability can also be a concern for these antibodies. Reproducibility with regards to the small molecule conjugation is also important to address, as variation between lots of these conjugates can greatly affect assay performance. Finally, protocols for these assays often require a great deal of hands-on time, incubations as long as 16 hours, and multiple wash steps. With this in mind, we set about expanding the SimpleStep catalog to include a 90-minute, one-wash competitive ELISA for small molecules, PTMs, and short peptides: Competitive SimpleStep ELISA (cSSE). Here we describe our adaptation of the SimpleStep workflow, development process and protocols to a competitive ELISA format, in addition to developing highly reproducible small molecule conjugation protocols. As with our sandwich ELISA offerings, cSSEs are validated in matrices of interest for each specific target, which can include serum, plasma, cell and tissue extracts, saliva, urine and CSF, along with the same robust sample validation. With this platform, we have produced a rapid, easy-to-use competitive ELISA platform, adhering to the rigorous performance standards our customers expect from Abcam.

Disclosures: **E.M. Swanson:** A. Employment/Salary (full or part-time): Abcam. **A.H. Heuberger:** A. Employment/Salary (full or part-time): Abcam. **J.N. Heath:** A. Employment/Salary (full or part-time): Abcam. **M. Mohammadi:** A. Employment/Salary (full or part-time): Abcam. **D.L. Davis:** A. Employment/Salary (full or part-time): Abcam. **A.C. Goering:** A. Employment/Salary (full or part-time): Abcam. **J.S. Monette:** A. Employment/Salary (full or part-time): Abcam.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.11/VV1

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Unraveling spatial signatures in glioblastoma using a two stage hyperplex to high throughput spatial platform approach

Authors: ***A. E. HAGGERTY**¹, **P. SAVICKAS**², **T. GUIDO**³, **K. PEREZ**², **Y. PEYMANFAR**¹, **Y. HOU**¹, **A. WHITLEY**¹, **M. MOORE**¹;

¹Akoya Biosci., Marlborough, MA; ²Histowiz, Brooklyn, NY; ³Histowiz, Staten Island, NY

Abstract: Glioblastoma (GBM) remains the most aggressive and lethal primary brain tumor, characterized by profound therapeutic resistance and dismal prognosis, necessitating novel therapeutic strategies. Its complex molecular heterogeneity and unique tumor microenvironment

significantly contribute to treatment failure, underscoring the urgent need for a deeper understanding of its underlying biology to identify vulnerable targets. Here, we employ a two-tiered approach to comprehensively interrogate the GBM microenvironment. Initially, we utilized the Phenocycler Fusion platform to simultaneously stain and image 42 neurologically relevant antibody markers on single slides. This hyperplex panel broadly characterized five key aspects: neuronal cell types, tumor aggressiveness and prognosis (via neuroplasticity and cellular remodeling markers), proteinopathies and neurodegeneration mechanisms, blood-brain barrier integrity and fluid dynamics, and the adaptive immune response within the tissue. Subsequent analysis with Qupath software identified the most critical markers for further investigation in a high throughput modality. Analysis of the hyperplex data lead to selection of a subset of highly significant markers, identified by their relative abundance and/or correlation with disease state. These markers were then applied to a larger set of GBM samples using PhenoCode Signature Panels, which utilize similar reagent chemistry and leverage a backbone of five preset markers combined with an open position for a custom sixth marker. Subsequently, IA and AI-based image analysis techniques quantify expression patterns to generate robust statistical datasets. This innovative two-step strategy, transitioning from high-plex spatial analysis to high-throughput statistical validation, allows for novel recognition of spatial relationships between biomarkers to enable targeted interrogation across multiple samples. This flexible approach is broadly applicable to various neurological diseases, facilitating the incorporation of disease-specific markers.

Disclosures: **A.E. Haggerty:** A. Employment/Salary (full or part-time): Akoya Biosciences. **P. Savickas:** A. Employment/Salary (full or part-time): Histowiz. **T. Guido:** A. Employment/Salary (full or part-time): Histowiz. **K. Perez:** A. Employment/Salary (full or part-time): Histowiz. **Y. Peymanfar:** A. Employment/Salary (full or part-time): Akoya Biosciences. **Y. Hou:** A. Employment/Salary (full or part-time): Akoya Biosciences. **A. Whitley:** A. Employment/Salary (full or part-time): Akoya Biosciences. **M. Moore:** A. Employment/Salary (full or part-time): Akoya Biosciences.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR195.12/VV2

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: SIP: 20250574

Title: Pramipexole is a DA receptor agonist that induce dopaminergic gene expresión and mature SH-SY5Y neurons

Authors: ***A. J. ESPADAS**¹, L. TEXCO²;

¹Inst. Politécnico Nacional (IPN), Mexico, Mexico; ²CCH, UNAM, Ciudad De Mexico, Mexico

Abstract: Parkinson's disease (PD) is a chronic progressive neurodegenerative disorder characterized by the profound loss of dopaminergic (DA) neurons of the nigrostriatal pathway. Current therapeutic options such as DA replacement strategies via supplementation with levodopa or DA agonists. Pramipexole (PXL) is a DA receptor agonist, has been approved for the treatment of PD. To date, the activity of PXL on dopaminergic gene expression has not been reported. We report the activity of PXL on gene expression of DAT, TH, Nurr1 and BDNF and its capacity to induce mature SH-SY5Y neurons.

Disclosures: A.J. Espadas: None. L. Texco: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.13/VV3

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Mounting media considerations for optimal fluorescence microscopy

Authors: *D. CASH, N. MOONEY;
Thermo Fisher Scientific, Eugene, OR

Abstract: Fluorescence microscopy is an essential tool for visualizing biological targets within cultured cells and tissue specimens. While significant attention is given to developing model systems and optimizing fluorescent probes and labeling protocols, the critical role of mounting media in imaging experiments is often overlooked. Mounting media, or mountants are the last reagent applied to a fluorescently labeled fixed biological sample prior to imaging. While these reagents adhere a sample between a coverslip and microscope slide, they additionally optimize fluorophore performance during imaging experiments, protect a mounted sample for archival, and tune the refractive index (RI) of a sample for improved image quality. Incompatibilities between mountants, fluorescent probes, and biological samples can compromise image quality and experimental results. This work guides mounting media selection for optimized fluorescence imaging. Fluorophore compatibility was demonstrated through fluorescence cell culture imaging. Fluorescently labeled sample preservation is discussed and demonstrated using archived rodent brain tissue in 2D and 3D. Using thick rat brain sections, we show how refractive index matching affects image quality. Strategies to minimize time between mounting and imaging are explored through comparative 3D imaging of rat brain samples.

Disclosures: D. Cash: A. Employment/Salary (full or part-time): Thermo Fisher Scientific. N. Mooney: A. Employment/Salary (full or part-time): Thermo Fisher Scientific.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.14/VV4

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Tissue processing influences brain perineuronal net analyses across species

Authors: *A. S. HENDRICKSON¹, J. LE¹, O. CERVANTES², C. BRYAN², A. KUMAR¹, C. MEURET¹, I. REDFORD², E. QUAH², C. W. FREVERT², C. S. LATIMER², K. S. KIDDER², M. A. BASSO², K. ADAMS WALDORF², J. RUECKEMANN², J. SCARLETT², D. A. TOVAR³, K. ALONGE¹;

¹Medicinal Chem., ²Univ. of Washington, Seattle, WA; ³Vanderbilt Univ., Nashville, TN

Abstract: Perineuronal nets (PNNs), which are specialized extracellular matrix structures that enmesh neurons involved in memory and cognition, are detected using aggrecan (chondroitin sulfate (CS) protein) and *Wisteria floribunda* agglutinin (WFA; CS glycan) labeling. Reports show striking differences in PNN detection between studies that we hypothesize may be influenced by tissue processing. For example, rodent studies often utilize 4%-paraformaldehyde (PFA) fixation and thick, free-floating (FF) sections, while human studies use 10%-formalin (FOR) followed by paraffin-embedding (PE) and direct, thin mount sections. To directly test whether tissue processing (FF vs PE) influences PNN analyses, we perfused n=7 adult, C57 mice with 0.1M PBS, cut the brain into sagittal hemispheres, and then post-fixed both sides in 4% PFA. After processing one hemisphere as 30-um PFA(FF) and the other as 4-um PFA(PE), we found an 89.9-90.3% reduction in aggrecan ($p<0.0001$) and 80.1-87.0% reduction in WFA ($p<0.0001$) labeling of PFA(EB) cortical (ctx) and hippocampal (hip) PNNs exhibited compared to PFA(FF) tissues generated from the same mouse. To determine whether PE also influences PNN CS composition, which is comprised of 0S-, 4S-, 6S-, 2S6S-, 4S6S-CS, and 2S4S-DS isomers, we analyzed extracted hip CS isomers by LC-MS/MS and observed a significant shift in all 6 major isomers between PE and FF samples. To exclude the possibility that fixative (PFA vs FOR) itself influences PNN analyses, we perfused n=6 adult, C57 mice with PBS, cut sagittal hemispheres, fixed one side in 4% PFA and the other side in 10% FOR, and then processed both as 30-um PFA(FF) or FOR(FF) sections. Here, we did not observe differences in PNN labeling or CS composition between samples, suggesting fixative does not influence PNN analyses. To translate our pre-clinical findings to higher-order species, we isolated hip and ctx CS isomers from n=7 adult FOR(FF) and n=12 adult FOR(PE) non-human primate (*M. nemestrina*) tissues. Here, we found that PE significantly influences five of the six CS isomers compared to FF tissues. Our previous work defined distinct CS composition between ctx and hip, including a ~1.5x increase in CS-O (0S) in the ctx. We hypothesize that despite baseline CS changes induced by PE, regional CS isomer differences would remain intact; indeed, ctx:hip %CS isomer ratios were not significantly altered by processing ($p=0.33$). Overall, these results provide evidence that tissue processing (FF vs PE), but not fixative (PFA vs FOR), influences PNN analyses across samples and species, but that regional differences in brain CS composition remain preserved.

Disclosures: A.S. Hendrickson: None. J. Le: None. O. Cervantes: None. C. Bryan: None. A. Kumar: None. C. Meuret: None. I. Redford: None. E. Quah: None. C.W. Frevert:

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Poster

PSTR195: Biochemical and Molecular Techniques I

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Program #/Poster #: PSTR195.15/VV5

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Chemically peptide-ligated protein standards enable antibody validation and quantification of phosphorylated Tau in Alzheimer's disease samples

Authors: ***P. HAJEK**¹, B. R. CAMEL², T. MCCRACKEN¹, J. MONETTE¹, C. ELLER¹;

¹Abcam Inc., Eugene, OR; ²Mol. Biosci., Univ. of Kansas, Lawrence, KS

Abstract: We previously developed a method to generate protein standards for Abcam's SimpleStep® sandwich ELISA kits, enabling quantification of specific post-translational modifications (PTMs). This approach uses proprietary chemical ligation to attach a synthetic peptide—mimicking the PTM site—to a recombinant protein. Here, we expand the application of these chemically ligated proteins to screen and validate rabbit monoclonal antibodies for sequence specificity facilitating their integration into SimpleStep® kits. We demonstrate this strategy in the development of ELISA kits targeting Alzheimer's disease biomarker Microtubule-associated protein tau, specifically phosphorylated at T181, S199, T217, T231, and S396 sites. These phospho-Tau standards also enable assessment of antibody cross-reactivity with other phosphorylation sites and the non-phosphorylated protein. Finally, we apply the developed kits to measure relative PTM levels in individual Alzheimer's disease patient samples, highlighting their utility in biomarker research and clinical studies.

Disclosures: **P. Hajek:** A. Employment/Salary (full or part-time): Abcam Inc.. **B.R. Camel:** None. **T. McCracken:** A. Employment/Salary (full or part-time): Abcam Inc. **J. Monette:** A. Employment/Salary (full or part-time): Abcam Inc. **C. Eller:** A. Employment/Salary (full or part-time): Abcam Inc..

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR195.16/VV6

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: Conahcyt PhD grant CVU 891162

Title: Fluorescent xenotransplants and tumor section imaging: redefining preclinical models in neuroscience

Authors: *S. E. OCHOA HUGO¹, Y. K. GUTIERREZ-MERCADO³, A. A. CANALES², R. HERNANDEZ GUTIERREZ¹;

¹CIATEJ, Guadalajara, Mexico; ²CIATEJ, Jalisco, Mexico; ³Dept. of Clin., Univ. de Guadalajara - Ctr. Universitario Los Altos, Guadalajara, Mexico

Abstract: The ethical and regulatory landscape of animal experimentation has evolved, with agencies like the FDA and EMA advocating for reduced in vivo testing. Historically, neuro-oncology relied on invasive models, but ethical concerns have driven the adoption of fluorescent imaging techniques. Among these innovations, fluorescent xenotransplants and ex vivo fluorescence imaging have reshaped preclinical research. Fluorescent xenotransplants enable continuous tumor visualization and therapeutic assessment in live subjects, eliminating repeated euthanasia while allowing longitudinal monitoring. This approach has been instrumental in tracking glioblastoma progression and neuroinflammatory responses, offering deeper insights into cellular interactions. Meanwhile, ex vivo fluorescence imaging allows precise tumor section evaluation under different treatments, optimizing consistency while preserving individual models. These techniques enhance reproducibility and refine therapeutic assessments, reducing reliance on endpoint histological analysis. The progression of imaging techniques reflects a shift toward humane, scientifically robust methodologies. Early fluorescence applications were limited to in vitro models, but advancements now enable high-resolution in vivo tracking, transforming tumor monitoring. Previously, neuro-oncology relied on invasive procedures and post-mortem analyses, whereas non-invasive imaging strengthens translational relevance while minimizing disruptions. Fluorescence imaging has become essential for studying tumor heterogeneity and therapeutic resistance. Beyond ethical considerations, these approaches refine neuroscience experimentation, replacing conventional models without compromising scientific rigor. They open avenues for personalized medicine, allowing dynamic therapeutic evaluation. Fluorescent xenotransplants offer an alternative to xenografts, facilitating tumor behavior studies. Similarly, ex vivo imaging enables localized treatment assessments while preserving experimental integrity, enhancing data quality and supporting sustainable research practices. As neuroscience integrates advanced imaging technologies, fluorescent xenotransplants and ex vivo imaging accelerate neuro-oncology discoveries while setting ethical research standards. Their ability to refine therapeutic strategies, improve reproducibility, and minimize invasiveness ensures methodological innovation aligns with regulatory policies and scientific integrity.

Disclosures: S.E. Ochoa Hugo: None. Y.K. Gutierrez-Mercado: None. A.A. Canales: None. R. Hernandez Gutierrez: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

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Program #/Poster #: PSTR195.17/VV7

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: National Institutes of Health (NIH) Grant (R35GM138003)
W.M. Keck Foundation (995337)
Agilent Early Career Professor Award

Title: Regulation of CNS glutamate homeostasis by mitochondrial metabolism

Authors: *M. MEKKITTIKUL¹, A. DIVAKARUNI²;

¹Mol. and Med. Pharmacol., UCLA, Los Angeles, CA; ²Pharmacol., Univ. of California Los Angeles, Los Angeles, CA

Abstract: The ketogenic diet has been described as an effective treatment for epilepsy for over a century, especially with its success in treating drug-resistant epilepsy. Excessive glutamatergic signaling is a key pathway underlying seizure activity, and previous work in our lab has shown mitochondrial metabolism can regulate this excitatory neurotransmission. Our results from experiments using respirometry and stable isotope tracing show that increasing glutamate oxidation (by decreasing mitochondrial oxidation of glucose-derived pyruvate) in neurons can attenuate glutamate levels allocated for signaling, thus providing protection against excessive glutamatergic signaling. The results also suggest that our current understanding of how glutamate levels in the brain are regulated (i.e. the canonical glutamine-glutamate cycle) may be incomplete.

Here we use plate based respirometry in conjunction with ¹³C stable isotope tracing to investigate the hypothesis that de novo synthesis of glutamate in neurons is an important contributor to overall glutamatergic homeostasis and neurotransmission in the CNS. Pharmacological inhibition of voltage-gated sodium channels increased both oxygen consumption and enrichment of isotopically labeled glucose into relevant metabolites, confirming the validity of assays used. Stable isotope tracing in primary cortical neuronal cultures and synaptosomes with uniformly labeled tracers (e.g. ¹³C-glucose, ¹³C-pyruvate, and ¹³C-glutamine) reveal substantial amounts of glucose-derived carbon is routed to intermediary metabolites involved de novo synthesis of glutamate. Results were confirmed with pathway-specific isotope tracers that specifically measure glucose anaplerosis (e.g. 1-¹³C₁-pyruvate). This work has the potential to reveal novel metabolic pathways that can regulate excitability, and could identify new pharmacologic targets to mimic the therapeutic benefits of the ketogenic diet.

Disclosures: M. Mekkittikul: None. A. Divakaruni: None.

Poster

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Program #/Poster #: PSTR195.18/VV8

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 1F31MH136717
NIH Grant 1R01MH129292
Braude Foundation

Title: Identifying miRNA : mitochondrial RNA interactions using chimeric RNA sequencing

Authors: *E. EISS¹, M. K. MEFFERT²;

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Abstract: MicroRNAs (miRNAs) are small noncoding RNA molecules that are loaded onto an Argonaute (Ago) protein to function as guides for the RNA-induced silencing complex (RISC) to bind and regulate the expression of target mRNAs, through repression of translation and target RNA degradation. Accurately identifying the mRNA targets of miRNAs is essential to understanding their physiological impacts, but biological factors can confound the ability of bioinformatic target prediction software to accurately predict these interactions. To circumvent the challenges of bioinformatic prediction, our lab optimized an Argonaute crosslinking and immunoprecipitation (Ago-CLIP) technique, which we call CIMERaseq (crosslinking and immunoprecipitation followed by intermolecular ligation of endogenous RNAs within Argonaute followed by high-throughput sequencing). In this technique, miRNAs and their target RNAs are immobilized in-vivo by UV-crosslinking, trapping them within the Argonaute protein, which is then immunoprecipitated using anti-Ago2 antibodies. Key subsequent steps of intramolecular ligation serve to ligate the 3' end of the miRNA to the 5' end of its target, forming a chimeric RNA molecule that can be sequenced to reveal endogenous interactions in a semi-quantitative fashion. We performed CIMERaseq on mouse forebrain homogenate and discovered an unexpected preponderance of miRNA : mitochondrial RNA interactions in the detected chimeric sequenced RNAs. It is currently unknown how miRNA and/or Ago enter mitochondria, although both RISC components are found in mitochondria in multiple tissues including neurons. RISC function within mitochondria is under investigation, with existing work having reported both translation activation or inhibition observed in different contexts. We focus our investigations on conserved miRNAs detected in our datasets as preferentially binding to mitochondrial transcripts relative to nuclear transcripts and pursue understanding of their impact on mitochondrial function and gene expression. Our ongoing research aims to address gaps in knowledge by furthering the fundamental understanding of miRNA:mt-RNA targeting, and downstream functional impacts in the central nervous system with implications for further understanding neurological development and disease.

Disclosures: E. Eiss: None. M.K. Meffert: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.19/VV9

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant UG3 MH126869

Title: Development of enhancer viruses for cell-type-specific interrogation in the marmoset brain

Authors: *C. CHEN¹, M. WIENISCH¹, K. CAPLAN², R. DEL ROSARIO⁴, F. M. KRIENEN⁷, Z. LIAN², I. R. WICKERSHAM³, K. CHAN⁵, B. E. DEVERMAN⁶, G. FENG¹;

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Abstract: Rodents have long served as important model organisms in neuroscience research. However, increasing studies have elucidated the numerous differences between rodent and primate brains, including neuron type, neuron composition, neuronal connections, and transcriptomic changes. However, conducting neuroscience research in non-human primates (NHPs) is challenging due to the lack of available tools to target and manipulate specific cell types in the NHP brain. Enhancer viruses have emerged as a promising solution to this problem and can deliver reporters or genetic tools in a cell-type-specific manner. Through analyzing multiomic single-cell datasets, I nominate cell-type-specific enhancers and screen them *in vivo* in the marmoset brain. The specificity of enhancer candidates is established using histology. We have found several functional enhancers that exhibit > 80% specificity, including a marmoset enhancer that selectively labels striatal cholinergic (ChAT) interneurons at over 90% specificity when delivered systemically both in mouse and marmoset. These characterized functional enhancers can then be employed for interrogating neuronal characteristics of a specific cell type. The outcome of this study will provide much-needed marmoset enhancer AAVs that can be leveraged to characterize specific cell types in NHP brains functionally.

Disclosures: C. Chen: None. M. Wienisch: None. K. Caplan: None. R. del Rosario: None. F.M. Krienen: None. Z. Lian: None. I.R. Wickersham: None. K. Chan: None. B.E. Deverman: None. G. Feng: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.20/VV10

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant UG3 MH126869

Title: Functional validation of an enhancer-based AAV for interrogating striatal D2 medium spiny neurons in mice

Authors: *Z. LIAN^{1,3,2}, C. S. CHEN^{2,1}, A. B. FATH^{2,1}, K. CAPLAN^{2,1}, M. WIENISCH^{2,1}, R. DEL ROSARIO⁴, F. M. KRIENEN⁵, G. FENG^{2,1,4};

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⁵Neurosci., Princeton Univ., Princeton, NJ

Abstract: Research in non-human primates (NHPs) presents the difficulty of targeting specific cell types without relying on transgenic lines, which are technically challenging to generate in primates. To enable the labeling and manipulation of specific neuron types in intended brain regions, this project aims to develop and functionally validate an enhancer-based adeno-associated viral (AAV) tool that selectively targets the D2-type medium spiny neurons (MSNs) in the striatum of wild-type mice, as foundational work toward manipulating D2-MSNs in NHPs. Enhancer AAVs are viral vectors that enable precise gene expression in specific cell types. Prior research supports the feasibility of this approach by establishing enhancer AAVs as a successful tool able to achieve cell-type specificity in viral manipulations of interneuron subtypes across rodents, NHPs, and humans. This project focuses on a D2 enhancer previously shown to exhibit conserved specificity (over 90% systemically administered) between mouse and marmoset, making it a promising candidate for cross-species application. Functional validation in mice can therefore serve as a preliminary indicator of the enhancer's effects in NHPs.

Due to the packaging limit of AAVs, D2 enhancer optimization is conducted. This involves the construction of enhancers with shortened, flipped, and tandem repeats of the enhancer peak sequences. Results from functionally assessing this enhancer will provide preliminary data supporting further functional studies in NHPs, including applications in cognitive and behavioral tasks.

Disclosures: Z. Lian: None. C.S. Chen: None. A.B. Fath: None. K. Caplan: None. M. Wienisch: None. R. del Rosario: None. F.M. Krienen: None. G. Feng: None.

Poster

PSTR195: Biochemical and Molecular Techniques I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR195.21/VV11

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Effect of XT1 peptide on iliococcygeal muscle regeneration in primiparous rats

Authors: *S. Y. RODRIGUEZ JAIMES¹, G. HERNÁNDEZ HERNÁNDEZ¹, M. XOCHITEMOL NAVA¹, M. CARRASCO RUIZ², F. CASTELÁN³;

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Abstract: The pelvic floor muscles play a crucial role in physiological and reproductive functions. However, their anatomical configuration makes them susceptible to some type of

damage due to events such as pregnancy, childbirth, and multiparity, which can lead to pelvic floor dysfunctions. Current treatments offer limited results, especially in cases of mild to moderate symptoms, which shows the need to explore new therapeutic strategies that favor muscle regeneration. Skeletal muscle expresses neurotrophin receptors that activate intracellular signaling pathways with regenerative potential. In this context, we evaluated the effect of XT1, an agonist peptide with affinity for all Trk receptors, on the iliococcygeus muscle (Icm) of primiparous rats, to analyze its impact on biochemical indicators of damage and regeneration, as well as isometric muscle strength in the postpartum period. Two groups of nulliparous rats and four groups of primiparous rats were used; two groups were treated with vehicle or XT1. Primiparity increased the body weight of primiparous rats ($p=0.0039$; $p=0.0006$) and reduced serum glucose levels ($p=0.0159$; $p=0.0012$). In the iliococcygeus muscle, the following were observed: a) normalized muscle weight increased in the PSS and PXT1 groups ($p=0.0091$; $p=0.0014$); b) muscle length increased in the PSS group ($p=0.0354$); c) increased activity of the enzyme β -glucuronidase in the PSS group ($p=0.0204$); d) Pax7 expression decreased in the PSS group ($p=0.126$); e) decreased the contraction force at 10, 20, and 50 Hz in the PSS group ($t(6.214)=0.042$); ($t(7.836)=0.0007$); ($t(7.847)=0.035$), and decreased the contraction force at 20 Hz in the PXT1 group. These findings suggest that administering the peptide XT1 on the first day postpartum could favor muscle regeneration of mIc in primiparous rats during the postpartum period, making it a possible therapeutic alternative for managing debilitating musculoskeletal dysfunctions.

Disclosures: S.Y. Rodriguez Jaimes: None. G. Hernández Hernández: None. M. Xochitemol Nava: None. M. Carrasco Ruiz: None. F. Castelán: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.01/VV12

Topic: J.04. Physiological Methods

Title: A machine learning approach for efficient analysis of vast amounts of data from HD-MEA

Authors: *Y. KATO¹, R. OKA¹, S. KAIZU¹, S. ISHIYAMA¹, J. HORIE¹, I. SUZUKI², N. NISHI¹;

¹Sony Semiconductor Solutions, Atsugi, Kanagawa, Japan; ²Dept. of Electronics, Tohoku Inst. of Technol., miyagi, Japan

Abstract: High-density microelectrode arrays (HD-MEA) enable non-invasive in vitro electrophysiological recordings from various samples, including iPS cell-derived neurons, brain slices, and brain organoids, and have been widely used in recent years. In particular, the HD-MEA developed by Sony Semiconductor Solutions has successfully recorded extracellular potentials of neurons with high spatiotemporal resolution at both the population network level and single-cell level.

However, due to its performance, the HD-MEA presents challenges in handling large volumes of data and constructing data analysis methods tailored to specific applications.

This study proposes a novel signal processing framework to efficiently analyze the vast amounts of data obtained from the HD-MEA. By utilizing a machine learning approach, we leveraged the high resolution of the HD-MEA to consider spatial features around the electrodes, accurately distinguishing between noise and significant signals derived from cellular activity, thus extracting the meaningful data necessary for analysis.

When applied to multiple types of iPS cell data obtained from HD-MEA, our approach demonstrated robustness against noise and superior signal detection capability compared to conventional rule-based methods using cosine similarity. The data reduction rate achieved an average of over 99%, demonstrating significant data reduction while retaining meaningful signals. This approach is adaptable to various cell types and is expected to contribute not only to the efficient reduction of measurement data volume but also to the improvement of accuracy in various neural activity analyses, such as spike sorting, single-cell detection, and axonal pathway detection.

These results provide a new solution to the critical challenge of efficiently processing large-scale neural activity recording data from HD-MEA.

Disclosures: **Y. Kato:** A. Employment/Salary (full or part-time): Sony Semiconductor Solutions. **R. Oka:** A. Employment/Salary (full or part-time): Sony Semiconductor Solutions. **S. Kaizu:** A. Employment/Salary (full or part-time): Sony Semiconductor Solutions. **S. Ishiyama:** A. Employment/Salary (full or part-time): Sony Semiconductor Solutions. **J. Horie:** A. Employment/Salary (full or part-time): Sony Semiconductor Solutions. **I. Suzuki:** A. Employment/Salary (full or part-time): Tohoku Institute of Technology. **N. Nishi:** A. Employment/Salary (full or part-time): Sony Semiconductor Solutions.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.02/VV13

Topic: J.04. Physiological Methods

Title: Electrophysiological and morphological profiling of human neuronal maturation using the CytoTronics' Pixel

Authors: *C. M. BANFILL, S. CHINTA, P. SURESH, S. SUTAR, S. CHITALE;
CytoTronics, Inc, Boston, MA

Abstract: High-throughput, non-destructive methods for monitoring longitudinal neuronal function and morphology are critical for advancing neurobiology, disease modeling, and drug screening. Traditional techniques such as patch clamp and calcium imaging offer limited throughput or spatial resolution and often require multiple assay types to assess both structure and function. CytoTronics' Pixel addresses these limitations by integrating high-resolution

extracellular electrophysiology with impedance-based electrical imaging, enabling multiplexed, longitudinal profiling of live neuronal cultures. Human iPSC-derived glutamatergic neurons (iCell Glutaneurons, FujiFilm) were cultured on 96-well Pixel microplates coated with poly-D-lysine and laminin. Cultures were maintained up to 30 days under standard conditions with electrical imaging performed every 2 hours and 1-minute electrophysiological recordings collected daily. The Pixel features >100,000 electrodes for electrical imaging per well and 144 flexibly-located recording channels per well, allowing for tunable spatial resolution from 12.5 to 400 μm . Neural activity metrics (e.g., spike rate, burst duration) and impedance-based morphology features were analyzed using integrated cloud-based software. Electrical imaging provided label-free, longitudinal visualization of neuronal attachment and health across the full culture duration. No detachment or cytotoxicity was observed. Electrophysiological recordings revealed progressive increases in spiking and bursting activity indicating robust network maturation. Plate-, well- and recording channel-level analyses demonstrated increased firing complexity and network activity over time. Quantitative metrics, such as burst rate and inter-burst interval captured dynamic changes in network activity, enabling high-content phenotyping of neuronal development. The Pixel enables real-time, label-free monitoring of both electrophysiological and morphological phenotypes in live neuronal cultures at high resolution and throughput. This integrated platform supports scalable applications in cell line validation, functional phenotyping, and drug discovery, delivering richer insights into neural biology and disease mechanisms.

Disclosures: **C.M. Banfill:** A. Employment/Salary (full or part-time): CytoTronics. **S. Chinta:** A. Employment/Salary (full or part-time): CytoTronics. **P. Suresh:** A. Employment/Salary (full or part-time): CytoTronics. **S. Sutar:** A. Employment/Salary (full or part-time): CytoTronics. **S. Chitale:** A. Employment/Salary (full or part-time): CytoTronics.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.03/VV14

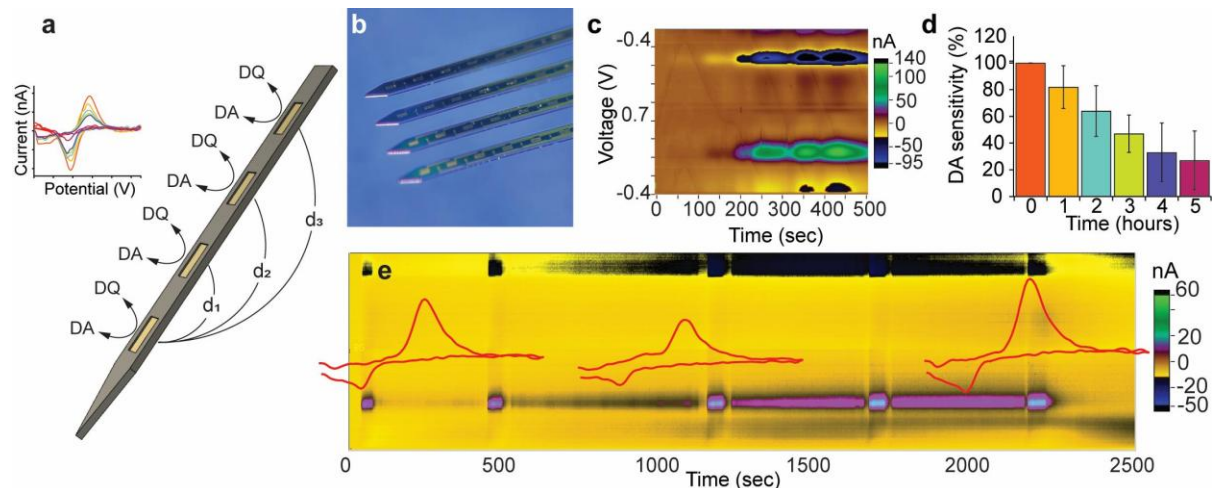
Topic: J.04. Physiological Methods

Support: AFOSR Grant FA9550-21-1-0117
NSF Grant 2143140
NSF Grant 2411567

Title: Toward High-Density Neurochemical Sensing: Gold Microelectrode Arrays with Optimized FSCV Cleaning Protocols

Authors: ***M. DARROUDI**, K. A. WHITE, V. S. BAPANAPALLI, C. S. LIPSCOMB, L. S. BARAKAT, B. S. JOHN, M. A. CROCKER, B. N. KIM;
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Abstract: Precise, real-time monitoring of neurotransmitters such as dopamine (DA) is central to advancing our understanding of motivation, reward, and neuropsychiatric conditions including Parkinson's disease and addiction. Fast-scan cyclic voltammetry (FSCV) remains a premier technique for probing rapid neurochemical dynamics due to its sub-second resolution and molecular specificity. While carbon fiber electrodes (CFEs) are the gold standard in FSCV, their scalability is limited. Traditional microfabrication techniques enable the use of gold microelectrodes to create dense arrays, offering enhanced reproducibility, miniaturization, and seamless integration with electrophysiological recording platforms. We are developing a neural probe consisting of a gold microelectrode array (MEA) with 32 channels for FSCV-based neurochemical sensing, capable of parallel monitoring of dopamine release, and 32 channels for concurrent recording of neuronal spike activity (Fig. a-d). Each neurochemical electrode features a surface area comparable to CFEs, providing comparable sensitivity while enabling array scalability. To enhance electrochemical stability and signal clarity, we implemented a brief pre-cleaning procedure inspired by established FSCV conditioning methods. For the presented data at 0s we observe the initial sensitivity to DA, at ~1000s the electrode is fouled and we see reduced oxidation signal in the voltammogram, then after using our cleaning process the signal strength for the voltammogram at ~2500s is rejuvenated (Fig. e). This approach improves redox peak resolution and stabilizes background current, making the system suitable for reliable in vivo recordings. These developments underscore the essential role of surface conditioning in obtaining consistent neurochemical signals and demonstrate the promise of gold MEAs for scalable, high-resolution mapping of neuromodulatory activity. Our platform lays the foundation for expanding FSCV applications in neuroscience and multisite neurotransmitter monitoring across distributed brain networks.



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Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.04/VV15

Topic: J.04. Physiological Methods

Title: From Circuits to Synapses: Engineering Nanoelectrodes for Subthreshold Neural Capture

Authors: *S. BANSAL¹, S. SHUKLA⁴, Z. JAHED², G. CAUWENBERGHS³;

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Abstract: Circuit modeling and analytical data play a crucial role in characterizing intracellular signals from extracellular recordings, revealing subthreshold synaptic fluctuations. While standard amplifiers and conventional electrodes cannot achieve the signal-to-noise-distortion ratio needed to resolve supra- and sub-threshold events, nanostructured electrode arrays (NEA) offer potential for recordings of both suprathreshold and subthreshold neural events. Existing nanoelectrode arrays exhibit waveform fidelity issues compared to patch-clamp methods, pointing to a large gap in circuit models needed to deconvolute NEA signals to achieve multiplexed, intracellular recording. Previous research demonstrated that simulated action potential waveforms depend on junctional membrane resistance increases, affecting amplitude, duration, and timing. However, existing circuit models have not completely recapitulated a detailed profile of the signal attenuation, broadening, and distortion observed during live recordings. Our work characterizes the interdependence among cellular and electrical structures—nonjunctional membrane, junctional membrane, electrodes, and bioamplifiers—as interconnected Resistor-Capacitor (RC) networks. A critical limitation we identify is that bioamplifier input impedance, while ideally very high, becomes compromised by parasitic capacitance coupling with the electrode-tissue interface, causing substantial signal attenuation. By simulating the signal chain across worst-case versus best-case seal resistances, we demonstrate how signal amplitude and phase change across biologically relevant frequencies due to filtering effects: high-pass effects from electrode-amplifier impedance interactions and low-pass effects from interconnect capacitance and bandwidth limitations. These simulations reveal three distinct waveform alterations—substantial attenuation from charge leakage, pronounced signal broadening, and noticeable distortion—that we validate are present in live recordings using a previously published nanoelectrode array. Our framework enables detailed and systematic analysis of nanostructured arrays. These insights provide a foundation for designing nano-functionalization of commercial microelectrode arrays, enabling hybrid systems to simultaneously record subthreshold activity, action potentials, and field potentials. Such advances will facilitate high-density synaptic mapping, plasticity monitoring, and highly accurate brain-computer interfaces.

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Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.05/VV16

Topic: J.04. Physiological Methods

Support: Japan Agency for Medical Research and Development (AMED)
23be1004203h0002
Japan Agency for Medical Research and Development (AMED)
24be1004203h0003

Title: Field Potential Imaging of neural culture networks with a 236,880-electrode CMOS MEA system for multiscale activity analysis

Authors: *H. KURASHIKI¹, X. HAN², N. MATSUDA³, Y. ISHIBASHI⁴, I. SUZUKI⁵;
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Abstract: Information processing in the brain spans synaptic spikes, local microcircuits, and millimetre-scale network oscillations; disruptions at any level underlie disorders such as epilepsy and autism. Existing techniques such as conventional microelectrode arrays (MEAs)—and even current high-density CMOS-MEAs—capture only a subset of these scales. We overcome this limitation with an ultra-high-density CMOS MEA system (UHD-CMOS MEA) that integrates 236,880 electrodes (11.22 μm sites, $5.9 \times 5.5 \text{ mm}^2$ area) and inaugurates field-potential imaging of entire cultures. Primary hippocampal neurons from E17 embryonic rats were cultured directly on the CMOS-MEA. To transform the terabyte-scale output into insight, we built an end-to-end analytics pipeline comprising three layers. (i) Single-neuron layer: a spike-sorting strategy isolates > 3,000 well-resolved units from 1-min recordings and tracks the recruitment of previously silent cells under pharmacological challenge. (ii) Connectivity layer: graph-theoretic inference generates > 100 metrics, pinpointing hub neurons that ignite bursts and mapping large-scale rewiring. (iii) Network-dynamics layer: centre-of-activity trajectories and activity-diffusion plots reveal that bursts comprise multiple reproducible phases. Baseline recordings revealed heterogeneous burst trajectories and rich functional connectivity. Under graded doses of the GABA_A antagonist picrotoxin and agonist muscimol, the platform quantified a ≈ 2 -fold recruitment of previously silent neurons (3404/1798), drug-specific rewiring of functional graphs (hub prevalence and edge strength), and striking shifts in burst-propagation diversity—picrotoxin driving stereotyped, system-wide waves, muscimol suppressing bursts altogether. In a single computational pass, ≈ 200 multiscale parameters were extracted, sensitively capturing the complex network remodeling induced by each drug. This combined UHD-CMOS MEA + multiscale analytics closes the “understanding gap” between massive extracellular recordings and interpretable biology, enabling rapid mechanistic studies, modeling disease-related network dysfunction, and high-throughput screening of compounds that act on any hierarchical level of neural organization.

Disclosures: H. Kurashiki: A. Employment/Salary (full or part-time): VitroVo Inc. X. Han: A. Employment/Salary (full or part-time): VitroVo Inc. N. Matsuda: A. Employment/Salary (full

or part-time): VitroVo Inc. **Y. Ishibashi:** A. Employment/Salary (full or part-time): VitroVo Inc. **I. Suzuki:** A. Employment/Salary (full or part-time): VitroVo Inc..

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.06/VV17

Topic: J.04. Physiological Methods

Support: NIH Grant R15NS133861
NSF Grant 2347299

Title: A low-cost automatic machine for in-house fabrication of custom microwire-based microelectrode arrays for electrophysiological recordings

Authors: K. C. LAT¹, D. YI¹, M. JOVIC¹, R. KINNEY¹, J. P. HARTNER², B. O. WATSON², ***L. CHEN**¹;

¹Dept. of Mechanical and Industrial Engin., Univ. of Massachusetts Lowell, Lowell, MA; ²Dept. of Psychiatry, Univ. of Michigan, Ann Arbor, MI

Abstract: Thanks to the affordability, ease of customization, and superior chronic recording performance, microwire-based microelectrode array (MEA) has been a popular and important tool for neuroscientists. However, microwire MEA's potential is limited by the labor-intensive fabrication process, which is worsened by current scientific needs for complex and large-scale arrays made of smaller (< 25 μm diameter) minimal-damaging microwires. Current labor-intensive manual fabrication methods, especially for these smallest wires, require highly skilled and experienced operators and dedicated effort to ensure quality and throughput. To address this fabrication challenge, we developed a low-cost automated machine to conduct the simple, mature, but tedious fabrication tasks with high accuracy and repeatability so custom microwire MEAs could be easily made in-house by neuroscience labs. The automatic microwire-based MEA fabrication machine is composed of low-cost linear and rotary stages, USB cameras with lighting, and easily duplicable 3D-printed parts for custom fixtures and actuators. A Python-based automated motion control algorithm is driven by image processing and custom-trained open source deep learning neural network. The machine consists of two major modules for (1) MEA wire placement and (2) custom Printed Circuit Board (PCB) printing based on Direct Ink Writing (DIW). The wire placement module has (1) custom extruder system for continuous feeding of wire as raw materials, (2) image and machine learning driven recognition enabling automatic live-time detection of both the PCB landing areas and the extruded microwire for 3D alignment and precise machine-controlled wire placement, and (3) laser-based tip sharpening and insulation stripping system for contract-less tip preparation. The PCB fabrication module conducts DIW printing of conductive ink to create custom circuit traces for electrical connections between microwires and user-chosen micro-connectors. A pick-n-place system then automatically positions the connector onto designated board location before final curing. Results

from proof-of-concept trials indicate that the developed machine is capable of automatically manufacturing both carbon fiber (4-9 μm diameter) and metal wire (Tungsten and Stainless Steel 12-100 μm diameter) based MEAs on both rigid FR4 and flexible Kapton substrate under various MEA configurations, including 4-32 channel count, 150 μm - 1 mm pitch, both Hirose and Omnetics end connector, and corresponding various PCB size. Wires in fabricated MEA falls within the 20 - 200 k Ω at 1 kHz desired impedance range with over 90% yield.

Disclosures: K.C. Lat: None. D. Yi: None. M. Jovic: None. R. Kinney: None. J.P. Hartner: None. B.O. Watson: None. L. Chen: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.07/VV18

Topic: J.04. Physiological Methods

Title: Evaluation of magnetic resonance susceptibility artifacts generated by microelectrodes in the cerebral cortex at 9.4 Tesla

Authors: K. AKSENOVA¹, L. LI², *E. DOUBOVNIKOV³;

¹Niles North High Sch., Skokie, IL; ²Ctr. for Basic MR Res., ENH Res. Inst., Evanston, IL;

³Endeavor Hlth., Evanston, IL

Abstract: Combined intracortical electrophysiological recording and magnetic resonance imaging (MRI) is increasingly utilized to correlate neuronal activity with anatomical and functional imaging data. A critical challenge in multimodal imaging is the selection of electrode materials that minimize susceptibility artifacts in high-field MRI. Susceptibility artifacts distort MRI signals, obscuring anatomical details adjacent to electrodes. Although several candidate materials, such as gold-silver (AuAg) and platinum-iridium (PtIr) alloys, are commonly used in electrophysiological studies, comprehensive data evaluating artifact profiles at ultrahigh fields ($\geq 9.4\text{T}$) are limited. The goal of this study was to systematically characterize MRI susceptibility artifacts produced by microelectrodes made from these materials. To assess artifact profiles, microelectrodes approximately 20-25 μm in diameter, composed of AuAg and PtIr alloys, were embedded in agar phantoms designed to mimic the magnetic and conductive properties of brain tissue. Imaging experiments were conducted using a 9.4 Tesla Bruker MRI scanner employing gradient-echo pulse sequences optimized for artifact visualization. The size and extent of susceptibility artifacts were qualitatively and quantitatively analyzed and compared between materials. Our results revealed distinct differences in the magnitude and spatial extent of MRI artifacts between AuAg and PtIr microelectrodes. PtIr electrodes demonstrated significantly smaller susceptibility artifacts compared to AuAg electrodes, preserving anatomical visibility near the electrode-tissue interface. AuAg microelectrodes produced moderate artifacts that noticeably compromised adjacent MRI signal integrity. Importantly, neither material showed evidence of excessive heating or additional image distortions beyond the artifact area under the

experimental conditions tested. These findings indicate that AuAg electrodes are advantageous for electrophysiological recordings combined with high-field MRI, as they minimize susceptibility artifacts and preserve anatomical fidelity. Our data provide critical guidance for selecting electrode materials suitable for integrated electrophysiological and neuroimaging studies at high magnetic fields.

Disclosures: K. Aksenova: None. L. Li: None. E. Doubovikov: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.08/VV19

Topic: J.04. Physiological Methods

Support: Hungarian Brain Research Program Grant (NAP2022-I-2/2022)
2019-2.1.7-ERA-NET-2021-00023
NKFIH-150574-STARTING_24
Bolyai Janos Scholarship
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NKFIH-PD143582
HUN-REN SA-114/2021

Title: Optimal inter-electrode distances for maximizing single-unit yield per electrode in neural recordings

Authors: *D. MESZENA^{1,2,3}, W. FADEL¹, R. TOTH⁵, A. C. PAULK³, D. J. KELLAR⁴, M. JAMALI⁴, S. S. CASH³, Z. WILLIAMS⁴, T. KISS⁶, M. STIPINGER⁶, L. WITTNER¹, R. FIÁTH¹, Z. SOMOGYVARI^{7,6};

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Abstract: State-of-the-art high-density multielectrode arrays enable the recording of simultaneous spiking activity from hundreds of neurons. Although significant efforts have been dedicated to enhancing neural recording devices and developing more efficient sorting algorithms, there has been relatively less focus on the allocation of microelectrodes—a factor that undeniably affects spike sorting effectiveness and ultimately the total number of detected neurons. Here, we systematically examined the relationship between optimal electrode spacing and spike sorting efficiency by creating virtual sparser layouts from high-density recordings through spatial down sampling. We assessed spike sorting performance by comparing the

quantity of well-isolated single units per electrode in sparse configurations across various brain regions (neocortex and thalamus) and species (rat, mouse, and human). Enabling the theoretical estimation of optimal electrode arrangements, we complement experimental results with a geometrical modeling framework. Contrary to the general assumption that higher electrode density inherently leads to more efficient sorting, both our theoretical and experimental results reveal a clear optimum for electrode spacing specific to species and regions. We demonstrate that carefully choosing optimal electrode distances could yield a total of 1.7 to 3 times increase in spike sorting efficiency. These findings emphasize the necessity of species- and region-specific microelectrode design optimization.

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Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.09/VV20

Topic: J.04. Physiological Methods

Title: Toward Standardized Chronic Electrophysiology: A Longitudinal Study of Age-Related Hearing Loss and Cognitive Decline

Authors: ***C. SIELAFF**^{1,2}, **R. LAND**², **A. KRAL**², **U. FRORIEP**¹;

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Abstract: Electrophysiological neuroscience faces significant challenges regarding the standardization and documentation of methods, which limits reproducibility and the ability to compare long-term data across studies. We address these methodological issues, while studying long-term age-related hearing loss (ARHL), which affects approximately one-third of individuals over 65 and is one of the most significant risk factors for dementia. The neurophysiological mechanisms linking ARHL to cognitive decline remain poorly understood and offer us a great opportunity to apply methodological rules derived from quality management. To address both these issues, we perform chronic, longitudinal recordings in awake mice to characterize the effects of progressive hearing loss on cortical processing across sensory and associative areas. We use two mouse strains: C57BL/6J, which exhibit early-onset ARHL, and CAST-Cdh23Ahl+/Kjn, a genetically similar strain with preserved hearing into old age. Using chronically implanted two-shank 32-channel silicon NeuroNexus probes, we record local field potentials and multi-unit activity from auditory, visual, and prefrontal cortices every 2 - 4 days for up to 6 months. During each session, animals receive auditory and visual stimuli to assess cross-modal plasticity, sensory reorganization, and age-dependent shifts in cortical activity. To

assess structural changes in the cortex over time, a subset of animals will be euthanized at 3- and 6-months post-implantation for histological analysis. We will evaluate neuroinflammatory markers (GFAP, Iba1, CD68), blood-brain barrier integrity (IgG), and neuronal density to identify long-term implantation effects and correlate histological findings with electrophysiological changes. Special attention will be given to connectivity between cortical regions, oscillatory dynamics, and potential compensatory recruitment of visual areas in response to ARHL. Additionally, we will observe changes in the prefrontal cortex as an indicator of cognitive decline. A key component of this study is the comprehensive documentation and dissemination of all protocols and procedures to enable a quality-based approach. By combining long-term physiological data, histological endpoints and an open discussion about the methodology far beyond usual publications, we aim to contribute both to the mechanistic understanding of ARHL-related cognitive vulnerability and to the development of quality criteria for electrophysiology. These efforts may support early interventions in ARHL and advance the stability and reliability of future neurotechnological applications.

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Poster

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Program #/Poster #: PSTR196.10/VV21

Topic: J.04. Physiological Methods

Support: NIH Grant R15NS133861
NSF Grant 2347299

Title: A piezoelectric inchworm inserter for automatic machine-controlled buckling-free implantation of miniaturized flexible microelectrodes through brain membranes

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Abstract: Large-scale chronic recording across the brain with minimal disruption will be critical for understanding the multi-region neural dynamics. But the possibility of such experiments is limited by (1) buckling of electrodes upon insertion, and (2) labor intensive surgeries. The least-damaging microelectrode arrays (MEAs) would be preferred for broad chronic recording but buckle against brain membranes during insertion, so larger more damaging electrodes/shuttles are used. Broad implantation is also difficult with slow manual surgical procedures. To address these challenges, we develop a piezoelectric inchworm insertion mechanism to enable currently-impractical high-density broad-scale brain implantation of miniaturized flexible MEAs in a fast and extensible machine-controlled manner. Instead of the conventional insertion method holding

the back-end of an MEA, the inchworm inserter conducts iterative grip-feed-release inchworm motion holding the electrode body. This reduces buckling by increasing lateral extracranial support along the electrode length during implantation and minimizing unsupported length (maximizing the MEA critical buckling load). The prototyped inchworm inserter is composed of three sets of piezoelectric actuators: two horizontal grippers alternately grip the implant and an extender moves the grippers vertically. The assembly is of miniaturized size of $14 \times 5.8 \times 3.6$ mm and 250 mg weight. Custom designed piezoelectric 're-curve' actuators together with adjustable gripping plates were used to produce up to 80 μ m of purely linear motion with minimal bending, up to 950 mN of force, and up to 200 Hz of bandwidth, enabling up to 14 mm/s precisely controlled insertion speed and iterative increments as little as 10 μ m. These specs are all further tunable by varying the actuator design and power input. To test the inserter's capability, benchtop tests were conducted against a triple layer (dura-pia-brain tissue) rodent brain-mimicking phantom. Findings include that we were able to insert (a) single 25 μ m diameter tungsten and stainless-steel wires, (b) a 50 μ m thick shank from Buzsaki64L silicon probe, and (c) a single-shank 50 μ m thick polyimide flexible probe, deep (> 10 mm) into the phantom through both dura and pia without buckling. In comparison, without the inchworm, no electrodes inserted. This result showed great potential of the inchworm inserter to achieve broadly applicable improvements in brain surgery methodology by enabling thick membrane penetration by miniaturized MEAs and machine-controlled automatic insertion with precise insertion speed and depth.

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Poster

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Topic: J.04. Physiological Methods

Support: NIH Grant U01NS126046

Title: Chronic performance of flexible parylene hippocampal arrays assessed through standardized long-term recording metrics

Authors: *Z. LU¹, Z. JIN¹, K.-W. YEH¹, J. LIN¹, Y. GAO¹, J. LIANG¹, K. SCHOLTEN^{3,1}, H. XU¹, E. MENG¹, D. SONG^{2,1};

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Abstract: Chronic electrophysiological recordings are essential for probing long-term neural dynamics underlying learning, memory formation, and brain-machine interface (BMI) applications. The hippocampus, with its well-defined anatomical structure and central role in

spatial and episodic memory, is a key target for such studies. However, obtaining stable, high-quality neural recordings from the hippocampus over extended periods remains a major technical challenge, largely due to the mechanical mismatch between rigid probes and soft brain tissue, which can induce inflammation, gliosis, and electrode degradation over time. To overcome these limitations, we developed and validated flexible parylene-based multi-electrode arrays (MEAs) specifically tailored for dorsal hippocampal implantation in freely behaving rats. The arrays were engineered to conform to the curvature and laminar architecture of the CA1-CA3 hippocampal regions, and featured flexible, biocompatible materials to reduce micromotion-induced damage and improve chronic tissue integration. We evaluated recording performance over a 16-week period using a comprehensive set of metrics consolidated in our recent review of chronic neural interface standards. These included single-unit yield, peak-to-peak spike amplitude, baseline noise floor, signal-to-noise ratio (SNR), and impedance magnitude at 1 kHz. Arrays implanted in rats ($n = 13$) demonstrated stable long-term recording performance, with 64 channels consistently capturing isolatable single-unit activity (mean SNR > 8). Spike amplitudes ranged from 80 to 480 μV , and impedance values remained within functional limits with minimal temporal drift, indicating a preserved electrode-tissue interface. Post-mortem histological analyses revealed reduced astrocytic and microglial activation, as well as improved neuronal preservation near the probe tracks, when compared to conventional silicon shank electrodes. These findings support the use of flexible polymer MEAs as a robust platform for long-term hippocampal recordings and provide quantitative benchmarks for evaluating next-generation chronic neural interfaces in vivo.

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Poster

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Program #/Poster #: PSTR196.12/WW1

Topic: J.04. Physiological Methods

Title: Optimization of electrical stimulation in microelectrode arrays to reduce variability in functional assays of neuronal network activity

Authors: *S. A. CHVATAL, P. J. ELLINGSON, D. SULLIVAN, B. STREETER, A. PASSARO, D. C. MILLARD;
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Abstract: *In vitro* models of neuronal networks can be powerful tools in the study of toxicology and neural disease. Microelectrode arrays allow for the probing and quantification of neural activity in these cultured networks and provide a foundation for the development of assays focused on the characterization of functional activity. A major hurdle that investigators face during assay development with these platforms is baseline variability in neuronal models from

culture to culture. While careful control of environment and cell culture processes can also reduce variability, here we discuss an additional approach - the use of applied electrical stimulation as a perturbational method of reducing culture-to-culture variability. Primary Rat Cortical Neurons were cultured in a 48-well microelectrode cell culture plate and dosed with 50uM Bicuculine on DIV14. Stimulation was introduced during the baseline and dosed recordings for half of the wells in the form of biphasic pulses (1 Volt, 100us per phase) applied at 0.1 Hz and spike activity metrics were recorded and computed using the Maestro Pro. Standard deviation across wells was reduced in 60 out of 66 computed metrics describing spiking activity, synchrony, bursting, and network bursting. For example, standard deviations across wells for Mean Firing Rate, Network Burst Duration, and Network Burst Frequency were reduced by 48.3%, 85.5%, and 94.8% respectively in baseline recordings in stimulated wells as compared to unstimulated wells. When dosed with Bicuculine, the standard deviation across wells for Mean Firing Rate, Network Burst Duration, and Network Burst Frequency were 25.1%, 24.4%, and 23.1% lower in stimulated wells compared to unstimulated wells. The decreased variability in the baseline can increase the statistical power to resolve small changes in activity. Assuming a two-tailed paired t-test with $\alpha=0.05$ and that the measured variances of the control and treated conditions are representative of the true distributions, the statistical power in resolving a 20% change in Network Burst Duration increases from 0.13 in the unstimulated conditions to 0.97 in the stimulated conditions. The choice of stimulation electrode is also meaningful and can be optimized to increase the probability of an evoked response in the cultures. Higher voltage stimulations and higher impedance of the stimulated electrode (a measure of neuronal attachment and cell viability) result in more reliable evoked responses, which ultimately lead to the described reductions in activity metric variability.

Disclosures: **S.A. Chvatal:** A. Employment/Salary (full or part-time): Axion BioSystems. **P.J. Ellingson:** A. Employment/Salary (full or part-time): Axion BioSystems. **D. Sullivan:** A. Employment/Salary (full or part-time): Axion BioSystems. **B. Streeter:** A. Employment/Salary (full or part-time): Axion BioSystems. **A. Passaro:** A. Employment/Salary (full or part-time): Axion BioSystems. **D.C. Millard:** A. Employment/Salary (full or part-time): Axion BioSystems.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

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Program #/Poster #: PSTR196.13/WW2

Topic: J.04. Physiological Methods

Support: AMED under Grant Number JP24gm1510010

Title: Development of three-dimensional electrode formation technology on flexible substrates

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Abstract: Recently, with the advancement of medical technology, the demand for implantable medical devices for the treatment of neurological diseases and sensory disorders has been rapidly increasing. Implantable devices require flexible substrates with thin metal wiring ranging from a few hundreds of nm to several μm to conform to the complex shapes and behaviors of biological tissues. In addition, devices for brain stimulation, for example, require high-density electrodes with high charge injection capacity. Therefore, three-dimensional electrodes are preferable to provide a small area for mounting. However, in mounting electrodes after flexible substrate fabrication, retaining the three-dimensional shape was difficult owing to handling and loading during mounting. In this study, we fabricated a novel method of mounting three-dimensional electrodes on a flexible substrate. Fabrication of a platinum (Pt) wiring flexible substrate was achieved through laser cutting 30 μm thick Pt foil on Dimethylpolysiloxane (PDMS) followed by the welding of a 200 μm thick cylindrical Pt electrode onto the Pt wiring. Then these mounted cylindrical electrodes were machined to bullet-shaped three-dimensional shape by laser irradiation after welding. In electrode welding, first we tried a method called parallel gap method, in which both ends of the welding electrode are placed on the same surface of welding object, but frequently insufficient welding was observed. Accordingly, we tried the indirection method, in which the location of one of the welding electrodes was shifted vertically to a location distant from the welding object. This significantly improved the success rate of welding. The laser machining process demonstrated the ability to create arbitrary shapes for bullet-shaped by machining a circular shape. In this process, the surface area contributing to the charge injection capability was increased by the formation of laser processing. These methods show the potential for application to various devices requiring three-dimensional shaped electrodes.

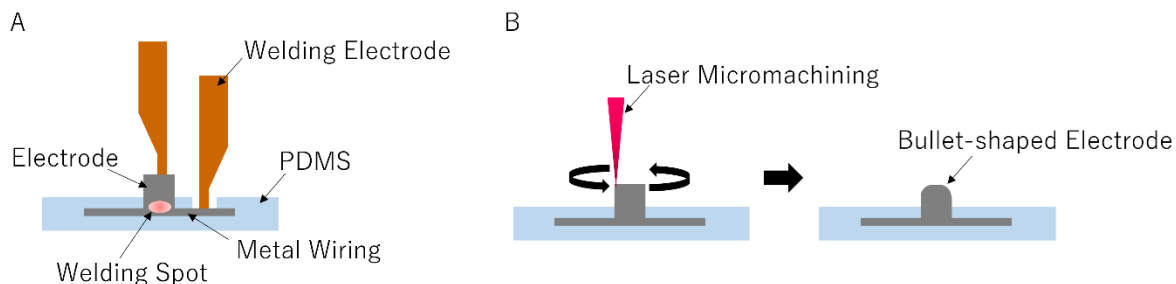


Fig. 1 Schematic of fabrication process.

(A) Schematic of the electrode and metal wiring arrangement during microwelding.

(B) Schematic of bullet-shaped electrode processing by laser machining

Disclosures: **T. Kono:** A. Employment/Salary (full or part-time): NIDEK Co., Ltd. **Y. Terasawa:** A. Employment/Salary (full or part-time): NIDEK Co., Ltd. **H. Tashiro:** Other; grant from NIDEK Co., Ltd. **J. Ohta:** Other; grant from NIDEK Co., Ltd.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

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Topic: J.04. Physiological Methods

Support: grant (RS 2024-00333012) from Ministry of Food and Drug Safety in 2024
Korea Medical Device Development Fund grant funded by the Korea government (Project Number: 2470000017, RS-2024-00404802)

Title: Continuous multimodal physiological monitoring in freely moving non-human primates using a fully implantable wireless device

Authors: *J. MIN^{1,2}, E. JEON¹, G.-S. BAE¹, S. Q. LEE³, Y. LEE¹;

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Abstract: Understanding long-term physiological and behavioral states in non-human primates (NHPs) under naturalistic conditions is critical for advancing translational neuroscience. We present a fully implantable, wireless multimodal physiological monitoring device with compact dimensions ($28 \times 17 \times 7 \text{ mm}^3$) capable of continuous real-time acquisition of multimodal physiological data such as electrocardiogram (ECG), heart rate, body temperature, and activity (x, y, z) in freely moving NHPs. The device is packaged in biocompatible titanium and implanted subcutaneously adjacent to the heart following plasma sterilization. We established a stable and reproducible surgical protocol for cynomolgus monkeys (*Macaca fascicularis*, female), enabling reliable long-term implantation with rapid postoperative recovery. The system supports chronic monitoring for over 40 days, guaranteeing instant data logging and high-resolution multimodal synchronization. The quality of data obtained from the device was comparable to that of conventional tethered commercial systems during intraoperative validation. Post-implantation, the device enabled stable long-term physiological signal acquisition in both open-field and home-cage environment, with no adverse biological effects observed in hematological or biochemical assessments. From the continuous long-term recordings, we extracted heart rate variability indices, including the percentage of successive normal-to-normal intervals that differ by more than 30 ms (pNN30), to assess sleep stages. Notably, while pNN values typically increase during deep sleep in humans, cynomolgus monkeys exhibited an inverse pattern, with lower pNN values corresponding to deeper sleep stages. This suggests potential species-specific differences in autonomic regulation during sleep, warranting further investigation of pNN metrics in NHPs. Our minimally invasive monitoring system provides high-fidelity physiological recordings without restricting natural behavior and offers a robust platform for ecologically valid, translational research in sleep, emotion, pharmacodynamics, and disease modeling in non-human primates.

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Poster

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Program #/Poster #: PSTR196.15/WW4

Topic: J.04. Physiological Methods

Support: 25-BR-02-02

Title: A Reconfigurable Multisite ECoG Electrode Array for Recording from Multiple Cortical Regions

Authors: *J. LEE^{1,2}, J. EUN¹, N. CHOU¹;

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Abstract: The simultaneous measurement of neural signals from multiple cortical regions in freely moving mice is fundamental for a comprehensive understanding of intricately connected neural circuits. However, in mice, which are commonly utilized in neuroscience research, the restricted dimensions of the brain and skull present significant challenges for the implantation of electrodes across multiple cortical areas. Furthermore, the acquisition of neural activity from multiple brain regions frequently necessitates extensive craniotomy, a procedure that inherently carries a substantial risk of neural damage. A micro-sized electrocorticography (ECoG) electrode arrays, fabricated utilizing micro-electromechanical system (MEMS) technology, have been developed for accurately accessing multiple cortical areas individually and for preventing damage to neural tissues. The micro-sized electrode. Nevertheless, such MEMS-fabricated arrays possess an immutable configuration post-manufacturing. Consequently, the interrogation of new cortical regions mandates complete device re-fabrication, thereby incurring substantial temporal and financial expenditure. To overcome these limitations, we have developed a reconfigurable multisite ECoG electrode array that allows access to multiple desired cortical regions within a single platform through simple adjustments. The design features a reconfigurable arrangement for packaging the ECoG electrodes and the printed circuit board (PCB), enabling flexible access to diverse cortical regions. While the ECoG electrodes are mass-produced using MEMS technology with a parylene substrate, their circular design for PCB packaging allows for flexible repositioning. This design enables the creation of an ECoG electrode array capable of simultaneous neural signal recording from various murine brain regions within a single platform, eliminating the need for re-fabrication. Furthermore, the electrodes are fabricated to a thickness of 6 μm for excellent conformance to the curved cortical surface, and coated with PEDOT:PSS via electrophoresis to enhance recording performance. Using this reconfigurable multisite ECoG electrode array, we successfully performed simultaneous and precise measurements of neural activity from two distinct cortical regions in freely moving mice. From these results, we believe that the flexible design and packaging method presented in the developed ECoG electrode can be widely used in various neuroscience studies.

Disclosures: J. Lee: None. J. Eun: None. N. Chou: None.

Poster

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Topic: J.04. Physiological Methods

Support: JSPS KAKENHI Grant Numbers 23K18512

Title: High-resolution mapping of beta rhythm induction in acute brain slices using field potential imaging with ultra-high-density CMOS-MEA

Authors: *N. MATSUDA¹, B. NODA², I. SUZUKI³;

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Abstract: Beta-band oscillations in the hippocampus are neural rhythms commonly associated with wakeful and cognitively active states. These oscillations are modulated by cholinergic input, particularly from the medial septum to the CA3 subfield, and are implicated in attention, memory encoding, and sensory integration. Disruptions in beta activity have been linked to neurological disorders such as Parkinson's disease and Alzheimer's disease, underscoring the importance of beta rhythms as biomarkers and therapeutic targets. Therefore, ex vivo models capable of inducing beta-band oscillations under arousal-like conditions are valuable for both basic and translational neuroscience. In this study, we applied field potential imaging (FPI) using an ultra-high-density (UHD) CMOS-MEA comprising 236,880 electrodes to simultaneously and spatially resolve carbachol-induced activity changes in the hippocampus and neocortex. The array comprises 236,880 electrodes spanning a 5.5×5.9 mm sensing area, enabling high-resolution, large-scale mapping of neural activity. Treatment with 10 μ M carbachol reliably induced rhythmic network events in the hippocampus, occurring at an average interval of 1.33 ± 0.33 Hz. These slow and periodic events consistently originated in the CA3 region and propagated toward CA1 with precise temporal coordination. Within each event, the average duration was 52.82 ± 6.44 ms, corresponding to an intra-event oscillation frequency of 18.93 ± 3.03 Hz—falling within the beta frequency band. Cluster analysis based on waveform morphology revealed spatial groupings that reflected underlying anatomical structures. Beta-band power was significantly enhanced in both hippocampal regions following carbachol treatment. These findings demonstrate that the FPI platform enables high-resolution mapping of relationships between anatomical structures and brain function in acute slices, and holds promise as a pharmacological evaluation tool for assessing compound effects on hippocampal and cortical networks under wakefulness-associated oscillatory patterns.

Disclosures: N. Matsuda: None. B. Noda: None. I. Suzuki: None.

Poster

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Program #/Poster #: PSTR196.17/Web Only

Topic: J.04. Physiological Methods

Support: JSPS KAKENHI Grant 23H03726
JSPS KAKENHI Grant 25K21561

Title: Precision neural activity mapping in brain organoids through field potential imaging with ultra-high-density CMOS microelectrode array

Authors: ***R. YOKOI**¹, **N. MATSUDA**¹, **Y. ISHIBASHI**¹, **B. NODA**², **I. SUZUKI**¹;
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Abstract: Human iPSC-derived brain organoids and assembloids are emerging as robust in vitro platforms for modeling human brain development, neurological disorders, and drug responses. However, detailed characterization of their electrophysiological properties requires advanced, high-resolution recording technologies. In this study, we present a comprehensive analytical framework utilizing ultra-high-density (UHD) CMOS microelectrode arrays (MEAs) comprising 236,880 electrodes (10.52 $\mu\text{m} \times 10.52 \mu\text{m}$ each) distributed across a sensing area of 32.45 mm², enabling large-scale field potential imaging (FPI) of brain organoids. Neural signals were recorded simultaneously from over 46,000 electrodes interfaced with organoids, allowing identification of single-neuron firing events and fine-grained analysis of network-level connectivity. In midbrain organoids, administration of L-DOPA evoked both excitatory and inhibitory responses; notably, excitatory activity increased in a dose-dependent manner, indicating enhanced network integration. Capitalizing on the spatiotemporal precision of UHD-CMOS-MEAs, we introduced novel quantitative metrics of network activity: propagation velocity and propagation area. In cortical organoids, the GABA_A receptor antagonist picrotoxin increased propagation velocity, whereas the NMDA receptor antagonist MK-801 broadly reduced propagation area with regionally localized enhancements. Frequency-domain analysis of spontaneous activity revealed region-specific oscillatory patterns, with distinct gamma-band signatures. In midbrain-striatal assembloids, spontaneous electrophysiological activity was detected in both compartments. Connectivity analysis further demonstrated that treatment with 4-aminopyridine significantly enhanced inter-organoid coupling. This single-cell-resolved, high-density FPI approach enables robust quantification of neuronal firing, connectivity, propagation dynamics, and frequency characteristics. Our platform offers a powerful tool for investigating functional neural circuits in brain organoids and assembloids, with significant potential for applications in drug screening and disease modeling.

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Poster

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Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.18/WW6

Topic: J.04. Physiological Methods

Title: Development of a neural network formation assay for iPSC-derived glutamatergic neurons

Authors: ***B. STREETER**, D. SULLIVAN, P. J. ELLINGSON, S. BARNES, D. C. MILLARD;
Axion Biosystems, Atlanta, GA

Abstract: The flexibility and accessibility of induced pluripotent stem cell (iPSC) technology has allowed complex human biology to be reproduced in vitro at high throughput scales. Indeed, rapid advances in stem cell technology have led to widespread adoption for the development of in vitro models of neuron electrophysiology to be used in disease models, drug discovery, and safety. And yet, the field lacks clear standards for evaluating the critical elements of iPSC-derived neuronal models. In this study, we developed a neural network formation assay using rat cortical neurons (RCNs) and human iPSC-derived glutamatergic neurons cultured on microelectrode arrays (MEAs). Spontaneous activity was monitored over several weeks and, at defined maturation stages (e.g. Day 14 for RCNs and Day 28 for iPSC-neurons), cultures were sequentially dosed with a panel of pharmacological compounds to quantify functional synaptic activity and the balance of excitation and inhibition. The assay involved a two-step dosing protocol: (1) bicuculline to block GABA-mediated inhibition and (2) CNQX and APV to block glutamatergic transmission via AMPR and NMDA receptors. RCNs were cultured in two commercially available media types. Post addition of bicuculline, cells in Media 1 showed a greater response in network burst frequency (730%) when compared to Media 2 (452%), while cells in Media 2 showed a larger increase in area under normalized cross-correlation (AUNCC) at 152%, compared to 52% in Media 1. The addition of CNQX and APV silenced most of the functional neural activity with significant in mean firing rate (Media 1: -92%, Media 2: -95%), network burst frequency (-100% for both), and AUNCC (-100% for both), confirming strong functional glutamatergic synapses. Human iPSC-neurons cultures demonstrated minimal response to synaptic blockers on day 14, indicating delayed network maturation and altered sensitivity as compared to RCNs. On day 28, bicuculline increased network burst frequency by 61%, burst percentage by 15% and AUNCC by 28% as compared to baseline. In contrast, the addition of CNQX and APV decreased network burst frequency by 93% and AUNCC by 92%. Unlike RCN cultures, CNQX and APV had little effect on overall mean firing rate of human iPSC-neurons, suggesting increased reliance on intrinsic excitability over synaptic connectivity. The differences observed between the primary and iPSC-derived neural populations and cells cultured in different media compositions underscore the need for standardized assays that consider cell-type specific timelines and analysis strategies when using MEAs to evaluate neural behavior.

Disclosures: **B. Streeter:** A. Employment/Salary (full or part-time): Axion Biosystems. **D. Sullivan:** A. Employment/Salary (full or part-time): Axion Biosystems. **P.J. Ellingson:** A. Employment/Salary (full or part-time): Axion Biosystems. **S. Barnes:** A. Employment/Salary (full or part-time): Axion Biosystems. **D.C. Millard:** A. Employment/Salary (full or part-time): Axion Biosystems.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.19/WW7

Topic: J.04. Physiological Methods

Support: RS-2024-00357432

Title: Parylene c based intraneural mesh interface for chronic peripheral nerve recording

Authors: ***B. PARK**¹, S. KIM¹, B. KIM², H. CHOE³;

²Brain sciences, ³Dept. of Brain and Cognitive Sci., ¹DGIST, Daegu, Korea, Republic of

Abstract: To advance peripheral nerve interfacing technologies, long-term recording of spike-level neural signals is essential. Achieving such resolution requires intraneural interfaces that are directly inserted into peripheral nerves. However, stable long-term recordings remain challenging due to the small size and continuous movement of peripheral nerves, which makes them more susceptible to foreign body responses caused by the mechanical mismatch between the interface and neural tissue. To address this issue, we developed an intraneural mesh interface based on parylene-C, which exhibits ultra-flexible mechanical properties compared to conventional peripheral nerve interfaces. The interface consisted of 20 μm -wide mesh and 10 μm -wide metal lines, with two thickness variants of 2 μm and 6 μm . The fabricated intraneural mesh interface was implanted into the tibial nerves of New Zealand rabbits, and in vivo neural recordings began at one week post-implantation. To evaluate tissue responses, immunohistochemical staining was performed. For comparison, the plane interface with dimensions and materials identical to the mesh interface was also fabricated and implanted into rat sciatic nerves. During in vivo recording, the intraneural mesh interface successfully captured spike-level proprioceptive signals corresponding to three distinct muscle spindle afferents. These units showed stable firing rates in response to identical stimuli over a four-week period. Histological analysis revealed that axonal fluorescence recovered within 20-40 μm of the mesh interface, whereas the plane interface required 100-120 μm for similar recovery. In conclusion, we developed a parylene-C-based intraneural mesh interface and validated its performance through chronic in vivo recording and immunohistochemistry. The interface enabled stable spike-level recording from muscle spindles over four weeks and suppressed fibrotic tissue formation by approximately 85% compared to plane interfaces. These results confirm that the intraneural mesh interface suppresses the foreign body response in neural tissue, enabling stable long-term functionality within the nerve.

Disclosures: **B. Park:** None. **S. Kim:** None. **B. Kim:** None. **H. Choe:** None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.20/WW8

Topic: J.04. Physiological Methods

Support: Wyss Center - Lighthouse Partnership

Title: High-channel-count bioelectronic interfaces via hybrid integration of CMOS chips into thin-film electrode arrays

Authors: ***H. LONDOÑO RAMÍREZ**, V. DRUET, I. FURFARO, A. DAWOUD, P. PALOPOLI, G. SCHIAVONE, S. P. LACOUR;
EPFL, Geneva, Switzerland

Abstract: Existing passive electrode array technologies are limited in the electrode count, as each recording channel must be individually routed from the tissue interface to the external recording electronics. Scaling the number of channels in electrode arrays to achieve large-area brain recordings with higher spatial resolution is further limited by bulky connectors, which restrict the miniaturization of implantable systems.

Here, we present a hybrid active implantable neuroelectronic system that addresses this challenge by integrating a low-noise, low-power and high-channel-count neural recording chip into a microfabricated thin-film electrode array. Specifically, we employed a flip-chip bonding process to integrate a 512-channel bare-die CMOS recording chip (Nixel 512, Science Corporation) with a flexible micro-electrocorticography (μ ECoG) array. To achieve this, we used a routing architecture with two-layer thin-film platinum metallization on polyimide (13 μ m total thickness) and developed an adapted flip-chip bonding process to ensure reliable electrical and mechanical connections.

The resulting system is designed to enable recording from up to 512 electrodes concurrently while requiring only 22 digital control, readout, and biasing connector pads. We present validation data from acute experiments that demonstrate both the robustness of the assembly and integration process, and the potential for large-scale electrophysiological recordings.

This hybrid platform integrates mechanically compliant thin-film electrodes with the signal acquisition and routing capabilities of CMOS technology, enabling high-channel-count, conformal neural interfaces with a compact footprint and minimal interconnect complexity. Although demonstrated with a specific neural recording chip, the strategy is broadly compatible with other CMOS chips and applicable beyond recording alone. Our approach overcomes the wiring and processing bottlenecks that restrict passive electrode arrays to low-channel-count devices, offering a scalable solution for large-scale, high-resolution brain mapping in both research and future clinical neurotechnology applications.

Disclosures: **H. Londoño Ramírez:** None. **V. Druet:** None. **I. Furfaro:** None. **A. Dawoud:** None. **P. Palopoli:** None. **G. Schiavone:** None. **S.P. Lacour:** None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.21/WW9

Topic: J.04. Physiological Methods

Support: 1R41MH141906-01

Title: Advancing Flexible Carbon Fiber Neural Arrays

Authors: *J. RICHIE;

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Abstract: Carbon Fibers are growing in popularity as an electrode material for neuroscience investigations. Commonly used for FSCV research, with recent advances, these electrodes can also be used for electrophysiology recording or stimulation with great specificity and selectivity. However, current commercial carbon fiber electrodes are limited to single glass capillary electrodes which are not suited for chronic or human studies. Spike Neuro has just released an acute carbon fiber array, however, it is not meant for chronic studies or human use. While there are research-use carbon fiber arrays, these are also supported with rigid silicon supports and locked to a single line of electrodes. By combining flexible ECoG arrays with carbon fibers, we have been able to create a penetrating electrode array that conforms to tissue shape and is able to target single unit recordings. The electrode support substrate is comprised of three layers: polyimide, metal electrodes and traces, and a final insulating layer of polyimide. Substrates were released from the device and then individually populated with carbon fibers. Fibers were aligned in a specialized mold and secured to the metal electrode with conductive silver epoxy. The entire device was then insulated with Parylene C. Fiber tips were re-exposed via heat. Arrays were brushed perpendicularly to assess the robustness of the connection. Finally, 1 kHz impedance was taken to assess the preliminary electrical properties of the arrays. This work shows the ability of the carbon fibers to remain attached to the thin ECoG array scaffolding. We also show the electrical characterization of the array and the carbon fiber tips compared to Spike Neuro's acute carbon fiber arrays. The brushing test resulted in a majority of the fibers remained upright and attached after 10 passes; Increasing the number of brushes to 100 showed no impact on the remaining fibers indicating that fibers with poor connections will fall away quickly, while fibers with good connections are secure. The 1 kHz impedance of the arrays in saline remain below 2 MΩ, well within the acceptable range for neural recording. In conclusion, flexible penetrating carbon fiber arrays are becoming a viable option for recording opening many avenues for low impact neural implants at the surface of tissues. Future work will include incorporating ECoG functionality with the carbon fiber penetrating electrodes. Additionally, as retina is of interest to the researcher, high density spacing of fibers and their ability to stimulate retinal ganglia cells will also be investigated through collaboration with an academic lab.

Disclosures: J. Richie: A. Employment/Salary (full or part-time): Spike Neuro.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.22/WW10

Topic: J.04. Physiological Methods

Support: NIH NBIB DP2-EB029757
NINDS R01NS123655-01
NINDS UG3NS123723-01
NIDA R01-DA050159
NSF 1728497
CAREER 1351980

Title: A 4096-Channel Wireless Subcutaneous ECoG System for Continuous Semi-Chronic Cortical Monitoring in Freely Behaving Pigs

Authors: *J. LEE¹, K. FORSETH², W. JEON¹, H. LE¹, K. LEE³, T. PORTER⁴, E. HALGREN⁶, A. RASLAN⁷, A. C. PAULK⁸, S. S. CASH⁹, S. BEN-HAIM¹⁰, S. DAYEH⁵; ²Neurosurg., ¹Univ. of California San Diego, San Diego, CA; ³Electrical Computer Engin., UC San Diego, San Diego, CA; ⁵Dept. of Electrical and Computer Engin., ⁴UC San Diego, La Jolla, CA; ⁶Ctr. for Human Brain Activity Mapping, Univ. of California at San Diego, San Diego, CA; ⁷Neurolog. Surgery, OHSU, Portland, OR; ⁸Massachusetts Gen. Hosp., Boston, MA; ⁹Dept Neurol, Mass Genl Hosp, Boston, MA; ¹⁰Neurosurg., Mount Sinai Sch. of Med., New York, NY

Abstract: Epilepsy is one of the most prevalent neurological diseases and over a quarter of all epilepsy patients experience drug-resistant epilepsy where surgical interventions or electrical stimulation paradigm become most effective paradigms for treatment. Phase 2 intracranial monitoring plays a critical role in surgical planning by enabling precise localization of epileptogenic zones, identification of irritative networks, and mapping of eloquent cortex. However, conventional wired systems constrain patient mobility and limit monitoring duration. To overcome these limitations, we developed a wireless, high-resolution cortical recording system capable of untethered, continuous monitoring over extended periods. The system features a 4096-channel high-density surface electrocorticography (ECoG) grid fabricated on flexible parylene-C with PtNR contacts, spanning a $32 \times 13 \text{ mm}^2$ area and incorporating 24 stimulation contacts (1 mm² diameter). The grid is integrated via a novel single-sided bonding method with a custom PCB and chip stack containing amplifiers, digitizers, and serializers, all encapsulated within a hermetically sealed titanium enclosure. The complete electronics module is implanted subcutaneously, with the wireless transmission link positioned beneath the scalp. Power and high-bandwidth data are transmitted wirelessly to an external backworn unit housed in a jacket worn by the animal, allowing continuous recordings in freely behaving subjects without physical connectors. We validated the complete platform in a survival pig model, recording from the frontoparietal convexity. Wireless subcutaneous transmission enabled stable, high-fidelity recordings out of the operating room. The pig maintained normal behavioral patterns of activity, feeding, and play in the postoperative period - unencumbered by fixed tether. Sensory stimulation via air-puff to the snout elicited robust and spatially distinct high-gamma responses across the grid, revealing fine-scale cortical modules and propagating activity patterns inaccessible to conventional low-density systems. This work represents the first successful long-term deployment of a 4096-channel wireless surface ECoG system with fully implanted

electronics and continuous real-time data streaming. The wireless architecture eliminates physical tethers, enabling naturalistic behavior and extended monitoring—offering a powerful new platform for Phase 2 epilepsy evaluation and future brain-computer interface applications.

Disclosures: J. Lee: None. K. Forseth: None. W. Jeon: None. H. Le: None. K. Lee: None. T. Porter: None. E. Halgren: None. A. Raslan: None. A.C. Paulk: None. S.S. Cash: None. S. Ben-Haim: None. S. Dayeh: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.23/WW11

Topic: J.04. Physiological Methods

Support: UG3NS123723

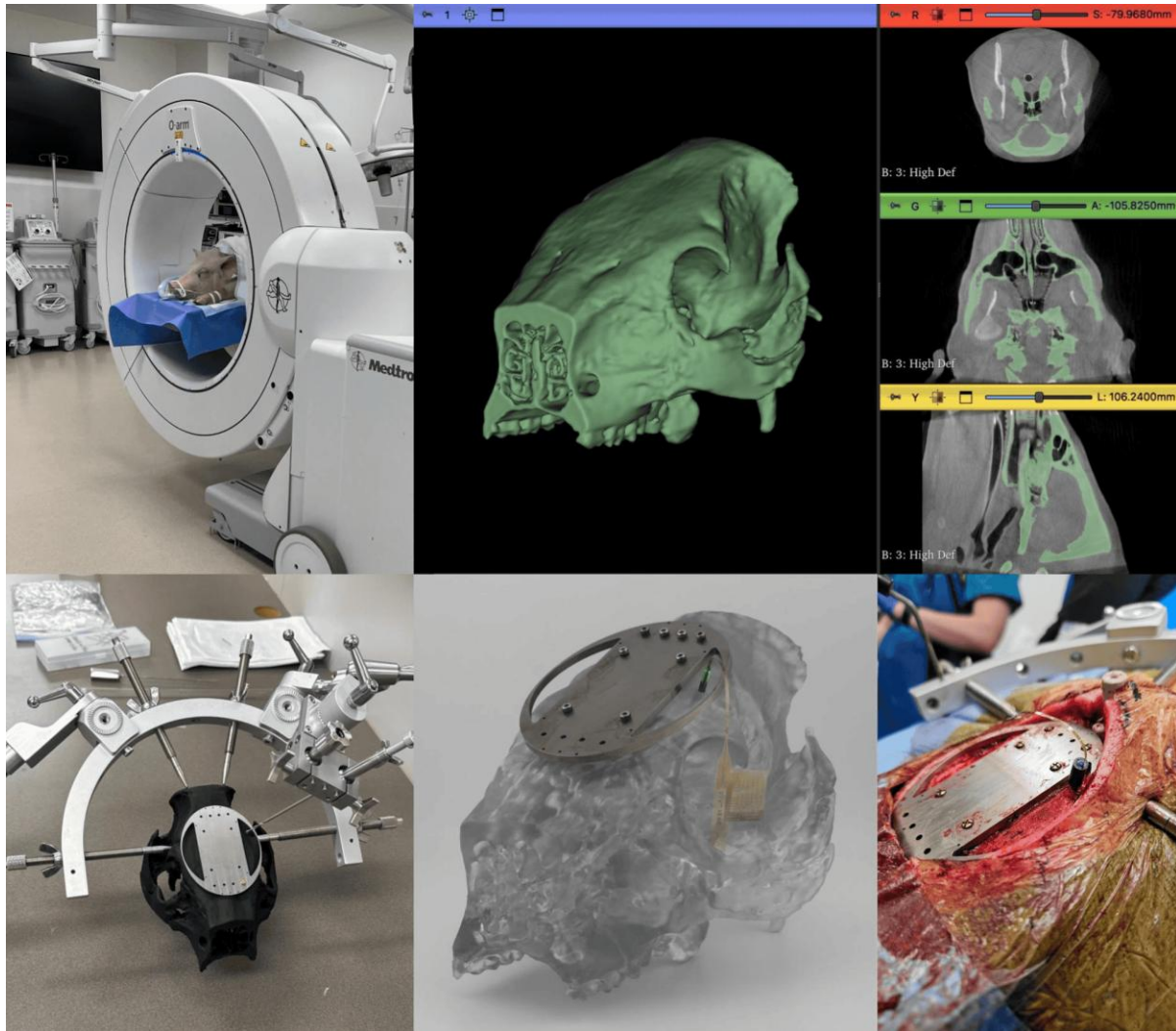
Title: Porcine cranium segmentation: utility of high-resolution 3D model in preoperative planning for novel surgical experiments

Authors: *H. SHIN¹, K. FORSETH², S. DAYEH³;

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Abstract: The pig is a well-established large-animal model in surgical training and translational research; in neurosurgery, pigs are instrumental for investigating neural circuits and developing brain machine interfaces. Our group is developing complex navigated depth electrode designs for next-generation thin-film microelectrodes with compact wireless transmission electronics. Robust cranium segmentation and multimodal 3D printing address the challenges of a novel surgical experiment with a practical subject-specific model, enabling visualization of critical anatomical landmarks and surgical system validation. A 74kg female Yorkshire pig underwent general anesthesia for CT (Medtronic O-arm) and MRI (GE 3T) imaging prior to a second staged implantation of novel electrophysiology system. Structural anatomical segmentations were derived (3D Slicer). Reconstructions were converted to STL meshes using marching cubes. G-code to produce components were optimized for curvature orientation, density, and efficiency, utilizing fused deposition modeling (Prusa MK4) and stereolithography resin (Formlabs Form 4). The tissue and hardware models enabled complete system tests prior to implementation in live animal models. The full surgical set comprised pin fixation, custom neuronavigation platform, depth electrode placement system, microelectrodes with headstage amplifiers, transmission board, and titanium baseplate with an accompanying headcap. 3D printed components critically addressed the unique challenges of pin placement, cranial plate fixation, and inter-system compatibility. Resin printing was demonstrably superior in both print speed (5 vs 26 hours for skull model) and resolution (0.025 vs 0.6mm layer height) resulting in exceptional organic detail and anatomic fidelity. High resolution multimodal imaging, modeling, and 3D printing were

essential for the safe and efficient design of this novel complex system for successful implantation in a large animal survival model.



Disclosures: H. Shin: None. K. Forseth: None. S. Dayeh: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.24/WW12

Topic: J.04. Physiological Methods

Support: This research was part of Project NAFAS, a tender awarded to Zander Labs by the German federal agency Agentur für Innovation in der Cybersicherheit - "Innovation for Cybersecurity".

Title: Flex-printed electrodes for mobile EEG applications

Authors: S. APPELHOFF¹, M. MOUSAVI¹, O. ZLATOV¹, P. SHARMA¹, E. QUIPEL¹, B. KORKA¹, W. PÄTZOLD², J. SCANLON², C. DA SILVA SOUTO², A. H. WINNEKE², K. WOLF², S. DEBENER³, *T. ZANDER¹, J. WAGNER¹, **M. PESCH**¹, L. R. KROL¹;
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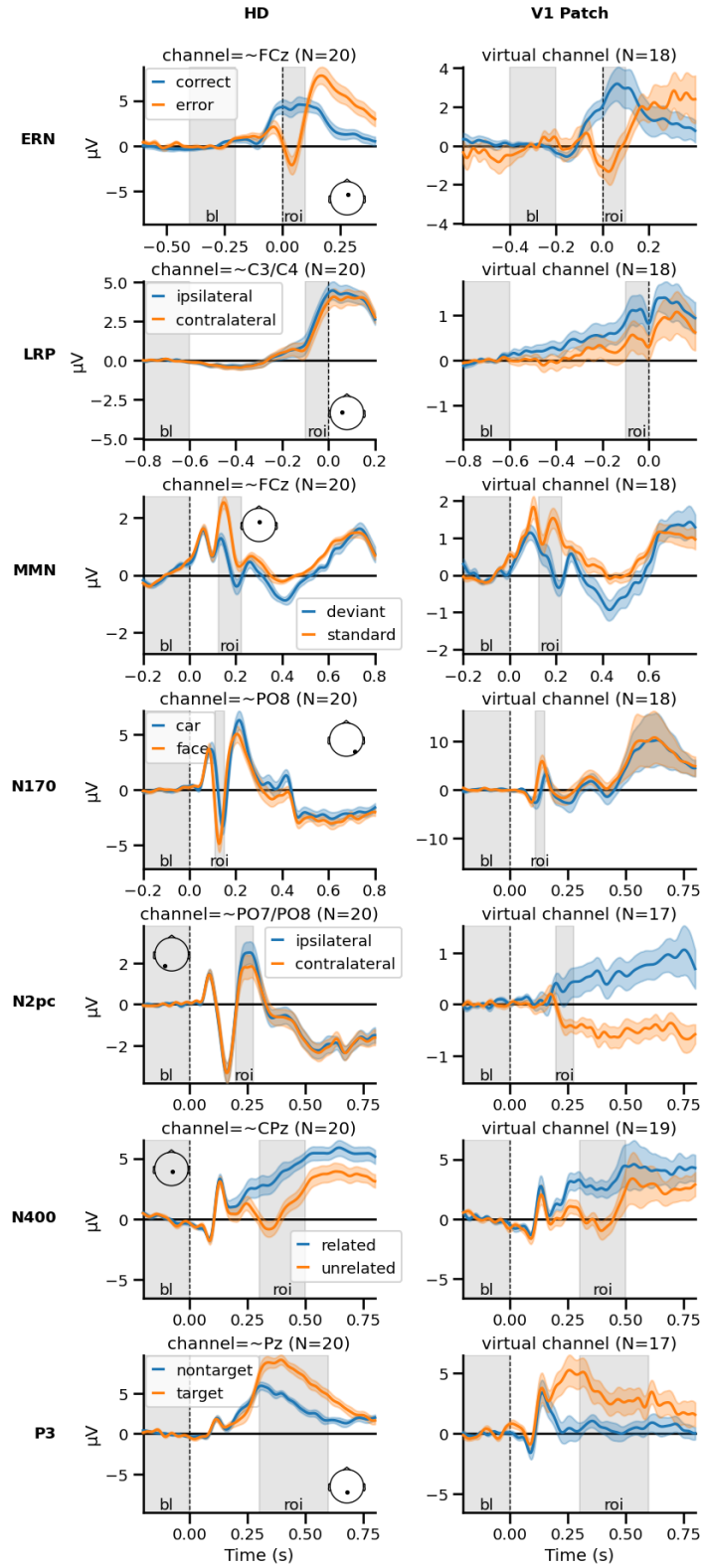
Abstract: EEG is one of the most widely deployed brain monitoring techniques for both research and clinical purposes, but the relatively bulky sensors, which require expert training to apply, still hinder deployment and limit the technique's wider uptake. We developed a printed electrode system that is lightweight, nearly imperceptible to the wearer, and provides high signal quality.

Our electrode system consists of printed Ag/AgCl sensors on a carrier of thermoplastic polyurethane, compatible with different contact materials between sensor and skin. The tests reported here used electrolyte gel. The printed design results in a patch less than .25 mm thick that is laid across the skin, and remains in place due to an additional adhesive layer. One patch has 4 periauricular sensors, 1 near the eye, and 5 on the forehead. Separate left and right patches allow uni- and bilateral use for different use cases. The right preauricular sensor served as ground.

We recorded bilateral data from 19 participants using the ERP CORE paradigms, and compared the brain responses to data recorded using state-of-the-art research-grade electrodes. We also surveyed participant comfort.

Differences in coverage precluded a direct comparison to the scalp electrodes. Instead, we projected the channel-time data for each participant and task onto a virtual channel using the first PCA component, which was calculated from the grand average ERP difference wave for each task, after data cleaning using independent component pruning. To investigate class separability, a Wilcoxon rank-sum test was performed across participants on mean amplitudes within the ROI. Patch data accurately showed all seven brain responses elicited by the ERP CORE. All ERPs showed statistically significant separation between classes within the respective ROI (all $p < 0.005$), even for the most distant cases, i.e. the parieto-occipital N170 and N2pc. Participants reported the patch to be nearly imperceptible once applied.

Results indicate the feasibility of printed electrode systems to provide comfortable, mobile EEG of high quality.



Disclosures: S. Appelhoff: None. M. Mousavi: None. O. Zlatov: None. P. Sharma: None. E. Quispel: None. B. Korka: None. W. Pätzold: None. J. Scanlon: None. C. da Silva Souto: None. A.H. Winneke: None. K. Wolf: None. S. Debener: None. T. Zander: None. J. Wagner: None. M. Pesch: None. L.R. Krol: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

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Program #/Poster #: PSTR196.25/WW13

Topic: J.04. Physiological Methods

Support: ERC Consolidator Award 818179
SNSF CRSII5_198739/1
Internal ETH Funds

Title: Magnetic resonance identification tags for ultraflexible electrodes

Authors: *E. ÖZIL¹, P. GOMBKOTO¹, A. APOSTOLELLI^{1,2}, T. YASAR¹, A. VAVLADELI^{1,3}, M. MARKS^{1,5}, W. VON DER BEHRENS^{1,4}, M. F. YANIK¹;
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Abstract: Ultra-flexible electrodes, due to their superior biocompatibility, are likely to lead the future of neuroprosthetics. However, identifying the locations of high-density ultra-flexible electrodes in the brain for accurately assigning neural signals to specific structures remains a major challenge. To address this, we developed magnetic resonance identification (MRID) -tags. Each ultra-flexible electrode bundle carries an MRID-tag with unique barcode patterns visible in MRI (MRI-barcode) for identification of the bundle and the anatomical positions of individual electrodes. We generate the MRI-barcode by patterning superparamagnetic iron-oxide nanoparticles into electrode fibers (10µm²) with dot-matrix nanoparticle coating technique. We chronically tested MRID-tagged ultra-flexible electrodes *in vivo* in the dorsal hippocampus of freely-moving rats (n=3), where distinct electrophysiological landmarks validated our electrode localization results. We were able to localize individual electrodes with a mean accuracy of 83 µm. MRID-tagged ultra-flexible electrodes demonstrated months-long recording stability with mean single-unit signal-to-noise ratios as high as 20.

Disclosures: E. Özil: None. P. Gombkoto: None. A. Apostolelli: None. T. Yasar: None. A. Vavladeli: None. M. Marks: None. W. Von Der Behrens: None. M.F. Yanik: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.26/WW14

Topic: J.04. Physiological Methods

Support: ETH Zurich, internal funds
ERC Horizon 2020 Grant Nr. 818719
SNSF Sinergia Project CRSII5_198739/1
UZH Forschungskredit FK19-041

Title: Ultra-flexible tentacle electrodes (UFTEs) provide large-scale recordings for months-long tracking of neuronal ensembles spanning multiple brain areas and are adaptable to rodent, non-human primate and human brains

Authors: *T. YASAR¹, P. GOMBKOTO², E. ÖZIL², A. L. VYSSOTSKI², A. VAVLADELI^{2,3}, C. M. LEWIS³, F. HELMCHEN³, W. VON DER BEHRENS², M. F. YANIK²;
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Abstract: Large-scale stiff electrode arrays enable reading out the activity of large populations of neurons, but they induce chronic inflammation in the brain and a decline in signal quality. On the other hand, existing flexible electrode arrays have limitations on how reliably they can be inserted into any targeted depth in the brain with minimal tissue damage while maintaining a high density of recording channels. To address these problems, we developed Ultra-Flexible Tentacle Electrodes (UFTE), where each recording channel is mechanically independent to provide maximal compliance with the brain tissue while packing many channels in the smallest possible footprint. Unlike existing fiber-based ultra-flexible electrodes, UFTEs can be implanted at a low speed of 12.5 $\mu\text{m/s}$ without any limitations in implantation depth, thanks to our novel insertion strategy that combines mechanical and chemical tethering. We also devised a modular scheme to implant UFTEs simultaneously into many brain areas at up to 8 arbitrary insertion locations without angle-of-insertion limitations, with up to 512 channels. Signal-to-noise ratios of spikes recorded by UFTEs were 1.5- 3x compared to the state-of-the-art. In freely moving rats, we achieved simultaneous recordings of stable single-unit activity from the medial prefrontal cortex, retrosplenial cortex, and hippocampus while tracking some units for up to 3.5 months. Immunostaining of brain slices revealed no detectable chronic damage caused by the electrodes to the surrounding brain tissue. We tracked inter- and intra-areal neuronal ensembles simultaneously from the hippocampus, retrosplenial cortex, and medial prefrontal cortex, which led to the identification of two distinct classes of neuronal ensembles based on their lifetimes and tuning to sharp wave ripples. In addition to the large-scale multi-area recordings from rats, UFTEs are also suitable for smaller-scale recordings from the mouse brain, where electrophysiological recordings can be combined with optical methods. We demonstrated that recording quality from the mouse hippocampus was stable for almost a year. We have also developed longer versions of UFTEs suitable for recordings in deep brain areas of non-human primates and acute intraoperative recordings in the human brain. We have demonstrated that the UFTEs can be sterilized with ethylene oxide for these purposes without compromising the

functionality of the electrodes. We are currently developing a prototype of the UFTEs for semi-chronic recordings in drug-resistant epilepsy patients and conducting further safety tests for such recordings.

Disclosures: T. Yasar: None. P. Gombkoto: None. E. Özil: None. A.L. Vyssotski: None. A. Vavladeli: None. C.M. Lewis: None. F. Helmchen: None. W. Von Der Behrens: None. M.F. Yanik: None.

Poster

PSTR196: Electrophysiology: Electrode Arrays I

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR196.27/WW15

Topic: J.04. Physiological Methods

Support: ChroMOS project (H2020-MSCA-IF-2019, GA 896996)
CrossBrain project (HORIZON-EIC-2021-
PATHFINDERCHALLENGES-01-02, GA 101070908)

Title: Advancing high-density chronic neural recordings with miniaturized ChroMOS probes and a closed-loop implantation strategy

Authors: *A. PERNA^{1,2}, G. ORBAN², C. STUBBENDORFF², M. VINCENZI², G. N. ANGOTZI², J. F. RIBEIRO², L. BERDONDINI²;

¹IIT, Genova, Italy; ²Microtechnology for Neuroelectronics (Nets3), Inst. Italiano di Tecnologia, Genova, Italy

Abstract: Achieving long-term continuous monitoring of high-quality neural signals at cellular resolution from numerous neurons is a significant challenge in neurotechnology. This challenge stems from the conflicting requirements of increasing the microelectrode count while simultaneously minimizing cross-sectional dimensions to reduce tissue damage and preserve long-term signal quality. To address this issue, we exploited the modularity and scalability of Simultaneous Active Pixel Sensor (SiNAPS) technology to drastically scale down the CMOS device cross-sectional dimensions (to 26 by 26 μm^2) while maintaining a high electrode count on such a narrow shank (64).

Here, we illustrate the chronic electrical interfacing performances of such miniaturized microwire-like device, referred to as ChroMOS probes, in comparison with larger (86 by 50 μm^2 cross section) SiNAPS 256 devices. The ChroMOS probes display a remarkable stability in signal quality over the six-months observation period, paving the way for their extensive use in chronic electrophysiology experiments. This excellent stability in signal quality is consistent with the quantification of foreign body reaction (FBR) at 1 month post implantation. A major factor leading to the excellent chronic performances of ChroMOS probes is the reduced magnitude of acute tissue damage they induce compared to larger devices. To further enhance this feature, we have recently devised a closed-loop implantation procedure which relies on

insertion force measurements to optimize speed during the different stages of implantation. This method is expected to enhance both the acute and the chronic performances of tissue penetrating neural probes and will be applied and validated in future experiments.

Disclosures: **A. Perna:** None. **G. Orban:** None. **C. Stubbendorff:** None. **M. Vincenzi:** None. **G.N. Angotzi:** A. Employment/Salary (full or part-time): Corticale Srl. **J.F. Ribeiro:** None. **L. Berdondini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Corticale Srl.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.01/WW16

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

Title: Neuromorphic Simulation of Drosophila Melanogaster Brain Connectome on Loihi 2

Authors: ***F. WANG**, W. SEVERA, B. H. THEILMAN, J. B. AIMONE, C. M. VINEYARD; Sandia Natl. Labs., Albuquerque, NM

Abstract: We demonstrate the first-ever nontrivial, biologically realistic connectome simulated on neuromorphic computing hardware. Specifically, we implement the whole-brain connectome of the adult *Drosophila melanogaster* (fruit fly) from the FlyWire Consortium containing 140K neurons and 50M synapses on the Intel Loihi 2 neuromorphic platform. This task is particularly challenging due to the characteristic connectivity structure of biological networks. Unlike artificial neural networks and most abstracted neural models, real biological circuits exhibit sparse, recurrent, and irregular connectivity that is poorly suited to conventional computing methods intended for dense linear algebra. Though neuromorphic hardware is architecturally better suited to discrete event-based biological communication, mapping the connectivity structure to frontier systems still faces challenges from low-level hardware constraints, such as fan-in and fan-out memory limitations. We describe solutions to these challenges that allow for the full FlyWire connectome to fit onto 12 chips of Loihi 2. We statistically validate our implementation by comparing network behavior across multiple reference simulations. Significantly, we achieve a neuromorphic implementation that is orders of magnitude faster than numerical simulations on conventional hardware, and we also find that performance advantages increase with sparser activity. These results affirm that today's scalable neuromorphic platforms are capable of implementing and accelerating biologically realistic models---a key enabling technology for advancing neuro-inspired AI and computational neuroscience.

Disclosures: **F. Wang:** None. **W. Severa:** None. **B.H. Theilman:** None. **J.B. Aimone:** None. **C.M. Vineyard:** None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.02/XX1

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

Title: In silico characterization of TrkB ligands: molecular docking to TrkB kinase domain

Authors: *C. CASTELLANOS CARRIZAL¹, V. ALATRISTE², L. MARTINEZ MENDIETA³, A. CARRASCO CARBALLO¹;

²Mol. and Cell Biol., ¹Benemérita Universidad Autónoma de Puebla, Puebla, Mexico;

³Benemérita Univ. Autónoma De Puebla, Puebla, Mexico

Abstract: The Tropomyosin receptor kinase B (TrkB) is a tyrosine kinase receptor involved in the development and the maturation of the central and peripheral nervous system through regulation of neuron survival, proliferation, migration, differentiation and synapse formation and plasticity. The neurotrophic activity from the activation of this receptor has been proven useful in a variety preclinical studies in animal models of neurodegenerative diseases. The endogenous ligand of TrkB is Brain Derived Neurotrophic Factor (BDNF), due to the peptide nature of BDNF, small molecule design TrkB agonists that cross blood brain barrier has been challenging, the exact nature in which agonists bind to the TrkB receptors is unknown and crystallization has only been reported with antagonists. In this work in silico study of the interaction of known ligands of TrkB and the design of new molecules based on known ligands was realized to characterize the interaction of small molecule ligands with TrkB and to propose effective pharmacophores for TrkB ligands. To this purpose the docking was performed on the Schrödinger platform. With the Protein Preparation Wizard tool, the crystallized structure of kinase domain of TrkB (PDB: 4AT4) was optimized to a physiological pH (pH=7.4). A database containing 41 ligands: 23 experimentally confirmed agonists, using 7,8-Dihydroxyflavone (PubChem CID: 1880) as reference, and 18 experimentally confirmed antagonists, using Entrectinib (PubChem CID: 25141092) and Larotrectinib (PubChem CID: 46188928) as reference, were loaded in LigPrep tool. From the results, the aminoacidic interactions and the interaction site between agonists and antagonists were analyzed, the effect of these interactions on the docking score of the ligands was also studied. From these results ligands with experimental reports on animal models and that had no violation of the Lipinsky and Veber's rule were selected, database, 6 molecules were selected (CID: 1880, 44610701, 71459675, 903, 2160, 133538), according to the previous results, in those 6 molecules a nitrogen or oxygen atom was inserted into their structure, or a primary amine or hydroxyl group were added into one site of their structure, with the objective of favoring the formation of hydrogen bonds which were observed to be related to an improved docking score. Molecules based on reported agonists with better docking scores were found and the differences in their aminoacidic interactions were analyzed. These results may be able to provide evidence for which types of interactions promote ligand interaction with the TrkB receptor.

Disclosures: C. Castellanos Carrizal: None. V. Alatrisme: None. L. Martinez Mendieta: None. A. Carrasco Carballo: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.03/XX2

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

Title: Towards multi-timescale neural dynamics inference

Authors: ***L. GONG**¹, Y. ZHANG², S. SAXENA³;

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Abstract: Neural dynamics span multiple temporal scales, from milliseconds to minutes. Traditionally, timescales in neural time series are estimated by fitting autocorrelation functions, but this approach often underestimates the true temporal structure of the data. More recently, researchers have turned to generative modeling, which uses statistical properties like autocorrelation and power spectral density to provide better estimates. However, these approaches are generally limited to analyzing simple, single time series and fail to capture the latent processes that drive neural activity. On the other hand, current approaches to inferring latent neural dynamics rely on dynamical models like linear dynamical systems (LDS) and recurrent neural networks (RNNs). While these models are effective in capturing certain aspects of neural activity, they often overlook the presence of diverse timescales, which limits interpretability and model accuracy. To address these challenges, we developed a new framework that enables efficient inference and learning of latent multi-timescale neural systems directly from neural recordings. Our framework models latent dynamics using enhanced LDSs with explicit timescale separations for different latent variables. We employ a variational inference technique that simultaneously estimates latent trajectories and learns model parameters by jointly optimizing the evidence lower bound and the match between the autocorrelation of predicted and observed data. This approach is validated on both synthetic and real neural datasets. First, we generated synthetic time series by combining multiple Ornstein-Uhlenbeck (OU) processes with distinct decay parameters representing different timescales. By applying our approach, we successfully recovered the ground-truth decay parameters and achieved high reconstruction accuracy, enabling detailed analysis of the latent dynamics. Next, we applied our method to publicly available spike data from the visual area V4 of a monkey during a fixation task. The inferred timescale parameters aligned closely with those obtained from other estimation methods, demonstrating the effectiveness of our approach. In the future, we will extend this framework to handle switching dynamics and nonlinearities, enabling adaptive inference of changing timescale structures in large-scale neural recordings. We will also integrate our approach with task-specific behavioral data to gain deeper insights into how multi-timescale neural dynamics evolve across different cognitive states.

Disclosures: **L. Gong:** None. **Y. Zhang:** None. **S. Saxena:** None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.04/XX3

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

Title: Voyagers in the Veins: Steering Microrobotics Spacecraft Through the Brain's Vasculature

Authors: *N. H. NGUYEN¹, Y. WANG²;

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Abstract: Efficient delivery of therapeutic agents across the blood-brain barrier remains a challenge in treating neurological disorders. Nanoparticle systems show promise, but their reliance on passive diffusion limits targeting precision, systemic side effects, and limited therapeutic efficacy. Microrobots offer a transformative leap with active, steerable navigation and on-demand release. Yet, clinical translation is hindered by limited understanding of propulsion in complex vasculature, capillary-scale fabrication, and biocompatibility concerns. To address these challenges, we developed a magnetic microrobot platform optimized for brain-targeted delivery using high-resolution digital light processing printing of hydrogel structures coated with iron oxide for magnetic actuation. Computational fluid dynamics (CFD) simulations incorporating patient-inspired vasculature, non-Newtonian viscosity, and rotating magnetic fields guided microrobot geometry and motion optimization. The system integrates a magnetic field setup with cerebral-mimicking microfluidic channels to study real-time navigation under physiological flows. Results revealed a complex interplay between geometry, magnetic actuation, and flow environment. In straight channels, varying pitch (0.85-2.85 mm) and major radius (0.85-1.25 mm) showed that under passive flow, high-pitch helices (2.85 mm/turn) aligned with streamlines, while low-pitch variants (<1.85 mm/turn) tumbled, revealing a trade-off between stability and maneuverability. Under active actuation, long-pitch helices (≥ 2.85 mm/turn) and smaller radii (0.85 mm) exhibited superior propulsion: up to 104% higher axial velocity and 1.42 times lower lateral deviation compared to the largest radius robot. The 0.85 mm design achieved peak speeds of 79.4 mm/s with 0.075 mm lateral wobble, outperforming 1.05 mm (62.81 mm/s, 0.101 mm) and 1.25 mm (38.8 mm/s, 0.107 mm) variants. CFD contours confirmed that smaller robots minimized transverse drag and enhanced magnetic alignment, while larger ones induced greater shear and recirculation zones that reduce axial speed and increase wobbling. At bifurcations, steering was maximized by combining high-pitch, multi-turn geometries for directional commitment, while small radii reduced resistance at entry points. Active control enabled consistent navigation into targeted branches, even against flow gradients, by tuning magnetic bias and robot design. These findings demonstrate that CFD-guided, magnetic microrobots can be engineered to navigate complex vasculatures, offering a viable platform for precise brain therapeutic delivery.

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Poster

PSTR197: Computational Approaches and Experimental Analyses II

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Program #/Poster #: PSTR197.05/XX4

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

Support: UMMS Research Scout Award
Alfred P. Sloan Research Fellowship
R01DK129366
University of Michigan/Start Up Funds

Title: Real-time Bayesian optimization system for efficiently characterizing multidimensional neural responses

Authors: *P. WU¹, A. SHANKAR², A. CHIU³, M. SHAHAB⁴, C. BURGESS⁵, E. SAVIER⁴, A. DRAELOS^{2,1};

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Abstract: A fundamental goal in neuroscience is to understand the relationship between sensory stimuli and neural responses (Dmochowski, 2016). Characterizing neural responses across multiple dimensions of visual stimuli - such as direction of motion, contrast and size - is essential for understanding complex sensory processing (Yerxa, 2020). Studying neural circuits under real-world conditions presents challenges due to large numbers of possible stimuli to present alongside in vivo experimental constraints. This presents a critical need for systems capable of adaptively selecting a manageable subset of stimuli in high dimensional parameter spaces, while also using real-time analyses to calculate neural responses to these stimuli. Such systems must be flexible enough to learn and identify neural tuning curves across various experimental platforms, brain regions, and behavioral conditions.

We developed an efficient system that integrates streaming modeling with experimental setups to capture and analyze neural responses in high-dimensional visual environments in vivo. This system uses improv (Draelos, 2021) to manage the real-time experimental workflow and connects analysis workstations with 2-photon calcium fluorescence microscopes (Bruker or Scanbox). To resolve the coding language discrepancy between Scanbox (MATLAB) and our algorithm (Python), we developed a data transfer method utilizing an existing rolling-average Scanbox plugin and the ZMQ library. Our system is capable of grabbing raw microscopic images (up to 30 Hz) and channeling them into downstream analysis pipelines, entirely managed by improv. We employed Bayesian optimization with Gaussian Processes and multidimensional kernels to identify stimuli predicted to maximize neural responses, all within ~40 milliseconds. The system built priors and hyperparameters from initial neural responses, then efficiently explored a four-dimensional stimulus space (angular direction of motion, speed, size, and number of objects). We tested the system in the mouse visual cortex, using two calcium indicators (GCaMP6s and 6f) and four C57B6 mice. It successfully characterized neural

responses across the visual space, adaptively selecting fewer than 50 stimuli to display (~5% of the possible 960). Preliminary results revealed how directional tuning can be simultaneously modulated by stimulus size and speed, interactions that would have been missed without such multi-dimensional sampling. With efficient real-time identification of neural tuning peaks in vivo, we aim to better characterize neural tuning properties by improving its robustness to noise and diverse tuning curve types.

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Poster

PSTR197: Computational Approaches and Experimental Analyses II

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Program #/Poster #: PSTR197.06/XX5

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

Support: R01-EY036594
P30 EY000331

Title: Designing RGC-specific stimuli with convolutional neural networks

Authors: *N. GHAZAVI¹, V. RAVAL⁴, S. IDREES^{7,8}, M. B. MANOOKIN⁵, F. M. RIEKE⁶, J. ZYLBERBERG^{9,2}, G. D. FIELD³;

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Abstract: The process of visual feature extraction originates in the retina, where the retinal ganglion cells (RGCs) extract features of visual scenes such as contrast, motion, and color, and transmit this information to the rest of the brain for further processing. As visual perception is the result of output from different RGC types, the ability to selectively activate or silence their activity would help determine how each RGC type contributes to perception. Simple artificial stimuli, such as bars, spots, gratings or checkerboard noise have been primarily used to identify how different RGC types encode different aspects of scenes. However, the presence of nonlinearities at each stage of retinal processing makes it challenging to generalize from these simple stimuli to more naturalistic ones. Our long-term goal is to understand how each RGC type contributes to perception by modifying the visual stimulus to activate or silence the activity of individual RGCs without affecting others under more naturalistic conditions.

RGC responses from ON and OFF parasol and midget cells from primate retina were collected using large-scale multielectrode arrays. We trained a deep convolutional neural network (CNN) to reproduce the responses of collections of RGCs to natural images with superimposed eye movements. In general, a visual stimulus will activate many RGC types. We used the CNN to

identify stimulus modifications that could silence or enhance the activity of individual RGCs or small collections of RGCs of a given type, while minimally altering the firing rates of other nearby RGCs. The CNN was capable of identifying stimulus modifications that were effective at suppressing the activity of small numbers of model RGCs while minimally perturbing the predicted firing rate of other model RGCs nearby. Our results demonstrate the feasibility of creating stimuli that can selectively stimulate or suppress a specific RGC type without affecting others. The future direction for validating this approach involves conducting closed-loop experiments with various RGC types, where we dynamically adjust the stimulus in real-time. This method eliminates the need for invasive inactivation techniques and allows for more controlled studies of neural function and/or human psychophysics.

Disclosures: N. Ghazavi: None. S. Idrees: None. M.B. Manookin: None. J. Zylberberg: None. G.D. Field: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

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Program #/Poster #: PSTR197.07/XX6

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

Title: Latent origins of information-limiting noise correlations

Authors: *F. DINC¹, C. FENG³, P. YUAN³, N. MIOLANE²;

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Abstract: Noise correlations have long been implicated in limiting the information that can be extracted from large populations of neurons. Earlier work has shown that the information-limiting components of noise correlation matrices are low-rank, but a fundamental question remains: if higher-dimensional, less noisy modes exist, why is information not encoded there? Here, we introduce a unifying framework grounded in noisy latent processing units, low-dimensional dynamical systems embedded in high-dimensional neural activity. We show that both correlated noise in neural activities and saturation of information readily available in neural populations can arise naturally from random noise accumulated in the latent units. Our framework resolves the dimensionality puzzle by demonstrating that low-dimensional latent dynamics necessarily produce low-rank noise correlation matrices. Moreover, even in the absence of shared inputs, correlated noise arises because latent variables integrate random fluctuations from individual neurons and feed them back through shared embeddings, entangling otherwise independent noise sources. This raises a fundamental tension: how can noisy latent variables support computation? We show that noise in latent variables accumulates over time but is normalized by the number of neurons. Thus, larger populations enable longer timescales for accurate latent computation before noise dominates. Using this theory, we provide a theoretical formula for computing the instantaneous noise added to specific neural subspaces, offering

theoretical tools to uncover emergent noise-suppression mechanisms in latent dynamics. We also derive an exact expression for the linear Fisher information recoverable from any neural subpopulation, generalizing prior theoretical work from binary classifications to regression on continuous variables. Overall, our findings offer a mechanistic explanation for information-limiting correlations in networks with low-dimensional population codes: they arise from random noise accumulated in latent variables, which also constrains the timescale of neural computations.

Disclosures: F. Dinc: None. C. Feng: None. P. Yuan: None. N. Miolane: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.08/XX7

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

Support: Neurtext Brain Research Institute

Title: Effect size and statistical power to evaluate spike sorting algorithms

Authors: *P. N. STEINMETZ¹, J. T. WIXTED²;

¹NeurTex Brain Res. Inst., Dallas, TX; ²Psychology, UC San Diego, La Jolla, CA

Abstract: Traditional measures of spike sorting quality attempt to separate similar waveform shapes and produce spike times that comply with known neurophysiological constraints. However, in most experiments, spike sorting is just one step in the identification of putative neural responses to stimuli. Both the presence and the magnitude of the identified responses may also depend on the particular spike sorting algorithm used. Here we use the measured effect size and statistical power to detect a neural response in simulated experiments to evaluate the quality of—and to better understand—one spike sorting algorithm.

We simulated neural responses (25% increase in background firing rate of 2.5 sp/s) of a single neuron firing in the presence of typical background activity and noise (colored noise, 5 μ V sd in 300-3000 Hz passband) during a visual categorization experiment (792 1 second trials with 198 responses). The spike waveform amplitude varied from 5-100 μ V. The detection threshold was varied between 1.8-5.2 X the sd in the passband. Using the BML technique for spike detection and sorting, we computed the effect size and statistical power of a one-way ANOVA of the spike times to detect the presence of a response to visual categories.

In general, increasing the spike amplitude increased the observed effect size, as expected.

However, for larger threshold multipliers (>3.6), increasing the spike amplitude beyond 35 μ V counterintuitively _decreased_ the observed effect size. Detailed examination of the spike counts showed that this pattern was due to a combination of interacting factors: an overall decrease in spike counts as the threshold multiplier increased and an increase in detection of false positives as the amplitude is increased. Changes in statistical power to detect an effect of stimulus

categories parallel those of effect size.

Changes in power and effect size can significantly influence the conclusions drawn from an experiment comparing responses between brain areas or between experimental conditions. Thus, examining the overall process of detecting neural responses, including variations of effect size and power of spike sorting, is a critical step when evaluating both neural responses and spike sorting techniques.

Disclosures: P.N. Steinmetz: None. J.T. Wixted: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.09/XX8

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

Title: Automated spike sorting pipeline for long-term freely moving electrophysiology recordings

Authors: *J. SHEPPARD, J. VOIGTS;
HHMI Janelia Res. Campus, Ashburn, VA

Abstract: Processing and curating electrophysiology data for spike sorting is crucial for understanding and developing neuroscience experiments in real-time. As the field increasingly adopts long-term and freely-moving paradigms, this challenge is amplified since current methodologies are not adequately adapted to the higher prevalence of artifacts these experimental conditions and are not well set up for processing large continuous recordings. Here we introduce a fully automated pipeline, based on combining Kilosort 4.0, unit heuristics from SpikeInterface, and curation tools like UnitMatch, Bombcell and UnitRefine designed to process raw electrophysiology data, spike sort the data, and automatically curate those resultant units. This workflow addresses complexities associated with freely moving behaviors, including artifacts from chewing, grooming, and general anomalies inherent in unstructured environments, while also being capable of handling longer recordings. This pipeline has been successfully implemented on multiple eight-hour datasets acquired from freely moving mice implanted with Neuropixels probes. Our pipeline provides a quick, user-friendly approach to spike sorting in a complex environment.

Disclosures: J. Sheppard: None. J. Voigts: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.10/XX9

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

Title: Peak to noise ratios indicate spike sorting quality

Authors: P. N. STEINMETZ¹, *J. T. WIXTED²;

¹NeurTex Brain Res. Inst., Dallas, TX; ²UC San Diego, La Jolla, CA

Abstract: The large height of an extracellular waveform relative to background noise is a primary indicator of isolating putative single neuron activity in microwire recordings. The ratio of peak height to the noise (PNR) is one of two components of the classic signal to noise ratio (SNR) in statistical signal processing. In intracranial microwire recordings, a variety of definitions of PNR have incorporated different numerators and denominators. Here, we provide standardized definitions and compare the values of these ratios to the false discovery rate in spike sorting of simulated recordings.

We simulated single neuron firing in the presence of typical background activity and noise (colored noise, 5 μ V sd in 300-3000 Hz passband) during a visual categorization experiment (792 1 second trials with 198 neural responses). The spike waveform amplitude varied from 5-100 μ V. The detection threshold was varied between 1.8-5.2X the sd in the passband. We performed spike detection and sorting with one commonly used technique and then computed the rate of correct identification of simulated spike times (hits) and false positive spike times (FP) for each sorted spike cluster in each simulation. Five previously used definitions of PNR (PNR1-PNR5) were computed and compared.

The different definitions of PNR resulted in mean values ranging from 1.2 to 33.0; thus the different definitions are not directly comparable. The mean false discovery rate (FDR) was near 1.0 for PNRs near 0 and trended downward as PNR increased. The highest FDR at the mean PNR, 0.64, was for PNR1 = height of the mean waveform above the first sample of the waveform / std of the last 8 samples. The lowest FDR at the mean PNR, 0.26, was for PNR5 = height of the mean waveform above the first sample of the waveform / std of the first sample. In most cases the false discovery rate remained above 25% for average achieved PNRs in these simulated recordings.

Overall, these simulations show that the PNR of recorded spike waveforms can be a useful indicator of spike sorting quality and that, for the typical range of PNR in these recordings, the false discovery rates are likely to be substantial.

Disclosures: P.N. Steinmetz: None. J.T. Wixted: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.11/XX10

Topic: G.07. Biological Rhythms and Sleep

Title: Automated Spike Curation after Kilosort

Authors: *D. ZUTSHI¹, D. KIM², J. HARTNER⁴, D. KIRCA⁵, B. O. WATSON³;

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Abstract: Automated spike sorting algorithms have revolutionized the way neuronal activity is extracted from extracellular recordings, yet they remain far from perfect. Issues such as oversplitting, overmerging, and misclassification of noisy units often leave researchers with clusters that require extensive manual curation, an essential but subjective and time-consuming process. In an era of high-density probes like Neuropixels, where an hour of data can exceed 80 GB, manual curation is no longer scalable. Here, we developed a semi-automated curation pipeline designed to bridge the gap between fully automated sorting and expert-quality labeling. Our algorithm assigns clusters into standardized labels: Low Firing Rate, Noise, Multi-Unit Activity (MUA), and Good Units. To benchmark, we compared the outputs of our algorithm to expert-labelings curated in Phy by two expert users across three recordings. Our algorithm achieved an average of 93.93% accuracy vs. experts & 87.26% F1 score in classifying Single Units. It achieved an accuracy of 94.2% & 85.13% F1 score in full-category agreement (SU, MUA, Noise), and 94.84% accuracy & 88.78% F1 score in distinguishing Neuronal vs. Non-Neuronal units.

Our method utilizes a combination of spike timing metrics (including firing rate and the central-to-shoulder bin ratio in the autocorrelogram) and waveform-based physiological features such as peak amplitude, slopes, half-width, and inter-channel correlation. Based on these features, clusters are assigned standardized labels (good, noise, multi-unit activity) that can be imported directly into Phy, where they serve as curation aids rather than absolute classifications, supporting but not replacing expert judgment.

To further improve cluster quality, we introduce a novel "split-merge-split sandwich" strategy to iteratively refine unit quality, leveraging KlustaKwik-based re-clustering (split) and similarity-guided merges. Our approach seeks to speed up curation, reduce the cognitive load on human curators, improve reproducibility, and pave the way for more objective cluster labeling in large-scale neural recordings. Finally, by ensuring clean and accurate unit isolation, we enable robust downstream analyses such as neural decoding and longitudinal tracking of neuron identity.

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Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.12/XX11

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

Title: Towards label-free prediction of protein channels from structural signals in lightsheet microscopy using a cloud-based workflow

Authors: *C. LAITON, C. BERRY, E. WIRSCHING, J. KELLY, Y. LIU, T. WANG, K. SVOBODA, D. FENG, S. SESHAMANI;
Allen Inst., Seattle, WA

Abstract: Selective Plane Illumination Microscopy (SPIM) enables high-resolution imaging of cleared tissues at whole-organ scales, making it a valuable platform for spatial proteomics. By capturing fluorescently labeled proteins across entire tissues, SPIM generates rich, terabyte-scale datasets. However, the increasing throughput of modern imaging systems has outpaced traditional data processing capabilities. These massive datasets introduce computational challenges in areas such as image correction, stitching, storage infrastructure, and downstream analysis, including protein distribution prediction. Furthermore, antibody labeling remains time-consuming and labor-intensive, limiting the scalability of large-scale experiments. To address these challenges, computational prediction of protein localization enables high-throughput proteomic analysis. Label-free deep learning approaches relying solely on structural signals from generic pan-protein stains can infer spatial distributions of multiple protein markers without antibody labeling. Our method adopts a two-stage approach: first, we leverage masked autoencoders (MAEs) to learn meaningful, high-level semantic representations without labeled data. In the second stage, these features are integrated into an image-to-image translation framework trained on real, paired datasets of structural stains and protein markers. This allows accurate inference of protein localization across diverse markers from structural images alone. This approach provides rich, context-aware representations of subcellular structures, facilitating identification of cell type characteristics. This accelerates large-scale data analysis enabling the discovery of spatial patterns and cellular phenotypes often overlooked with traditional methods. We present a scalable, cloud-based image processing pipeline for large-scale spatial proteomics datasets. The pipeline integrates open-source tools and cloud infrastructure to efficiently store and process large volumetric data. Key steps include: 1) Metadata generation, image compression, and fast upload to Amazon Web Services; 2) Optical correction, including radial and camera-based adjustments; 3) Tile stitching to produce seamless 3D reconstructions; 4) Prediction of protein markers. Outputs are accessible through Neuroglancer links, enabling easy data exploration. The pipeline is implemented using Nextflow within the Code Ocean platform, and all raw data, code, and results are openly available. This approach supports FAIR, open, and reproducible science, providing a valuable resource for the broader research community.

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Poster

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Program #/Poster #: PSTR197.13/XX12

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

Support: NSFC (82371525)

Title: Dsct: a novel deep learning framework for rapid and accurate spatial transcriptomic cell typing

Authors: *Y. XU;
Zhejiang Univ., Hangzhou, China

Abstract: Unraveling the complex cell-type composition and gene expression patterns at the cellular spatial resolution is crucial for understanding intricate cell functions in the brain. In this study, we developed Deep Neural Network-based Spatial Cell Typing (DSCT), an innovative framework for spatial cell typing within spatial transcriptomic datasets. This approach utilizes a synergistic integration of an enhanced gene selection strategy and a lightweight deep neural network for data training, offering a more rapid and accurate solution for the analysis of spatial transcriptomic data. Based on comprehensive analysis, DSCT achieved exceptional accuracy in cell-type identification across various brain regions, species, and spatial transcriptomic platforms. It also performed well in mapping finer cell types, thereby showcasing its versatility and adaptability across diverse datasets. Strikingly, DSCT exhibited high efficiency and remarkable processing speed, with fewer computational resource demands. As such, this novel approach opens new avenues for exploring the spatial organization of cell types and gene expression patterns, advancing our understanding of biological functions and pathologies within the nervous system.

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Poster

PSTR197: Computational Approaches and Experimental Analyses II

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Program #/Poster #: PSTR197.14/YY1

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

Support: Simons Foundation Pilot Extension Award - 00003245
NSF EFRI 2223822

Title: Coupled Transformer Autoencoder for Disentangling Multi-Region Neural Latent Dynamics

Authors: *R. SRISTI¹, S. NARASIMHA², J. HUANG¹, V. GILJA¹, G. MISHNE³;
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Abstract: Simultaneous large-scale multielectrode recordings (e.g., Neuropixels probes) from thousands of neurons across multiple brain areas reveal rich mixtures of activity that are shared

between regions and dynamics that are unique to each region. When analyzing such datasets, existing alignment or multi-view methods neglect temporal structure, whereas dynamical latent-variable models capture temporal dependencies but are usually restricted to a single area or conflate shared and private signals. We introduce *Coupled Transformer Autoencoder (CTAE)*—an end-to-end sequence model designed to uncover latent population dynamics while simultaneously addressing (i) non-stationary, non-linear dynamics and (ii) separation of shared versus region-specific structure. CTAE employs Transformer encoders and decoders to capture long-range neural dynamics, and explicitly partitions each region’s latent space into orthogonal shared and private subspaces through reconstruction, alignment, and orthogonality losses, and scales to many brain regions without a parameter explosion. We demonstrate the effectiveness of CTAE on two high-density electrophysiology datasets of simultaneous recordings from multiple regions, one from motor cortical areas-dorsal premotor cortex (PMd) and primary motor cortex (M1)-and the other from sensory areas-primary (V1) and secondary (V2) visual cortices. In the PMd-M1 motor dataset (Perich et al.), CTAE identifies a communication subspace that captures almost all reach-related variance: linear decoders trained on CTAE’s shared latents predict hand kinematics more accurately than decoders trained on shared latents extracted by prior methods or on the raw spike data. In V1-V2 recordings of drifting gratings (Semedo et al.), a linear classifier achieves high orientation-decoding accuracy using CTAE latents. The model captures direction-relevant information in both shared and private subspaces, reproduces the expected periodicity of grating responses—most strongly in V1-private latents—and avoids the tendency of existing techniques to concentrate all behaviourally relevant variance in a single shared space. By providing a simple and scalable computational tool, CTAE offers an interpretable representation for dissecting how multiple brain areas interact through shared and private latent factors to modulate behavior. Each factor may serve as a potential target for causal manipulation in closed-loop perturbation experiments.

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Poster

PSTR197: Computational Approaches and Experimental Analyses II

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Program #/Poster #: PSTR197.15/YY2

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

Title: Bracket-based neural coding: a hybrid framework integrating rate and temporal information in cortical circuits

Authors: *T. SAMIEI¹, E. ZAGHA³, E. NOZARI²;

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Abstract: Despite long-standing debate over how the brain balances rate and temporal coding, the mechanisms by which these schemes integrate during sensory processing remain unclear. Here, we report fast-switching integration of rate and temporal coding in the visual cortex of mice viewing static images. Using Neuropixels recordings of n=9 mice from the Allen Institute Visual Coding dataset and a custom decoding pipeline for high-dimensional single-unit data, we found that neural encoding of visual stimuli is not continuous but segmented into distinct “brackets” that tile each trial. Within each bracket, information is encoded primarily via stable firing rates (within-bracket rate coding), enabling robust decoding via averaging. Brackets are separated by precisely timed boundaries, suggesting an additional layer of information conveyed through temporal precision (between-bracket temporal coding). The sequence of these brackets creates an oscillatory, mesoscale temporal structure, yielding a new hybrid coding framework. To validate bracket segmentation, we compared real data against shuffled surrogates across nine nonoverlapping image-class sets. Bracket boundaries in real data were significantly consistent across sets ($p < 0.05$, randomization test), whereas shuffled data showed no such consistency. Systematic randomizations over time or space degraded boundary precision progressively, with complete loss of structure when both dimensions were randomized—demonstrating that precise temporal and spatial coordination is required to preserve bracket boundaries. To investigate the underlying mechanisms of bracket coding, we examined how different visual stimulus classes are represented over time. Each stimulus class exhibited a unique temporal pattern, suggesting a multiplexed coding scheme. We hypothesized that points of abrupt transition in class-specific patterns correspond to bracket boundaries, marking shifts in encoded information. Indeed, we observed a significant correlation between bracket boundaries and peaks in both the variance and local similarity of decoding accuracy (absent in shuffled data), underlining the temporal precision and coordination inherent in bracket coding. Overall, our findings provide strong evidence for a hybrid neural coding strategy in visual cortex—combining the reliability of rate coding with the temporal precision of synchronized spiking. This bracketed organization may reflect a general principle of cortical information processing and holds promise for improving decoding-based neurotechnologies such as brain-computer interfaces.

Disclosures: T. samiei: None. E. Zagha: None. E. Nozari: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.16/YY3

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

Support: NIH Grant MH133181
NIH Grant MH132940

Title: Convolutional Neural Network-based barcode assignment enables robust large-scale barcoded connectomics.

Authors: *A. ZHANG¹, S. KHEM⁴, M. RUE², X. CHEN³;

¹Brain Sci., Allen Inst., Issaquah, WA; ²Barcoded Connectomics, Allen Inst., Des Moines, WA;

³Allen Inst., Seattle, WA; ⁴Allen Inst. for Brain Sci., Seattle, WA

Abstract: BARseq is a high-throughput barcoded connectomics method that uses in situ sequencing of RNA barcodes to map neuronal projections with high throughput and associate projections with gene expression at cellular resolution. In a BARseq experiment, we sequence both endogenous genes and viral RNA barcodes in neuronal somas, and matching barcodes to those found in axons reveals the projections of individual neurons. Thus, associating barcodes with the correct soma is critical for accurately relating transcriptomic identities to projections. In an ideal scenario, RNA barcodes would fill the somas completely, and base calling the average sequencing signal across the somas would be sufficient to assign the barcode to the correct neuron. In practice, barcodes may not completely fill the somas in some cells, and/or barcodes from other neurons (e.g., a passing dendrite) may appear to overlap with the soma, causing errors in barcode assignment to cells. We previously solved this problem by manually filtering out cells with incorrect barcode assignments based on sequencing images, but this approach is not scalable to large datasets. To solve this problem, we trained a convolutional neural network model to distinguish somas with properly assigned barcodes versus incorrectly assigned barcodes based on images alone, using a set of 1,200 manually annotated somas as ground truth. Due to the limited size of the training data, we incorporated domain-specific knowledge in the preprocessing of image data to enable faster convergence and better performance. To validate the model's accuracy, we applied it to an axonal BARseq dataset with 128,746 barcoded cortical neurons. The model identified 59,369 correctly barcoded neurons within half an hour, demonstrating its applicability to larger datasets. We further established a quality control pipeline to match high-quality axonal barcodes to those in the somas. To estimate the model's error rate, we used the fact that L6 corticothalamic (CT) neurons project to the thalamus but not the contralateral cortex. Of 830 transcriptomically defined L6 CT neurons, 56 had projections to the contralateral cortex, indicating an error rate of 7%. This likely represents an upper bound of the error rate, since it reflects a combination of transcriptomic cell typing error and barcode assignment error. These results indicate that our model is accurate and efficient and can scale to large in situ sequencing-based barcoded connectomics datasets.

Disclosures: A. Zhang: None. S. Khem: None. M. Rue: None. X. Chen: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.17/YY4

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

Support: NIH Grant 1U24NS140384-01
NIH Grant N010260407

Title: Building Secure Neurodata Portals Using AI-Enhanced brainlife.io Hub

Authors: *T. GRAFFT¹, A. HEINSFELD², F. PESTILLI³;

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Abstract: Sharing neuroscience data among researchers and organizations poses significant challenges, particularly balancing early-stage data accessibility with compliance to stringent governance mandates and data user agreements (DUAs). To address these complexities, we developed the brainlife.io Hub, an AI-enhanced platform empowering diverse organizations—including individual researchers, institutions, research teams, and small groups—to securely and efficiently manage, collaborate, and share their neuroscience data. The brainlife.io Hub, deeply integrated with artificial intelligence (AI), transforms how neuroscience research is conducted by enabling users to easily create customized neurodata portals. These portals securely advertise and share datasets kept within private projects, offering personalized access control—including individual and group-based permissions—managed through detailed DUAs. By safeguarding data behind controlled, private projects, researchers are encouraged to share and collaborate even while data is still undergoing collection, preprocessing, pipeline development, or analysis for publications. This significantly accelerates data-driven discoveries, optimizes research workflows, and creates extensive collaboration opportunities among diverse research groups. Through the Hub, organization owners, managers, and members can effectively monitor, coordinate, and manage their computational resources, datasets, project statuses, and research pipelines. The integrated AI assists researchers by simplifying complex tasks such as the creation of tailored dashboards and dynamic portals. These personalized dashboards feature advanced analytics, detailed data visualizations, and actionable insights derived from project metadata, data modalities, research progress metrics, and organizational priorities. The AI-driven system significantly reduces administrative burdens, enhances organizational oversight, and provides intuitive tools for data-driven decision-making. The brainlife.io Hub supports compliance, improves data discoverability and integrity, and streamlines how neuroscience data is shared and used. By enabling secure and collaborative research practices, the Hub helps accelerate the pace, scale, and impact of neuroscience globally.

Disclosures: T. Grafft: None. A. Heinsfeld: None. F. Pestilli: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.18/YY5

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

Title: The brain emulation challenge: A synthetic data platform to evaluate neural reconstruction methods

Authors: *R. A. KOENE;

Carboncopies Brain Res. Fndn., Anacortes, WA

Abstract: Progress in neuroscience has been driven largely by correlational analyses and mechanistic hypotheses tested against observational data. Yet, the field has struggled to achieve functional reconstructions of brain tissue that reproduce the original system's information processing capabilities. The final step toward brain emulation - the *translation* from high-resolution structural and physiological data to executable, validated models of neural circuits - remains an open challenge. A key limitation is the absence of ground-truth systems that allow rigorous evaluation of candidate emulation methods. To address this gap, we present the **Brain Emulation Challenge**, a community platform designed to accelerate progress in neural system identification through structured challenges based on synthetic brain data with known ground truth. Using our open-source BrainGenix platform, we generate realistic in-silico neural circuits with embedded structure-function mappings. These synthetic brains, created with tools such as Netmorph (Koene, Neuroinformatics, 2009) and Braingenix-NES, yield multimodal data outputs (e.g., virtual EM, Ephys voltage traces, Calcium imaging) and support detailed benchmarking of emulation strategies via success metrics grounded in cognitive plausibility and dynamical similarity. Like ImageNet in computer vision, our challenge provides tiered datasets and validation metrics to establish a quantitative foundation for iterative method development. Each round introduces greater complexity, guiding participants toward progressively more powerful emulation techniques. This framework enables rapid debugging, standardized evaluation, and cumulative progress across the community. We invite the neuroscience community to participate in shaping and competing in the Brain Emulation Challenge. The platform is positioned to foster innovation in neural data interpretation, validate candidate brain emulation implementations, and catalyze new approaches in neuroprosthetics, disease modeling, and synthetic cognition.

Disclosures: R.A. Koene: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.19/YY6

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

Title: Modeling the Human Visual System: Comparative Insights from Response-Optimized and Task-Optimized Vision Models, Language Models, and Different Readout Mechanisms

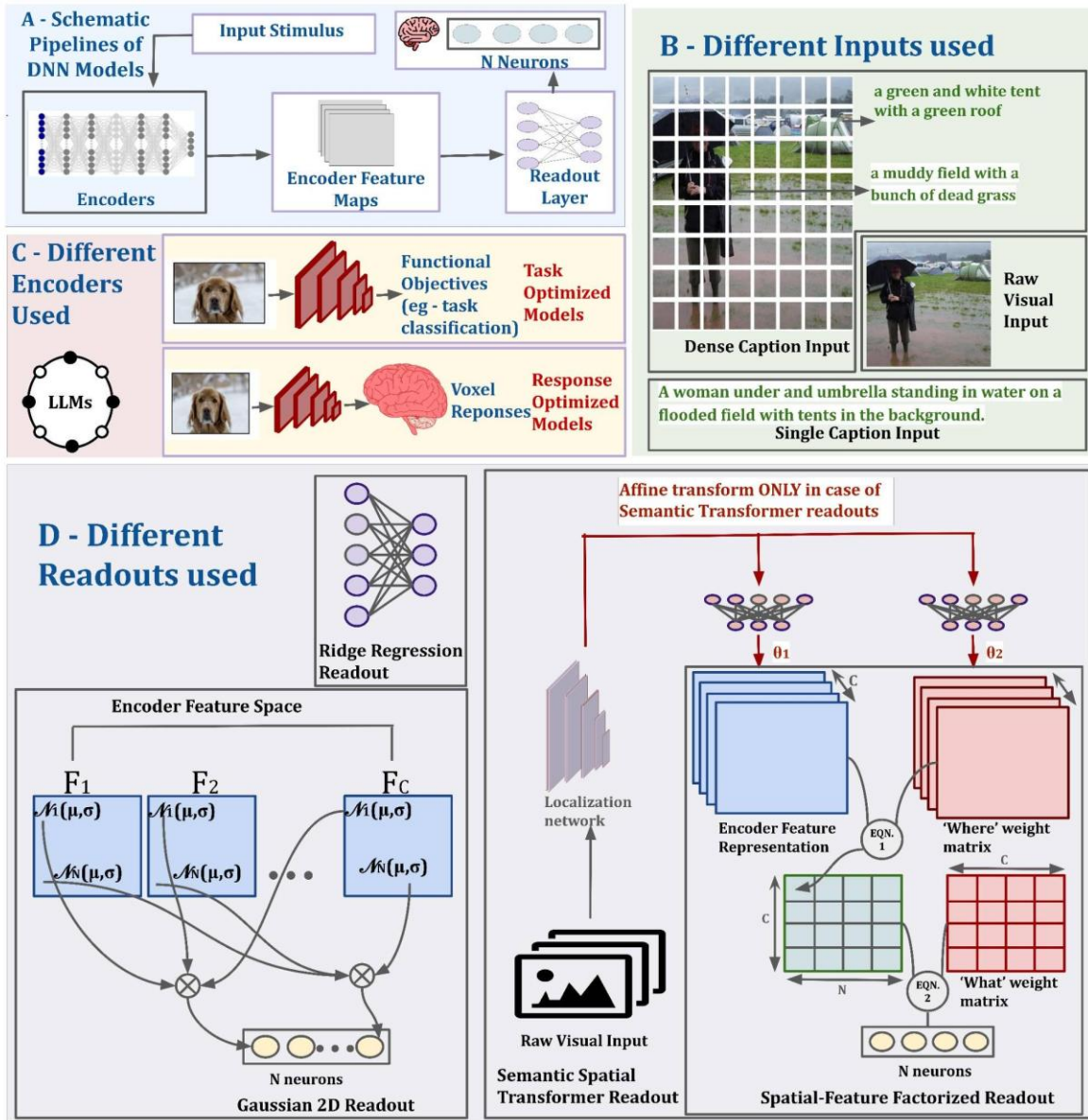
Authors: *S. SAHA¹, I. CHADHA², M. KHOSLA³;

²Halicioglu Data Sci. Inst., ³Cognitive Sci. Dept., ¹Univ. of California San Diego, La Jolla, CA

Abstract: Over the past decade, predictive modeling of neural responses in the primate visual system has advanced significantly, driven by diverse deep neural network approaches. These include models optimized for visual recognition, methods that align visual and language information, models trained directly on brain data, and representations from large language models (LLMs). Additionally, various readout mechanisms have been developed to map network activations to neural responses. Despite this progress, it remains unclear which approach performs best across different regions of the visual hierarchy.

In this study, we systematically compare these methods for modeling the human visual system and propose novel strategies to enhance response predictions. We demonstrate that the choice of readout mechanism significantly impacts prediction accuracy and introduce a biologically grounded readout that dynamically adjusts receptive fields based on image content and learns geometric invariances of voxel responses directly from data. This novel readout outperforms factorized methods by 3-23% and standard ridge regression by 7-53%, setting a new benchmark for neural response prediction.

Our findings reveal distinct modeling advantages across the visual hierarchy: response-optimized models with visual inputs excel in early to mid-level visual areas, while embeddings from LLMs—leveraging detailed contextual descriptions of images—and task-optimized models pretrained on large vision datasets provide the best fit for higher visual regions. Through comparative analysis, we identify three functionally distinct regions in the visual cortex: one sensitive to perceptual features not captured by linguistic descriptions, another attuned to fine-grained visual details encoding semantic information, and a third responsive to abstract, global meanings aligned with linguistic content. Together, these findings offer key insights into building more precise models of the visual system.



Disclosures: S. Saha: None. I. Chadha: None. M. Khosla: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.20/YY7

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

Title: Spirit in Physics: An Information-Physics Model for Quantifying Self-Expansion

Authors: *J. KAWASAKI¹, K. TAINAKA², T. TAKEUCHI³;

¹Grad. Sch. of Med. and Dent. Sciences, Niigata Univ., Niigata, Japan; ²Brain Res. Inst., Niigata Univ., Niigata, Japan; ³Dept. of Biomedicine, Aarhus Univ., Aarhus C, Denmark

Abstract: We propose a novel model for structuring and quantifying the human “spirit” within an information-physics framework. Two core hypotheses underpin our approach: (1) information is a physical quantity subject to thermodynamic laws (Landauer’s principle), and (2) the self-boundary of consciousness can plastically extend into information space, as evidenced by the rubber-hand illusion. Based on these, we define an information-physical space $S = (V, E, T)$ and introduce an informational energy term $E = -\ln P(w_O \mid w_I)$ alongside a “spirit” observable $\psi(S) = \frac{\{\Delta S\}}{\{\Delta E(S)\}}$.

To operationalize this framework, we conducted a Jungian word-association experiment integrating four measures: semantic similarity (word-vector dot product), reaction latency α , electrodermal-activity changes γ, λ evoked by the rubber-hand illusion, and emotional arousal score η derived from facial and vocal analysis. These were combined into a unified probabilistic model: $P(w_O \mid w_I) \propto \exp(w_I \cdot w_j), [r(w_I, w_j)]^\alpha, \exp(\gamma \lambda \Delta SP), \exp(\eta, F)$. We collected and analyzed data from 100 stimulus words under ICH-GCP guidelines (Niigata University IRB No. 2024-0269; approved March 1, 2025). Our results show that variations in latency, skin conductance, and emotional score significantly contribute to the informational energy E , and that the self-expansion index $\psi(S)$ quantitatively reflects associative structures among stimuli.

These findings support the view that self-expansion is an essential characteristic of the spirit. We introduce the “Spirit Transformer” model as a dynamic information paradigm for spirit and discuss potential extensions to neural information processing and applications across cognitive science and related fields.



Spirit in Physics

Jun Kawasaki(root@junkawasaki.com), Kazuki Tainaka, Tomonori Takeuchi;
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Department of Biomedicine, Aarhus University, Denmark

Structuring and Quantifying Human Spirit Using the Informational Vector Space

Information is Physics: Information is inherently physical—it obeys the laws of thermodynamics and directly influences energy exchange. Experimental validations of Landauer's principle (Bérut et al., 2012) reinforce that computation and energy are fundamentally intertwined.

Self-expansiveness into information space: Based on the rubber hand illusion (Botvinick & Cohen, 1998), self-boundaries are not fixed but can extend to incorporate external objects. We assume that the neural mechanisms underlying multisensory integration—demonstrated by the rubber hand illusion—provide a measurable basis for transforming physical self-perception into an expansive, information-rich state that underpins Spirit.

Spirit Physical Space (Kawasaki Model)

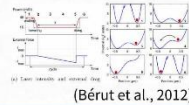
Mathematical Model:

$$S = V, E, T$$

$$E = -\ln P_{\text{MH}}(w_O | w_I), \quad V = \{\vec{v}_{w_I}, \vec{v}_{w_O}, \dots\}, \quad T = \text{time axis.}$$

Physical Definition of Spirit:

$$\psi(S) = \frac{\delta E(S)}{\delta S}.$$



(Bérut et al., 2012)

1 Vectorization Spirit Using the Word Association Experiment (Jung, 1910)

$$P_{\text{MH}}(w_O | w_I) = \frac{\exp(\vec{v}_{w_O} \cdot \vec{v}_{w_I}) \cdot [r(w_I, w_O)]^\alpha \cdot \exp\left(\gamma \frac{\Delta SP(w_I, w_O)}{\lambda}\right)}{\sum_{w \in V} \exp(\vec{v}_w \cdot \vec{v}_{w_I}) \cdot [r(w_I, w)]^\alpha \cdot \exp\left(\gamma \frac{\Delta SP(w_I, w)}{\lambda}\right)}$$

Elements: (51)

Word Asso...	head
green	water
to sing	dead
long	ship
to pay	window
...and 41 more	



Conventional Word2Vec: Quantify the strength of association using the inner product of word vectors.

Jung's association method element: Introduce a factor that is the inverse of reaction time.

Integrated model: Adjust the reaction speed factor with the hyperparameter λ and define a modified probability function as follows:

2 Measurement via Emotion Analytics (Quantitative Analysis)

$$r(w_I, w_O) = \frac{1}{\tau(w_I, w_O) + \epsilon}$$

The facial recognition system defines an emotion score $F(w_I, w_O)$ obtained from the subject's facial expression.

This score is treated as an integrated index of the intensity of each emotion, such as "happiness," "sadness," and "surprise."

Conclusion

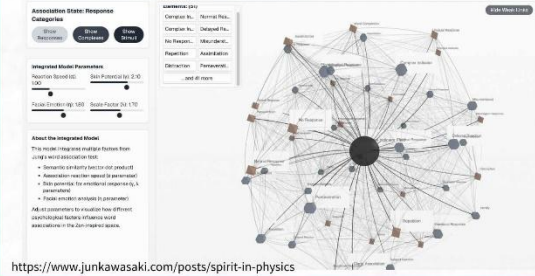
Self-expansiveness is Spirit: Self-expansiveness plays a key role in shaping personal, physiological, and societal phenomena.

Spirit Transformer Model: The Kawasaki Model proves that the spirit can be structured, measured, and quantified as dynamic physical information.

$$P_{\text{MH}}(w_O | w_I) = \frac{\exp(\vec{v}_{w_O} \cdot \vec{v}_{w_I}) \cdot [r(w_I, w_O)]^\alpha \cdot \exp\left(\gamma \frac{\Delta SP(w_I, w_O)}{\lambda}\right) \cdot \exp(\eta F(w_I, w_O))}{\sum_{w \in V} \exp(\vec{v}_w \cdot \vec{v}_{w_I}) \cdot [r(w_I, w)]^\alpha \cdot \exp\left(\gamma \frac{\Delta SP(w_I, w)}{\lambda}\right) \cdot \exp(\eta F(w_I, w))}$$

Results

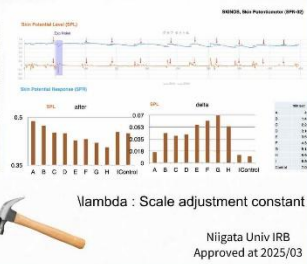
Spirit in Physics (Jung's Word Association Test Embedding Model)



<https://www.junkawasaki.com/posts/spirit-in-physics>

3 Measurement via Skin Potential Using the Rubber Hand Illusion (Qualitative Analysis)

$$s(w_I, w_O) = \exp\left(\frac{\Delta SP(w_I, w_O)}{\lambda}\right)$$



λ : Scale adjustment constant

Niigata Univ IRB
Approved at 2025/03

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You Can Try Now
Spirit in Physics(Emotional Analytics)



Another Research / High-IQ Japanese GWAS: Explore IQ Genes

Leveraging Japan's unique genetics, a GWAS targeting individuals with IQ ≥ 140 will compare genetic and cognitive data to identify SNPs linked to intelligence. The study begins in 2024 with results slated for publication.

Dataset: 92 people / CAMS IQ140 sd15 - IQ180t / SNPs.

ref. Jonathan R. I. Coleman et al, *Mol Psychiatry* 24, 182–197 (2019)



Disclosures: **J. Kawasaki:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Gftd Japan Ltd. **K. Tainaka:** None. **T. Takeuchi:** None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.21/YY8

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

Title: Enabling scientific innovation with GenAI for hypothesis generation and validation

Authors: ***J. M. KERR;**

Google Publ. Sector, Washington, DC

Abstract: Large-language models (LLMs) and their multi-modal counterparts (which operate on video, images, and audio - alongside text) and the ‘generative AI’ era are fast-changing. These technologies afford both opportunities and challenges for biomedical research. Also, validating and falsifying hypotheses that do not warrant scientific investigation is key to providing researchers the best path to narrowing their research objectives. Here we present findings for the potential of LLMs to accelerate hypothesis generation and testing with a systematic consideration of the key parameters relevant to providing accurate and useful outputs. This includes: 1) native model capabilities (how to choose a model, performance improvement from ‘reasoning’ and ‘mixture of experts’ approaches); 2) significance of grounding the results on the published research literature (using retrieval-augmented-generation (RAG) approaches); and 3) how to build structured and repeatable methods for effective prompting of large models. We found that prompting and prompt engineering (what the model is supplied as inputs) are key, but the elements in the chain of considerations are multiplicative. We show that each step in this chain amplifies accurate information and the impact of context from ‘expert-in-the-loop’ architecture to apply scientific discipline-specific expertise. In one clinically-oriented example, the quality of results was significantly improved via a ranking system that was developed in collaboration with an oncologist. These findings have direct implications for use cases where the latest research findings are key, such as tumor review boards that must employ the latest potential treatment information for complex cancer cases, where the existing standard of care does not address what is needed. These results also provide a framework for research institutions and individual research groups/researchers to best leverage and evaluate ‘GenAI’ to enable and accelerate their research objectives.

Disclosures: **J.M. Kerr:** A. Employment/Salary (full or part-time): Google, LLC.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.22/YY9

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

Support: Israel Science Foundation Grant # 2418/24

Title: Unraveling Cortical Network Reorganization During Learning and in Parkinson's Disease Using a Novel Geometric Approach

Authors: Y. KLEEREKOPER¹, M. KURTAM¹, Y. SCHILLER¹, *H. BENISTY²;

¹Neurosci., Technion Israel Inst. of Technol., Haifa, Israel; ²Fac. of Med., Technion, Haifa, Israel

Abstract: Learning is a dynamic neural process that reshapes cortical networks and has significant implications for understanding both normal brain function and neurological disorders. Parkinson's Disease (PD), a progressive neurodegenerative condition, impairs previously learned motor skills, often requiring individuals to relearn motor tasks. In this study, we investigate how motor learning influences cortical network dynamics before and after the onset of experimental PD induced by 6-hydroxydopamine (6-OHDA) in mice trained on a lever-pull task. We specifically examine dendritic network activity in the tuft regions of layer 5 pyramidal tract neurons in the primary motor cortex, which is central to motor planning and execution. Using our novel analytical framework, we analyze the dynamics of the correlational structure of these networks to identify sub-networks driving correlational dynamics during motor learning. Our results reveal that, prior to the onset of PD, neurons identified as dynamic drivers are highly tuned to the motor task, actively supporting learning. However, post-PD onset, task-specific tuning and network reorganization become disrupted. These findings provide insights into the neural basis of motor learning and the deficits caused by PD.

Disclosures: Y. kleerekoper: None. M. Kurtam: None. Y. Schiller: None. H. Benisty: None.

Poster

PSTR197: Computational Approaches and Experimental Analyses II

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR197.23/YY10

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

Support: NSF GRFP
R01 NS094184 NINDS

Title: Learning driven dynamics of cell type specific functional networks in mouse motor skill learning

Authors: *G. WHEELER FOX¹, E. WIENER¹, J. N. MACLEAN²;

¹Univ. of Chicago, Chicago, IL; ²Neurobio., The Univ. of Chicago, Chicago, IL

Abstract: When animals learn a new motor skill, neurons in motor cortex reorganize, producing new spatiotemporal activation patterns that correspond to the learned behavior. However, the circuit level mechanisms underlying this reorganization remain unclear. Inhibitory interneurons, which are known to play a role in learning, are prime candidates for shaping network dynamics because of their ability to regulate both the activity of and interactions between excitatory neurons. Parvalbumin (PV) inhibitory interneurons target the soma of excitatory cells, enabling them to regulate excitatory neuronal activity, while Somatostatin (SOM) inhibitory interneurons target distal dendrites, enabling them to regulate spike timing relationships between excitatory neurons. Using two-photon calcium imaging, we recorded GCaMP6f fluorescence activity from all cell types in mouse motor cortex over 10-12 sessions of training in a dexterous reach-grasp-carry task, with PV neurons (n=3 mice) or SOM neurons (n=4 mice) labeled. To quantify the kinematics of the behavior, we tracked keypoints on each mouse's digits, wrist, and elbow. We tracked the same neurons across all sessions in each mouse, and for each session we computed a functional network in which neurons are nodes and the inferred spike timing correlations between them are edges. To measure higher order modulation by inhibitory neurons, we used an information theoretic approach to infer triadic interactions, which are defined as triplets of neurons in which an inhibitory neuron modulates the edge, or spike timing correlation, between two excitatory neurons. We find that SST neurons best predict the activity of excitatory neurons when their relationship is modeled as triadic (regulating edges), while PV neurons best predict the activity of excitatory neurons when their relationship is modeled as a direct negatively weighted edge. Using this framework, which includes direct and triadic interactions between PV/SOM cells and excitatory cells, we measure the relationship between PV and SOM connectivity with excitatory cells in early sessions and the likelihood that edges or highly active nodes are maintained, deleted, or added in the stable, late-stage version of the network. We also directly relate these measured network changes to changes in kinematics, including paw trajectory and shape. By leveraging network science and information theoretic tools in combination with sophisticated imaging techniques to identify cell types, we quantify how pairwise and higher order relationships between excitatory cells and inhibitory subtypes shape network dynamics in M1 to support behavioral improvement in a difficult motor task.

Disclosures: G. Wheeler Fox: None. E. Wiener: None. J.N. MacLean: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.01/YY11

Topic: J.07. Data Analysis and Statistics

Support: National Natural Science Foundation of China 32100896
Institute of Artificial Intelligence of Hefei Comprehensive National
Science Center Y10200902
The strategic priority research program of Chinese Academy of Science
XDB32030200.

Title: Neatmapv2: a high-efficiency deep learning approach for whole mouse brain neuronal activity and cell-type analysis

Authors: *W. ZHENG^{1,2}, H. MU³, H. WANG⁴;

¹Anhui Univ., Anhui, Hefei, China; ²Inst. of Artificial Intelligence, Hefei Comprehensive Natl. Sci. Ctr., Anhui, Hefei, China; ⁴Sch. of Life Sci., ³Univ. of Sci. and Technol. of China, Hefei, China

Abstract: Whole brain neuronal activity mapping with immediate early genes (e.g., c-Fos) is primarily used to determine the distribution of responsive neurons across the brain for almost every study using a behavior test. Moreover, identifying the cell-types of these activated neurons is essential for further neural circuits tracing with viral vectors and functional manipulation with Optogenetics or Chemogenetics. However, the precision and efforts required by these screenings have long been a challenging and tedious work for most researchers. Recently, we have established a whole-brain neuronal activity trace mapping method NEATmap, as well as a whole-brain cell-type mapping paradigm with multiplexed fluorescence *in situ* hybridization (multi-FISH) and VISoR imaging. Here we present NEATmapV2, an updated deep learning-based high-throughput, high-precision, and user-friendly approach for whole brain **NE**uronal **A**ctivity and cell-**T**ype **m**apping. NEATmapV2 performs fully automated segmentation and quantification of activated neurons and the cell-types labeled either by immunofluorescence or multi-FISH. This integrated framework offers a powerful, scalable, automated, and reproducible method to comprehensively decode functional neuronal ensembles along with their precise cell-type identities throughout the entire mouse brain.

Disclosures: W. Zheng: None. H. Mu: None. H. Wang: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.02/YY12

Topic: J.07. Data Analysis and Statistics

Title: UNETR (UNet Transformer) for denoising functional ultrasound imaging

Authors: *A. UKUDEEV-FREEMAN, A. PAMARTHI, N. SATHISHKUMAR, G. VENUMBKA;
UCLA, Los Angeles, CA

Abstract: Functional Ultrasound imaging (fUSI) is a powerful, emerging neuroimaging technology based on the transmission and reception of highly sensitive Doppler signals to detect variations in cerebral blood flow and volume. As a result, noise from unrelated physiological processes often interferes with the display of spatiotemporal data. Current architectures based around convolutional neural networks (CNNs), specifically the 3D U-Net encoder-decoder, have been used to reconstruct imaging with increased accuracy. However, limitations to CNNs include their inability to capture long-range temporal dependencies across frames. While recent hybrid models such as ViT-V-Net incorporate transformers into 3D U-Nets, they are primarily designed for static volumetric data and do not account for fUSI's dynamic temporal structure. In this paper, we introduce a novel denoising architecture that combines a 3D CNN with a TimeSformer-style transformer core to enable both local spatial refinement and global temporal reasoning. Utilizing publicly released fUSI data, we use image segmentation to generate synthetic noise, then train our model to reconstruct the clean signal. Compared to CNN-only baselines, our results demonstrate improved preservation of spatiotemporal structure based on frame-to-frame SSIM, providing more coherence across sequential frames. This is an exploratory study that highlights the importance of temporal dynamics and provides the groundwork for a more robust neuroimaging model.

Disclosures: A. Ukudeev-Freeman: None. A. Pamarthi: None. N. Sathishkumar: None. G. Venumbaka: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.03/YY13

Topic: J.07. Data Analysis and Statistics

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NIH Grant P50MH132642
NIH Grant RO1 EY017699
NIH Grant R01MH137624
NIH Grant R01MH123687

Title: Kiasort: knowledge-integrated automated spike sorting for geometry-free neuron tracking

Authors: *K. BANAIE BOROUJENI¹, T. WOMELSDORF³, S. KASTNER²;

²Princeton Neurosci. Inst., ¹Princeton Univ., Princeton, NJ; ³Dept. of Psychology, Vanderbilt Univ., Nashville, TN

Abstract: Identifying and distinguishing single units from extracellularly recorded neural signals is a key step toward understanding brain circuit dynamics. Over the past decade, with the exponential growth of large-scale neural recordings (e.g., Neuropixels probes), the demand for

efficient, precise, and automated methods to parse and sort neural data has become increasingly critical. Existing approaches, however, often face challenges in meeting this demand. These challenges include variability in channel signal quality, neuron-specific waveform drifts, and nonlinear temporal changes in spike shapes and polarities related to differences in neuronal morphology, electrode proximity, and heterogeneous drift patterns. Here, we introduce KIASORT (Knowledge-Integrated Automated Spike Sorting), which integrates knowledge from channel-specific classifiers trained on clustered spike waveforms to sort neural spiking data. KIASORT evaluates channel quality, automatically excludes noisy recordings, and identifies spike classes using a hybrid dimensionality reduction approach combining PCA with nonlinear UMAP embeddings. To validate our approach against existing methods, we developed biophysical simulations demonstrating that conventional one-dimensional drift correction methods cannot address heterogeneous neuron-specific drift and nonlinear waveform changes. KIASORT's per-neuron tracking approach is geometry-free and overcomes these limitations without assumptions about cluster shape or temporal stability. Specifically, KIASORT achieved ~10% higher precision and identified 5-15% more high-quality units than Kilosort4 in ground-truth simulations with neuron-specific drift, while maintaining real-time processing capability. In addition to these advances, KIASORT also includes a unified graphical interface for data inspection, sorting, and curation, which is freely available online.

Disclosures: K. Banaie Boroujeni: None. T. Womelsdorf: None. S. Kastner: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.04/YY14

Topic: J.07. Data Analysis and Statistics

Support: Ingrassia Family Echols Scholars Research Grant
NIH NS124728
Gift from the Pelican Fund

Title: Applying Multivariate and Nonparametric Statistical Methods in HD Mouse Model Behavioral Analyses

Authors: *S. GANGADARI, J.-P. LIU, S. O. ZEITLIN;
Neurosci., Univ. of Virginia, Charlottesville, VA

Abstract: Background:

Huntington's disease (HD) is a fatal neurodegenerative disorder marked by progressive motor, cognitive, and psychiatric symptoms. It is caused by a CAG repeat expansion in the HTT gene, leading to production of mutant Huntingtin protein (mHTT), which disrupts neuronal function. 50% mHTT lowering early in life delays symptomatic onset in HD mouse models, but benefits

diminish with age. We are now using knock-in HD mouse models with 50% or 75% reduction in mHTT to investigate the effects of further reducing mHTT levels on motor and cognitive function as they age.

Rationale:

Small sample sizes and weight differences are common confounds in behavioral analyses of motor and cognitive behavior in HD mouse models. While two way ANOVA is typically used to assess differences between genotypes/treatment groups in multi-day testing, we aimed to explore alternate statistical analysis methods to address these confounds and identify nuanced trends in performance.

Methods:

Permutation-based multivariate analysis of variance (PERMANOVA) was used to provide a more sensitive and representative statistical framework for detecting complex behavioral trend differences in HD mouse models compared to standard methods. We control for varying mouse weights by employing weight distribution standardization and adjustment methods across different groups. To assess applicability, these methods were applied to accelerating rotarod trials (testing motor function and learning) at 6, 12, and 18 months of age.

Results:

After adjusting for weight in the 12- and 18-month groups, the negative control mice (0% mHTT, LacIR) had the highest latency to fall, matching biological predictions. PERMANOVA analysis of 12-month-old male mice showed significant behavioral trend differences between controls (0% and 100% mHTT expression; $p = 0.031$) as well as between the 75% mHTT lowering mice and the 100% mHTT positive control HD mice ($p = 0.027$). At 12 months, female mice displayed a more pronounced genotype effect than males, especially in comparisons between the negative control and other HD expression groups. Overall, more group genotype differences were observed at 18 months, likely due to disease progression.

Conclusion:

The results of our analyses are consistent with our prediction that >50% mHTT lowering is beneficial in older mice. Future studies should focus on refining adjustments for other potential confounding variables and expanding multivariate approaches for evaluating other behavioral tests in mice.

Disclosures: S. Gangadari: None. J. Liu: None. S.O. Zeitlin: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Topic: J.07. Data Analysis and Statistics

Support:

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Title: Xbrainlab: AI-powered open-source platform for end-to-end EEG analysis

Authors: *C.-S. WEI;

Natl. Yang Ming Chiao Tung Univ., Hsinchu, Taiwan

Abstract: Electroencephalogram (EEG) recordings provide crucial insights into human brain dynamics by capturing oscillatory responses with high temporal resolution. However, systematically deciphering EEG signals remains challenging due to the typically low signal-to-noise ratio, artifact contamination, and inherent complexity of the data. Despite the popularity of deep neural networks for decoding EEG data, limited attention has been given to easily accessible software that integrates both EEG-specific preprocessing routines and cutting-edge explainable artificial intelligence (XAI) techniques. Here, we present XBrainLab, a fully open-source platform designed to streamline the entire EEG analysis workflow, from raw data import to post-hoc model interpretation. Implemented in Python, XBrainLab features an interactive graphical user interface (GUI) that mirrors script-based functionality. This design enables researchers with varying programming proficiencies to implement cutting-edge XAI analyses for EEG data without extensive coding. The architecture of XBrainLab is organized into six primary modules: (1) Data Import, which automatically accommodates several popular file formats; (2) Data Preprocessing, where users can apply standard methods including filtering, resampling, epoching, and channel selection; (3) Training Scheme Configuration, allowing subject-, trial-, or session-based data splits for flexible experimental protocols; (4) Deep Learning, incorporating well-known EEG data-oriented network architectures; (5) Analysis and Visualization, offering real-time training progress monitoring as well as performance metrics; and (6) Scripting, which generates Python code from GUI actions so that analyses can be seamlessly reproduced, extended, or customized. By integrating XAI methods, XBrainLab addresses the “black box” problem that often accompanies deep learning models. Specifically, the platform employs saliency-based methods for interpreting feature maps in the temporal, spectral, and spatial domains. Through practical demonstrations on well-known EEG datasets, XBrainLab highlights consistent neural markers in line with prior neuroscience findings. These visual explanations provide a data-driven foundation for forming new hypotheses and validating established neuroscience knowledge. In summary, XBrainLab aims to significantly lower the barrier to employing deep learning and model interpretability in EEG studies. The code repository and documentation are available at: <https://github.com/CECNL/XBrainLab>.

Disclosures: C. Wei: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR198.06/YY16

Topic: J.07. Data Analysis and Statistics

Support: National Institute of Mental Health, Intramural Research Program,
ZICMH002960

Title: Consensus guidelines for tabular data representation in BIDS data sets, a Brain Imaging Data Structure extension proposal

Authors: *E. EARL¹, S. GUAY², S. URCHS³, A. BASAVARAJ⁴, A. G. THOMAS¹, D. MORACZEWSKI¹;

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²Psychology, Univ. de Montréal, Montréal, QC, Canada; ³Montreal Neurolog. Inst., McGill Univ., Montréal, QC, Canada; ⁴E-Health Res. Ctr., Intl. Inst. of Information Technol., Bangalore, India

Abstract: Most studies collect spreadsheets and other tabular data, but not all shared data sets contain them. As of May 30, 2025, 78% of the 1,360 data sets on OpenNeuro have a single tabular participants file. Yet only 2.5% of the 1,360 OpenNeuro data sets utilize the directory for tabular phenotype data where assessments, surveys, and other tabular data should go. In order to lower the difficulty of preparing these data to share and to increase adoption of the phenotype directory, our international collaborative team created tabular phenotypic data guidelines for the widely used Brain Imaging Data Structure (BIDS) standard as extension proposal 36 (BEP036) and are currently seeking comments from the community at <https://github.com/bids-standard/bids-specification/pull/2123>.

After limited consensus at a 2021 meeting with representatives from open science data standardization initiatives like Neuroimaging Data Model (NIDM), Psych-DS, and BIDS, our BEP036 team developed and tested this proposed extension to the BIDS specification. A key contribution is detailed guidance on organizing phenotypic assessment data. Currently most data curators only combine minimal phenotypic data into a single, high-level tabular file (participants.tsv) like age, sex, study group assignments, and handedness. This minimal tabular phenotypic data makes reusability more limited, especially in alternative analyses that could be performed given more tabular phenotypic measures. BEP036 encourages splitting these data into separate files per assessment within a dedicated phenotype directory. To improve adoption, we developed example datasets covering use cases gathered by discussions with the community. The proposed revision is currently under community review and is planned to be included in the next release of the BIDS specification in late 2025.

With clearly documented guidelines and examples, the ability to share rich tabular phenotypic data in BIDS should now be easier. With this lowered barrier to access, we expect more data curators to adopt BEP036's best practices. Future planned work includes integrating Psych-DS and BIDS tabular phenotypic data guidelines together to be able to interoperate between the two open data standards using community-maintained software tools.

Disclosures: E. Earl: None. S. Guay: None. S. Urchs: None. A. Basavaraj: None. A.G. Thomas: None. D. Moraczewski: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.07/YY17

Topic: J.07. Data Analysis and Statistics

Title: Minis Search: A new method for minis analysis with a streamlined workflow, simplified process, and accurate measurement

Authors: *K.-C. TANG;
Mol. Devices, LLC, San Jose, CA

Abstract: Miniature excitatory post-synaptic currents (mEPSCs) or inhibitory post-synaptic currents (mIPSCs), commonly referred to as "Minis", are important bioelectrical signals that facilitate neuronal communication. These events are considered to be postsynaptic responses to the neurotransmitter release from vesicles at the presynaptic terminals and play a critical role in modulating membrane excitability and integrating synaptic inputs in postsynaptic neurons. These minis can be recorded from neurons using whole-cell voltage-clamp electrophysiology techniques. Many commercial and proprietary software tools have been developed for minis analysis. However, these tools have limitations in terms of usability and functionality. These limitations include cumbersome process to add missing event, incapability of editing events, and restricted options for saving ongoing work. To overcome these challenges, we have developed a new analysis tool called "Minis Search" which is specifically designed to analyze miniature or spontaneous excitatory post-synaptic currents (mEPSCs or sEPSCs) and miniature or spontaneous inhibitory post-synaptic currents (mIPSCs or sIPSCs). We utilized Minis Search to analyze postsynaptic events recorded from neurons using whole-cell voltage-clamp techniques. We examined the capability to add missing events and remove unwanted events. We assessed whether the baseline and duration of detected events could be modified. We evaluated the ability to resolve multiple peaks in superimposed events. We also tested whether the unfinished work could be saved and restored. The collected data demonstrate that event detection, deletion, and editing are implemented through a streamlined and simplified process. Inaccurate baselines and durations can be corrected, facilitating precise measurements of event amplitude and kinetics. Furthermore, incomplete analyses can be saved and resumed, enhancing workflow efficiency. In summary, Minis Search provides an intuitive and streamlined workflow for analyzing minis events, enables accurate measurements on detected events, and simplifies the process of event addition and deletion. It offers a comprehensive and user-friendly solution that enhances the speed, accuracy, and ease of minis event analysis for neuroscientists.

Disclosures: K. Tang: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Program #/Poster #: PSTR198.08/YY18

Topic: J.07. Data Analysis and Statistics

Support: NIH R01-NS094399
NIH K01-ES026839

Title: ieeg2bids: user-friendly software for converting clinical iEEG data/metadata into the iEEG BIDS standard

Authors: *S. V. GLISKE¹, G. BARKELEW², W. C. STACEY²;

¹Dept. of Neurosurg., Univ. of Nebraska Med. Ctr., Omaha, NE; ²Neurol., Univ. of Michigan, Ann Arbor, MI

Abstract: Community standards for storing human neuroscience data facilitate efficient creation and use of multicenter databases, accelerating robust and reproducible scientific findings. One area of particular interest is human intracranial EEG data, as it provides unequalled access to brain electrophysiology but is difficult to acquire due to cost, patient burden, and ethical considerations. The iEEG extension to the Brain Imaging Data Standard (BIDS) is a community supported standard with growing use. However, transforming clinical data and metadata into the standard is time consuming, with large heterogeneity in the clinical metadata annotations and the raw data itself, such as the number, name and placement of the electrodes. The goal of this project was to create a user-friendly software interface to optimally balance automation of some tasks while keeping a human-in-the-loop to address the multitude of possible inconsistencies in the source data. Our solution uses the Matlab App Designer. This solution produces software for Windows, iOS, and Linux operating systems and does not require the user to have a Matlab license or have Matlab installed. We tested, verified and validated our software on a large set of patients from the University of Michigan Intracranial EEG database and the University of Nebraska Medical Center Database. The software accurately produces all necessary sidecar files in the iEEG BIDS standard and can convert between the Persyst format (lay/dat), Brain Vision Core Data Format (BVCDF), and European Data Format (EDF) files. Use of the software is expected to significantly increase efficiency, accuracy and reliability for converting clinical data into the BIDS standard, facilitating an increase in open sharing of iEEG data.

Disclosures: S.V. Gliske: None. G. Barkelew: None. W.C. Stacey: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Topic: J.07. Data Analysis and Statistics

Support: NIH R24-MH-114793
NIH R24-MH-114683

Title: Evolving Metadata to Support the Next Generation of Neuroscience: Shaping Standards at the Brain Image Library

Authors: *A. J. ROPELEWSKI¹, M. KENNEY², P. M. BAKER³;

¹Pittsburgh Supercomputing Ctr., Carnegie Mellon Univ., Moon Township, PA; ²Pittsburgh Supercomputing Ctr., Carnegie Mellon Univ., Pittsburgh, PA; ³Data and Technol., Allen Inst. for Brain Sci., Seattle, WA

Abstract: High-quality metadata is essential for ensuring that large imaging datasets are FAIR, especially as brain imaging techniques evolve. The Standard metadata for 3D microscopy, published in 2022, has been in use at the Brain Image Library for approximately three years. During this period, new technologies have emerged. Here, we will reflect on how the standards have held up in a rapidly evolving field and how it has adapted to support emerging technologies while maintaining interoperability across diverse neuroscience datasets.

A key design principle has been modularity. This structure allows for the integration of new components without disrupting the core metadata components framework. As imaging data becomes increasingly diverse and complex, the metadata needs to evolve. We have successfully created new modules for emerging techniques, including spatial transcriptomics. Additionally, we developed modules for neuron tracing data as more of these datasets were submitted to the repository, reflecting the maturation of the projects as they gathered and analyzed data. These updates are driven by ongoing community feedback, with new modules undergoing regular review and adoption. This community-driven process has been integral to the success of the metadata standards, fostering widespread buy-in and ensuring that the metadata remains relevant and useful.

However, evolving data complexity also poses challenges for the adoption of this metadata standard. The flat structure of the metadata, while suitable for some data types, can prove to be limiting for complex hierarchical relationships inherent in certain datasets. This was identified early in the adoption of this standard, and we have continued to refine our approach to data and metadata structure.

Looking forward, our goal is to ensure the metadata standard remains responsive to both scientific innovation and community priorities. We anticipate that further refinement and community input will ensure that these standards evolve in step with technological advances. As neuroscience methods grow more integrative and data-rich, our ability to anticipate future needs and integrate feedback will be essential to the long-term success of these standards and data sharing.

Disclosures: A.J. Ropelewski: None. M. Kenney: None. P.M. Baker: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Topic: J.07. Data Analysis and Statistics

Support: NIH/NIDCD R01 DC014701
NIH/NIDCD R01 DC019124

Title: Automatic behavior classification over short sequences in Annolid based on zero-shot tracking and segmentation

Authors: *C. YANG¹, T. A. CLELAND²;
²Psychology, ¹Cornell Univ., Ithaca, NY

Abstract: The quantitative analysis of animal behavior is essential to neuroscience, but often is constrained by the labor-intensive process of manual video annotation. We here introduce a robust and scalable computational pipeline for the automated classification of dyadic mouse social interactions. Our approach leverages Annolid, a software package that coordinates multiple contemporary machine learning models for the analysis of animal behavior from video data. The pipeline begins with zero-shot instance segmentation in a single frame, using the Grounding-DINO and Segment Anything (SAM) models, guided only by a text prompt (e.g., “mouse”). These initial masks then are propagated across the entire video using Cutie, a video object segmentation (VOS) model, automatically tracking multiple animals without further human intervention (unless corrections are warranted). To demonstrate the pipeline’s capabilities, we applied it to the task-1 video group from the Caltech Mouse Social Interactions (CalMS21) dataset, which record the dyadic interactions of pairs of mice. Using the above pipeline, Annolid successfully tracked individual mice across complete video sequences, generating instance polygons (masks of mouse body shapes) in each frame. From these propagated instance polygons, we extracted a rich, 87-dimensional spatiotemporal feature set (including polygon coordinates, area, centroid, perimeter, and motion indices) from each frame for both interacting mice. These features were input into a custom 1D convolutional neural network designed for frame-level classification. The model uses an 11-frame temporal window, six residual blocks, and a 128-dimensional hidden layer, and channels attention to classify four behaviors: 'attack', 'investigation', 'mount', and 'other'. The classification model was trained on 447,446 frames and evaluated on a hold-out test set of 503,178 frames. The system achieved a mean Average Precision (mAP) of 0.840 across the four behavioral classes. Individual class mAP scores on the test set were 0.817 (attack), 0.737 (investigation), 0.843 (mount), and 0.964 (other). These results demonstrate the efficacy of integrating advanced segmentation and tracking techniques for high-throughput feature extraction with a simple deep learning architecture for behavior classification. By minimizing manual effort, this pipeline enables high-throughput, reproducible behavioral analysis—opening new avenues for large-scale neuroscience research. Annolid is open-source and freely available at <https://cplab.science/annolid>.

Disclosures: C. Yang: None. T.A. Cleland: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.11/YY20

Topic: J.07. Data Analysis and Statistics

Title: Brain alignment via heteroscedastic prediction of spatial transcriptomics

Authors: *I. CONVY, R. GALA, U. SÜMBÜL;
Allen Inst., Seattle, WA

Abstract: Cross-brain alignment is a critical step in the creation of accurate three-dimensional atlases that can aid in the interpretation of neuronal data. Previous efforts in the mouse brain have relied on cell staining and single-channel fluorescence to align neuron densities across samples and identify region boundaries. With recent advancements in high-throughput spatial transcriptomics protocols such as Multiplexed Error-Robust Fluorescence In Situ Hybridization (MERFISH), it is now possible to characterize patterns of gene expression across whole brains at a high resolution. In this work, we devise a heteroscedastic graph neural network regression model that can predict the location of a cell given the transcriptomic profile of its neighborhood. By characterizing both the magnitude and direction of the model's uncertainty across different parts of the brain, we are able to identify areas of high confidence that are consistent across individual brains. Using these transcriptomically- and anatomically-stereotyped cells as landmarks, we demonstrate effective cross-brain alignment that is grounded in robust transcriptomic correlation.

Disclosures: I. Convy: None. R. Gala: None. U. Sümbül: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Michael J. Fox Foundation's PPMI – award #8283.03

Title: Advancing neuroscientific communication through reader accessible data embedding with Schol-AR

Authors: ***T. D. ARD**¹, M. S. BIENKOWSKI², J. STANIS⁵, S.-L. LIEW³, A. W. TOGA⁴;

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Abstract: Although neuroscience is largely a digital discipline, its communication remains largely confined to static text and images within PDF articles. This format typically presents only selected snapshots of key findings, excluding much of the rich quantitative and qualitative data generated during research. Efforts to improve data accessibility through supplementary online materials have had limited success, with access rates measured below 0.04% (Flanagin et al., 2018), indicating most supplementary data remains unseen. As a result, critical research data is often missing from standard articles, limiting transparency and the effective dissemination of neuroimaging research. As previously discussed (Ard et al., 2022), Schol-AR addresses these challenges by embedding interactive scientific data directly into standard PDF articles as digital augmentations. These augmentations include 3D models, image stacks, videos, and volumetric datasets, which readers can access seamlessly with a single click on laptops, tablets, or mobile devices. For printed materials and conference posters, Schol-AR supports “point and view” augmented reality (AR), allowing readers to interact with data overlays on physical documents. Here we demonstrate recent advances in Schol-AR’s adoption and capabilities, including expanded support for new 3D formats and 3D animations, enabling authors to embed more dynamic and complex data. These enhancements are openly accessible to authors and readers and do not require programming or other technical capabilities. Schol-AR’s compatibility has been validated through published augmented articles across numerous major publishers, including Elsevier, Nature Publishing Group, Wiley, IOS Press, and IOP Publishing, ensuring that augmented articles can be submitted and accessed broadly without technical barriers. By integrating richer, interactive data directly within scientific articles, Schol-AR continues to enhance the transparency, thoroughness, and accessibility of neuroscience communication worldwide.

Disclosures: **T.D. Ard:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ardist Inc.. **M.S. Bienkowski:** None. **J. Stanis:** None. **S. Liew:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Ardist Inc.. **A.W. Toga:** None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.13/YY22

Topic: J.07. Data Analysis and Statistics

Title: Standardizing Systems Neuroscience Analyses with Open Source Software

Authors: S. C. VENDITTO¹, *E. BALZANI³, W. F. BRODERICK², G. VIEJO⁴;

¹Neurosci., ²Flatiron Inst., New York, NY; ³Simons Fndn., New York, NY; ⁴Flatiron institute, Flatiron institute, New York, NY

Abstract: Systems neuroscience is generating increasingly complex experiments, datasets, and models. While initiatives like Neurodata Without Borders (NWB) have advanced data standards and management, many widely used analytical tools still lack robust, accessible implementations. We introduce four Python packages designed to address this gap by facilitating time series analysis, neural modeling, investigation of perceptual models, and learning from a set of curated examples. Pynapple is a lightweight library for neurophysiological data analysis. It provides a flexible interface for working with time series (e.g., spike times, behavioral events) and intervals (e.g., trials, brain states), along with generic neuroscience functions such as tuning curves and cross-correlograms. NWB support ensures fast and universal access to data. NeMoS is a modeling framework offering GPU-accelerated implementations of well-established statistical methods. It currently supports Generalized Linear Models for spike trains (Poisson), calcium imaging (Gamma), and behavioral data (Binomial), with options for regularization. NeMoS includes composable basis functions for building design matrices and integrates with pynapple for discontinuous data handling and with scikit-learn for model selection. Plenoptic is a library for model-based synthesis of perceptual stimuli, used in vision science and psychophysics. It enables interpretation of model behavior by generating stimuli such as “model metamers”—visually distinct images that are functionally equivalent to a model. Plenoptic includes GPU-compatible implementations of visual system models and perceptual metrics. NeuroStatsLib is a forthcoming tutorial-based package that walks users through complete analyses of publicly available datasets. Tutorials integrate with the other packages to demonstrate full workflows, from loading data to applying state-of-the-art tools. NeuroStatsLib also streamlines environment setup, making it easier for new users to begin working with neural data. Together, these packages provide standardized, tested tools that reduce implementation burden, promote transparency and reproducibility, and encourage code sharing across labs.

Disclosures: S.C. Venditto: None. E. Balzani: None. W.F. Broderick: None. G. Viejo: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Topic: J.07. Data Analysis and Statistics

Support: Italian MUR - Grant MNESYS (PE0000006)
Italian MAECI - Grant PGR02066

Title: A quantitative model for brain-wide, IEG-based analysis of neuronal activation

Authors: L. CHICCHI^{1,3}, *L. SILVESTRI^{2,4};

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Abstract: Immediate Early Genes (IEGs) represent a powerful tool to infer neuronal activation from *ex vivo* samples. This approach has become popular in the last years, thanks to the development of advanced transgenic strategies for IEG tagging - like TRAP mice - and of experimental pipelines for the unbiased quantification of fluorescently labelled cells across the entire mouse brain. All these innovations, however, are far from perfect. Indeed, every analysis pipeline can be characterized by a finite accuracy in terms of labelling intensity, cell detection, and atlas registration. These error sources introduce experimental noise in the data, which must be carefully modelled to avoid drawing false conclusions. Here, we developed a quantitative model of the generation of regional cell counts in typical IEGs experiments and simulated the generation of noisy data from an a priori known 'real' distribution. In this way, we can show the effect of different experimental errors on final data and analysis, including the generation of functional connectivity networks.

Disclosures: L. Chicchi: None. L. Silvestri: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR198.15/ZZ2

Topic: J.07. Data Analysis and Statistics

Title: Spikeinterface-gui: a desktop and web app for spike sorting visualization and curation

Authors: S. GARCIA¹, J. H. SIEGLE², *A. P. BUCCINO²;

¹Ctr. De Recherche En Neurosciences de Lyon, Lyon, France; ²Allen Inst. for Neural Dynamics, Seattle, WA

Abstract: Spike sorting is a critical yet inherently challenging step in extracellular electrophysiology, especially with the increasing use of high-density probes that generate large, complex datasets. While recent advances in automated spike sorting algorithms have improved performance, manual review and curation remain essential for assessing data quality and correcting errors. Effective visualization tools are crucial for inspecting, validating, and correcting these outputs, as well as for evaluating the outcome of automated strategies for spike

sorting curation.

Existing tools partially address this need: *Phy* offers a robust and powerful desktop interface with rich and interactive views, but it is limited to local execution and is no longer actively maintained. *JRCLUST* includes a fast, Matlab-based curation GUI, but this is also restricted to local use and is not actively maintained. *SortingView* provides a modern, web-based experience, but it lacks access to raw traces and individual spikes, and it has no compute capabilities (being a serverless app).

SpikeInterface-GUI (<https://github.com/SpikeInterface/spikeinterface-gui>) is a new, open-source solution built directly on SpikeInterface, a widely adopted framework for building spike sorting pipelines. The GUI supports comprehensive curation workflows, including labeling, merging, and splitting units, alongside automated tools that assist and guide users through these processes. It can be run either as a QT-based desktop or a cloud-friendly Panel app, enabling flexible deployment across local machines and cloud environments. For example, it can be deployed on servers from cloud providers, on a lab workstation for several lab members, or simply run locally.

By combining seamless integration with SpikeInterface, support for cloud-scale workflows, and rich interactive features, SpikeInterface-GUI is positioned a powerful, forward-looking option for spike sorting visualization and curation.

Disclosures: S. Garcia: None. J.H. Siegle: None. A.P. Buccino: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.16/ZZ3

Topic: J.07. Data Analysis and Statistics

Support: NIH U24NS120057
The Kavli Foundation

Title: Ten years of NWB: past, present, and future of standardization in neurophysiology

Authors: *R. LY¹, S. M. PRINCE¹, M. AVAYLON¹, E. HENNESTAD², H. MAYORQUIN², J. MAGLAND³, B. DICHTER², O. RUEBEL¹;

¹Lawrence Berkeley Natl. Lab., Berkeley, CA; ²CatalystNeuro, Fredericksburg, VA; ³Ctr. for Computat. Mathematics, Flatiron Inst., New York City, NY

Abstract: Over its ten-year history, the Neurodata Without Borders (NWB) neurophysiology data standard has grown from a small community-driven effort as part of NWB 1.0 to a comprehensive, leading platform for reproducible, collaborative neuroscience research at scale, data reuse, and AI-driven discovery via NWB 2.0.

NWB 2.0 established a machine-readable schema with production-ready Python and MATLAB

APIs and added integrations with many modern technologies, e.g., data streaming from cloud storage for efficient analysis, advanced I/O via Zarr and HDF5 support, sharing and reuse via the DANDI data archive, and enhanced metadata for linking to ontologies and external resources and cross standard integrations with HED and BIDS. The NWB software ecosystem has grown substantially with NeuroConv and NWB GUIDE streamlining data conversion, NWB Inspector enhancing validation, and NeuroSift enabling interactive file exploration.

Today, NWB adoption is substantial: Over 370 NWB datasets, consisting of over 120,000 experimental sessions, are publicly available on DANDI. Over 35 community tools have integrated with NWB to analyze, visualize, and manage NWB data. Over 20 extensions expand the scope of NWB to encompass new methods, from pose estimation to C. elegans volumetric imaging. Over 100 publications have reused NWB data for secondary analysis and method development. Recent innovations include LINDI, an efficient “virtual” representation of NWB data where large data chunks are accessed on demand; AqNWB, a C++ API enabling direct NWB recording during data acquisition; and a formal process for enhancing NWB governed by the Technical Advisory Board.

Looking ahead, integrated support for virtual datasets will streamline data conversion and modification while enabling linking of data across distributed sources. AI systems will automatically curate datasets and generate tailored educational materials, lowering barriers to data reuse. Cross-standards efforts through BIDS BEP32 and LinkML harmonization will bridge neurophysiology with broader scientific ecosystems. Together, these advances will create analysis and AI-ready datasets that are optimized for cloud computing and enable training of AI foundation models.

Disclosures: R. Ly: None. S.M. Prince: None. M. Avaylon: None. E. Hennestad: None. H. Mayorquin: None. J. Magland: None. B. Dichter: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CatalystNeuro. O. Ruebel: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.17/ZZ4

Topic: J.07. Data Analysis and Statistics

Title: Deeplabcut 3.0: efficient deep learning for single and multi-animal pose tracking and identification

Authors: *M. W. MATHIS, A. MATHIS;
EPFL, Geneva, Switzerland

Abstract: Quantifying behavior is crucial for many applications in neuroscience. Videography provides easy methods for the observation and recording of animal behavior in diverse settings,

yet extracting particular aspects of a behavior for further analysis can be highly time consuming. DeepLabCut was the first tool to innovate in this space, and since the initial publication (Mathis et al. Nature Neuroscience 2018) has been downloaded more than half a million times. While the code-base was actively developed and maintained, after 6 years it is time for a major new release. Here we present DeepLabCut 3.0, which builds on DeepLabCut but with PyTorch as a deep learning framework. DeepLabCut 3.0 comes with more powerful network architectures for pose estimation, reaching state of the art performance for multi-animal interactions in crowded scenes and outperforming DeepLabCut2.0+ and other tools on single and multi-animal benchmarks. Furthermore, it integrates several pre-trained models (SuperAnimal models for mice, quadrupeds and faces) from the DeepLabCut Model Zoo that can be used on over 45 species, without additional manual labels. These models show excellent performance across several pose estimation benchmarks. We demonstrate how to fine-tune the models (if needed) on differently labeled data and provide tooling for unsupervised video adaptation to boost performance and decrease jitter across frames. If fine-tuned, SuperAnimal models are 10-100x more data efficient than prior transfer-learning-based approaches. Overall, DeepLabCut 3.0 provides an integrative suite of tools for project management, deep learning for animal pose, and simple analysis. Additionally, its outputs plug into many downstream applications for behavioral and neural analysis, such as CEBRA, DLC2Kinematics, DLC2Action, Keypoint-MoSeq and beyond. The code remains available at <https://github.com/DeepLabCut/DeepLabCut>.

Disclosures: M.W. Mathis: None. A. Mathis: None.

Poster

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Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.18/ZZ5

Topic: J.07. Data Analysis and Statistics

Support: The Price Family Center for the Social Brain Fellowship

Title: Feral: a video understanding system for behavioral segmentation without tracking

Authors: *J. RAZZAUTI¹, P. SKOVORODNIKOV²;

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Abstract: A quantitative description of behavior is essential for understanding the neural mechanisms underlying it. Current methods for detecting discrete behavioral motifs from videos require keypoint tracking, which in turn requires manual annotations, the training of a separate model, and often involves considerable challenges in achieving accurate and reliable results. Here we present FERAL (Feature Extraction for Recognition of Animal Locomotion), a video understanding system specifically optimized for animal behavior analysis that bypasses keypoint detection entirely. We fine-tuned InternVideo2, an open-source video understanding model, and

enhanced its performance through several technical improvements: Exponential Moving Average (EMA) applied to model weights during training, and ensemble predictions across overlapping video chunks to improve temporal consistency. We also explore a self-supervised pre-training stage to leverage unlabeled videos within behavioral datasets, aiming to maximize the utility of available data. FERAL achieves state-of-the-art performance on standard benchmarking datasets. On CalMS21, we obtained a mean average precision of 0.917, surpassing both the competition winner (0.914) and Google's recent VideoPrism results (0.915). Our system reliably detects discrete behavioral motifs across diverse experimental setups and animal species without requiring keypoint tracking, enabling a direct path from raw video and labels to predictions. We are releasing FERAL as a ready-to-use package, enabling researchers to apply the state-of-the-art system to behavioral video data without the need for additional coding or model development.

Disclosures: J. Razzauti: None. P. Skovorodnikov: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR198.19/ZZ6

Topic: J.07. Data Analysis and Statistics

Title: Improving the detection of sleep stage transitions using Detach-ROCKET algorithm

Authors: *C. SMITH, A. B. SOLANO, V. M. DELLA-MAGGIORE;
UNSAM-CONICET-ICIFI, San Martin, Argentina

Abstract: Accurate classification of sleep stages is essential for evaluating sleep quality, diagnosing sleep disorders and understanding the role of sleep in brain function, learning, and disease. However, the gold-standard method—manual scoring of polysomnographic recordings (PSG)—is time-consuming, costly, and subject to inter-rater variability. While recent machine learning approaches have advanced automatic sleep staging, they often underperform in detecting transitions between stages, particularly between Wake and N1, where EEG signatures are subtle and ambiguous. This limitation is especially relevant in conditions such as obstructive sleep apnea, which involve frequent micro-arousals and fragmented sleep architecture. To address this challenge, we implemented Detach-ROCKET, a lightweight and interpretable linear classification model based on temporal convolutional kernels and feature pruning. Unlike standard ROCKET, which may overfit due to its large feature set, Detach-ROCKET selects only the most informative features—reducing up to 90% of the total—thereby simplifying the model, improving interpretability, and lowering the risk of overfitting. The model operates directly on raw multichannel signals (EEG, EOG, EMG), performs well even with limited data, and enables identification of the most relevant channels for classification. We trained and evaluated the model using 5-fold cross-validation on full-night PSG from 42 healthy young individuals, each recorded with 14 channels (11 EEG, 2 EOG, 1 EMG). Preliminary results show robust

classification performance, with an overall accuracy of 79%, macro F1-score of 76%, and macro recall of 72%. Class-wise accuracy was 85% for Wake, 57% for N1, 74% for N2, 81% for N3, and 84% for REM. Detailed analysis revealed strong performance during stabilized sleep stages, but also promising sensitivity to detect transitions between epochs, particularly between Wake-N1 and N1-N2. N1 sleep stage classification is especially noteworthy, performing much better than the 20% score expected from random guessing and outperforming other current methods, even though N1 sleep has low prevalence and its transitional nature makes it difficult to identify. Ongoing work involves applying Detach-ROCKET to a clinical cohort of patients with obstructive sleep apnea (n = 80), whose abundant stage transitions provide a valuable opportunity to continue refining the algorithm itself with the aim of improving accuracy across all sleep stage transitions.

Disclosures: C. smith: None. A.B. Solano: None. V.M. Della-Maggiore: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Program #/Poster #: PSTR198.20/ZZ7

Topic: J.07. Data Analysis and Statistics

Support: UM1 NS132173
R01 NS121761

Title: A deep learning approach for deformable alignment of 2D microscopy images without training data applied to mouse and marmoset

Authors: *S. FANG¹, D. J. TWARD²;
²Computat. Medicine, Neurol., ¹UCLA, Los Angeles, CA

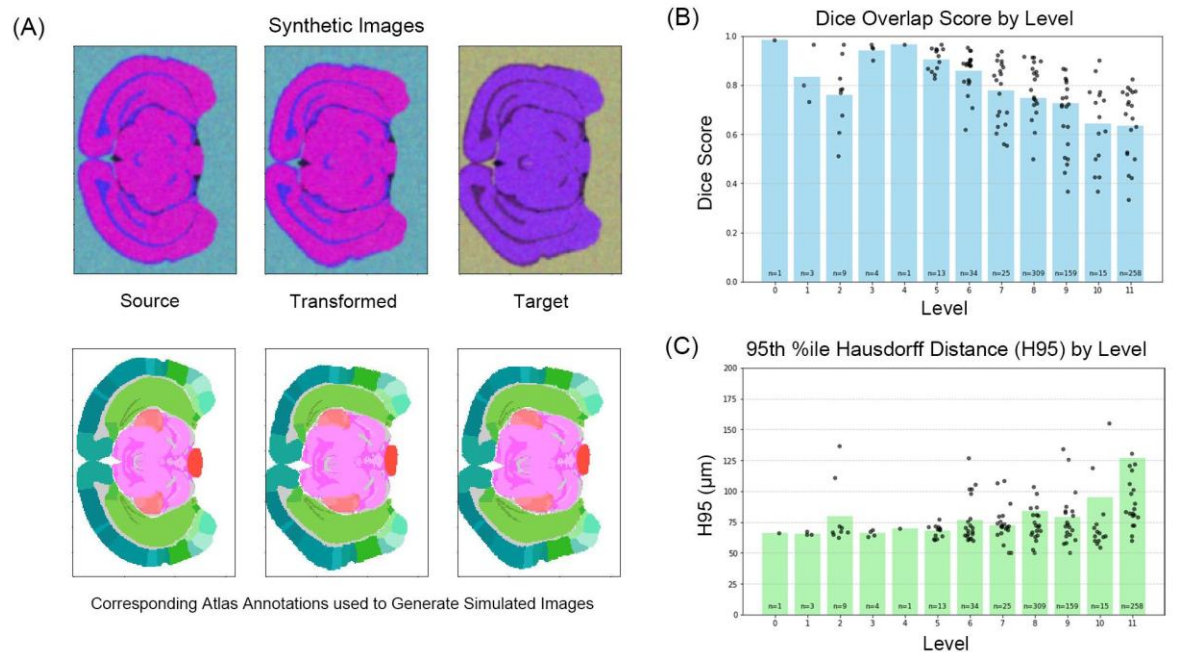
Abstract: Image registration is a fundamental task in neuroimaging, allowing integration of information across imaging modalities and acquisitions. However, differences in contrast and tissue distortion make registration especially challenging. Classical methods are often slow and require manual tuning, while deep learning approaches typically demand large annotated datasets.

We present a deep learning-based framework that overcomes both limitations by rapidly aligning 2D brain sections while being trained entirely on simulated data. Our model jointly predicts affine and non-linear deformations using a convolutional U-Net architecture. The network outputs deformation fields via a scaling-and-squaring algorithm and estimates affine parameters through an auxiliary head. Training used 2 million synthetic image pairs derived from the Allen Mouse Brain Common Coordinate Framework (CCF), eliminating the need for manual annotations.

We evaluate registration performance hierarchically using the Allen Reference Atlas Ontology at

50 μm resolution. On simulated data, the model achieves average Dice overlaps above 80% and exceeds 60% across all ontology levels. The 95th percentile Hausdorff distances remain within 2 pixels for all but the finest level. We further validate the model on real histological data, aligning Nissl-stained sections to an atlas and registering Nissl to myelin sections.

To demonstrate cross-species generalizability, we extend the approach to the marmoset using the Brain/MINDS 3D digital atlas. The reliance on synthetic training data allows robust model development even in data-sparse settings. This method reduces registration time from approximately one minute (traditional methods) to under one millisecond per image pair, enabling scalable, high-throughput analysis of microscopy data. Future work will extend the current 2D framework to full 3D registration.



(A) Example of an image pair with differing contrasts, showing the source image, its predicted deformation, and alignment with the fixed target.

(B) Dice similarity scores evaluated across hierarchical structural levels, demonstrating overlap accuracy between registered and reference segmentations.

(C) 95th percentile Hausdorff distances at corresponding structural levels, capturing boundary alignment error and worst-case spatial deviations.

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Poster

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Topic: J.07. Data Analysis and Statistics

Support: European Union's Horizon Europe Framework Programme under grant agreement number 101136607
European Union and the Ministry of Education and Science under the Operational Programme Jan Amos Komenský (OP JAK), project number CZ.02.01.01/00/23_029/0008437

Title: From Data Integration to Discovery: A Transparent, AI-Driven Framework for Multidisciplinary Brain Research

Authors: *J.-M. C. BOUTEILLER^{1,2}, A. KAKOLLA³, A. S. KHACHATURIAN^{4,1}, Z. KHACHATURIAN^{4,1}, V. DOCKAL^{1,5}, V. SNASEL¹;

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Abstract: On a global scale, there is a massive push to develop and deploy artificial intelligence tools, driven by rapid advances in generative artificial intelligence, large foundation models, and the growing performance of supercomputers/quantum computers. Major financial initiatives such as NIH, NSF, Horizon Europe, the EURO HPC AI Factories network, and similar programs around the world are increasingly focusing on GEN AI, large language models (LLMs), federative machine learning and other AI tools, thus recognizing its transformative potential across industries, with clinical research among the most impacted areas.

Ambitious initiatives such as CLARA, AI-MIND, and the NIH BRAIN Initiative reflect a shared imperative: to create integrative tools that synthesize and contextualize multidisciplinary findings to identify critical parameters and mechanisms—both independent and interacting—that define and measure neuronal and network function. We introduce a modular computational manifold, developed within CLARA, that integrates heterogeneous datasets across biological scales to support hypothesis generation and translational discovery. While developed in neuroscience, the platform is adaptable for broader systems biology use.

Our implementation builds on open-source large language models (LLMs) enhanced through Retrieval-Augmented Generation (RAG) and domain-specific fine-tuning. The current system uses expert-curated literature and subject-matter guidance—initially from calcium signaling researchers—to ensure biologically relevant, auditable outputs. This forms the foundation for a deep learning and generative AI framework, where domain experts iteratively refine logic and extend applicability. Complementing this, a dynamic knowledge graph encodes biological relationships among genes, pathways, and systems-level functions, allowing transparent, explainable traversal of causal mechanisms. Users can explore conceptual links and generate hypotheses traceable to primary sources and expert logic. The platform is being piloted within CLARA and is currently accessible to collaborating institutions, with plans for open-source release of core modules. A visual interface is under development to support researchers without programming expertise. We highlight early results in modeling neuronal resilience and signaling pathways, and outline a roadmap for broader cross-domain translation. These developments underscore the platform's potential as a transparent, hypothesis-generating tool for therapeutic discovery.

Disclosures: J.C. Bouteiller: 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.; CLARA Center, INDRC - Institute for Neurodegenerative Disorders Research Center - Prague (Czech Republic). **A. Kakolla:** None. **A.S. Khachaturian:** 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.; CLARA Center, INDRC - Institute for Neurodegenerative Disorders Research Center - Prague (Czech Republic). **Z. Khachaturian:** 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.; CLARA Center, INDRC - Institute for Neurodegenerative Disorders Research Center - Prague (Czech Republic). **V. Dockal:** None. **V. Snasel:** None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.22/ZZ9

Topic: J.07. Data Analysis and Statistics

Title: High-throughput immunohistochemistry imaging and quantification using PMT-generated images and cloud-based ML-powered software

Authors: ***E. CASTILLO**¹, N. GUANZON¹, A. CERVANTES¹, C. CHARLINE BARABAN², P. BOREL², D. G. WHEELER³;

¹Translucence Biosystems, Irvine, CA; ²Innopsys, Carbonne, France; ³Translucence Biosystems Inc, Irvine, CA

Abstract: High-throughput slice immunohistochemistry studies remain limited by conventional wide-field microscopes, which illuminate each slide with an LED source, capture mosaics with a CMOS camera, and then stitch dozens of fields of view—one slide at a time—under continuous user supervision. In contrast, Innopsys' InnoQuant slide scanner uses laser excitation and PMT detection to scan entire sections line by line. Because no tiling or stitching is required, the scanner delivers uniform, stitch-free images at cellular resolution and can process up to 24 slides in a fully automated run, eliminating throughput bottlenecks. In collaboration with Innopsys, Translucence Biosystems extended its Voxels™ machine-learning platform—originally built for 3D whole-mount analysis—to handle 2D datasets. The adapted workflow reduces background artifacts, isolates true signal, and exports robust metrics at slice-wide and regional scales. To validate the InnoQuant system, brain sections from PBS- and LPS-treated mice were stained for the microglial marker Iba1 and imaged on both the InnoQuant scanner and a research-grade wide-field scope. Intensity profiles and quantitative read-outs were nearly identical across platforms, and both detected a statistically significant LPS-induced increase in the Iba1 signal. Images captured by the slide scanner exhibited higher signal-to-background ratios, enhancing

assay sensitivity and fidelity. Building on this validation, we performed a 24-slide experiment, capturing whole brain slice images in four fluorescent channels (DAPI, GFAP, Iba1 and CD68) and generated cellular resolution count and intensity data on each channel as well as colocalization metrics. The combined InnoQuant + Translucence Biosystems' Voxels pipeline delivers rapid, reproducible quantitative IHC data—accelerating R&D and early drug discovery timelines, supporting regulatory-grade documentation and saving hundreds of hours compared to conventional methods.

Disclosures: **E. Castillo:** 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. **A. Cervantes:** 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. Charline BARABAN:** A. Employment/Salary (full or part-time): Innopsys. **P. Borel:** A. Employment/Salary (full or part-time): Innopsys. **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

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Topic: J.07. Data Analysis and Statistics

Support: NIMH Grant MH122023 to SSN

Title: Characterization of local field potentials for statistical forecasting

Authors: ***A. TAYLOR**¹, V. OMELYUSIK², S. S. NAIR²;

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Abstract: Neural oscillations in the gamma (30-90 Hz) band have been linked to motor and cognitive functions in rodents. Closed-loop control of oscillatory activity in local field potentials (LFPs) requires accurate signal forecasting that may be attainable with deep learning (DL) models. However, the complexity of DL architectures calls for a deeper understanding of predictive properties of LFPs to assist with the development of optimal hyperparameters for DL models. Prior research indicates that LFP signals can be decomposed into a mixture of aperiodic and periodic components, including colored ($1/f^\alpha$) noise. Careful estimation of statistical

properties of these signals allow to rank them on a scale from low (non-informative) to high (deterministic) predictability. Thus, the overall predictive capability of an LFP signal varies based on the influence of each component and needs to be considered when fitting a DL model. Here we compared properties of experimental LFP traces with those of deterministic, pink noise and white noise signals and used these comparisons for the selection of optimal hyperparameters for a convolutional DL model to predict future LFP. Specifically, we analyzed resting-state LFP recordings from 30 channels located in the basolateral amygdala (BLA) of a single rat. For each channel, we estimated the optimal ARIMA order, the last significant lag of autocorrelation (ACF) and partial autocorrelation (PACF) functions, and the maximum spectral power over the significant gamma peaks. We then repeated this procedure for the other signals. ARIMA and ACF estimates demonstrated that LFPs had the highest number of significant lags among the signals, and the last significant ACF value was between the pink noise and the deterministic signal. PACF analysis showed that LFPs had the same last significant lag as the pink noise, and this lag was lower than that of the deterministic signal. Additionally, no trends were found in LFPs or deterministic signals as opposed to the pink noise. Significant gamma power was the highest in LFPs compared to noise signals. Together, these results so far indicate that LFP is positioned between the pink noise and the deterministic signal in terms of predictability, and the deterministic component of LFP is primarily in the gamma band. We then trained and tested a convolutional DL model while systematically varying the kernel size. We found that smaller kernel sizes (less than 20 ms) gave a lower prediction error. Notably, this corroborated the PACF analyses (last significant lag was less than 10 ms). On-going work is focused on improved characterization of both the LFP and of the linkage to optimal hyperparameters of the DL model.

Disclosures: A. Taylor: None. V. Omelyusik: None. S.S. Nair: B. Contracted

Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; This work was supported in part by NIMH grant MH122023 to SSN.

Poster

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Program #/Poster #: PSTR198.24/ZZ11

Topic: J.07. Data Analysis and Statistics

Support: NIH 5U24NS116470-04

Title: A Principled Framework for Compression and Standardization of Multiphoton Data

Authors: *T. T. NGUYEN¹, L. PORTA², J. LECOQ³, D. YATSENKO⁴;

¹DataJoint Inc, Houston, TX; ²HHMI Janelia Res. Campus, Ashburn, VA; ³Mindsight, Allen Inst., Seattle, WA; ⁴Neurosci., DataJoint Inc., Houston, TX

Abstract: Multiphoton imaging generates massive datasets that challenge storage, while signals reported in arbitrary units hinder reproducibility. We present a framework that addresses both issues by combining principled data compression with quantitative signal standardization. Our approach first infers the detector's photon sensitivity (q) by analyzing the linear relationship between signal variance and mean intensity (the Photon Transfer Curve). This q value determines the optimal grayscale quantization for the raw data, enabling highly efficient subsequent compression. The entire process is implemented as a custom zarr codec in an open-source Python package, distributed via PyPI under an MIT license. This implementation allows for transparent data handling, and we have developed extensions for ScanImage to perform this analysis at the push of a button during acquisition.

We have adopted this codec as the primary method for storing raw, unprocessed data in our analysis pipelines. We validated this framework on large-scale 2-photon (2p) and 3-photon (3p) datasets from the MICRONS project, the Allen Institute, and the Sainsbury Wellcome Centre. On MICRONS 2p data, we achieved compression ratios in the range of 3.5 - 9.0x. We confirm that this compression does not affect the downstream analysis of biological signals. Furthermore, converting signals to physical units provides a robust quality benchmark, with peak 2p fluorescence from active neurons reaching over 10^4 photons per second across different systems in quality data.

Our work provides the neuroscience community with a validated, open-source tool to significantly reduce data volume and standardize fluorescence signals. This framework, integrated into acquisition software, improves data management rigor and facilitates more efficient and reproducible large-scale neuroscience.

Disclosures: T.T. Nguyen: None. L. Porta: None. J. Lecoq: None. D. Yatsenko: None.

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Program #/Poster #: PSTR198.25/ZZ12

Topic: J.07. Data Analysis and Statistics

Title: A simple method to identify nonlinear transformations across brain regions

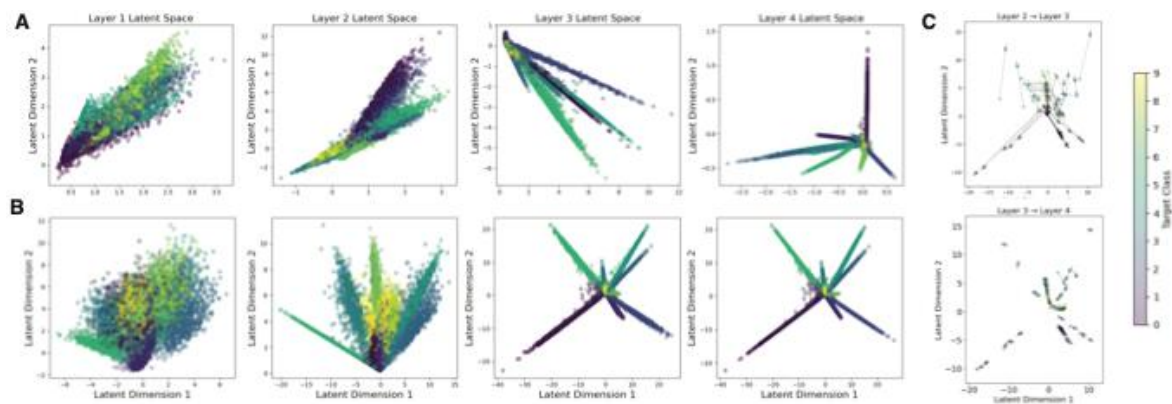
Authors: M. CAO¹, *M. AOI², S. KEELEY¹;

¹Fordham Univ., New York, NY; ²UCSD, San Diego, CA

Abstract: Linear transformations of latent information across brain regions [1, 2] have the following shortcomings. 1) The true (linear) dimensionality of the latent space varies from region to region, as well as the true shared latent dimensionality, presenting a challenge for identification and visualization of the latents. 2) linear models may lack the expressivity to faithfully capture the computation. Here, we address this issue by asserting a \textit{nonlinear} latent variable model, flexible enough to characterize the variability in neural populations in a

small number of latent variables that can be easily visualized. Nonlinear models often have transformation-invariant latent spaces, complicating the alignment and mapping between them; we address this by jointly learning latent representations for multiple brain regions while penalizing their pairwise Euclidean distance.

The linear latent dimensionality of each layer increases, then decreases, suggesting that a linear approach to visualizing and identifying transformations may be challenging (not shown). Figure 1A shows latent representations for VAEs trained on all layers independently, resulting in unaligned latent spaces but showing consolidation of digit manifolds as deep layers progress. Figure 1B shows the latents with a moderate regularization parameter, suggesting identifiable latent transformations from region to region. Figure 1C visualizes this transformation from layers 2 to 3 and 3 to 4, noting the much larger movement from 2 to 3, especially for digits 0 and 1, and minimal movement from 3 to 4, suggesting a more important computation occurs between the second and third layer. Further evaluation (reconstruction accuracy, decoding performance on reconstructed activations, linear vs nonlinear comparison, hyperparameter learning, as well as preliminary results on neural data) not shown here due to space constraints



Disclosures: M. Cao: None. M. Aoi: None. S. Keeley: None.

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Topic: J.07. Data Analysis and Statistics

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NIH Grant N010260407

Title: An AI-Driven Discovery Platform for Brain Connectivity

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Abstract: Understanding the organizational principles of brain connectivity requires systems that can scale with the volume, heterogeneity, and complexity of modern neuroimaging data. As neuroscience transitions into the era of big data, AI tools capable of interfacing with human researchers are essential for extracting meaningful insights from large-scale connectome datasets. In this context, we introduce Brani, an AI-driven discovery platform that leverages large language models (LLMs) and retrieval-augmented generation (RAG) to transform how scientists explore, interpret, and derive hypotheses from brain connectivity data. Rather than focusing solely on data processing or modeling, Brani functions as an interactive scientific collaborator, capable of managing data repositories, retrieving domain-specific knowledge, executing preprocessing workflows, and assisting with both exploratory analysis and scientific reporting. By streamlining these high-level cognitive workflows, Brani enables accelerated, reproducible, and context-aware discovery within the field of brain connectivity. Brani operates using natural language instructions and context upkeep through a chat-based interface. Brani interprets user requests, queries APIs and vector databases, and returns a variety of results. Human-agent interactions are stored in a database, enabling complex contexts to be maintained. The context is used for the agent's heuristics as well as to integrate user interface components, such as visualizations, text outputs, and embedded systems interfaces. Brani uses LLMs and employs plugins to allow system extensibility. Using plugins, developers can integrate Brani with API-based data platforms. Plugins are defined by two constructs: Entities (data structures and metadata within each platform) and Workflows (user actions stored in the agent's knowledge base, operating on the entities). This design enables Brani to interact with platform-specific components for data visualization and metadata management, maintaining a simple yet powerful integration infrastructure. This work contributes an extensible and community-driven infrastructure that bridges methodological innovation with practical usability for neuroscientists. Brani leverages modern research infrastructure to advance neuroscience research. Brani lowers access barriers to neuroscience research, supporting reproducibility, and automating complex analyses. Brani can lay the foundations for future progress toward AI-assisted, data-driven research, empowering a new generation of AI-augmented neuroscience investigations.

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Topic: J.07. Data Analysis and Statistics

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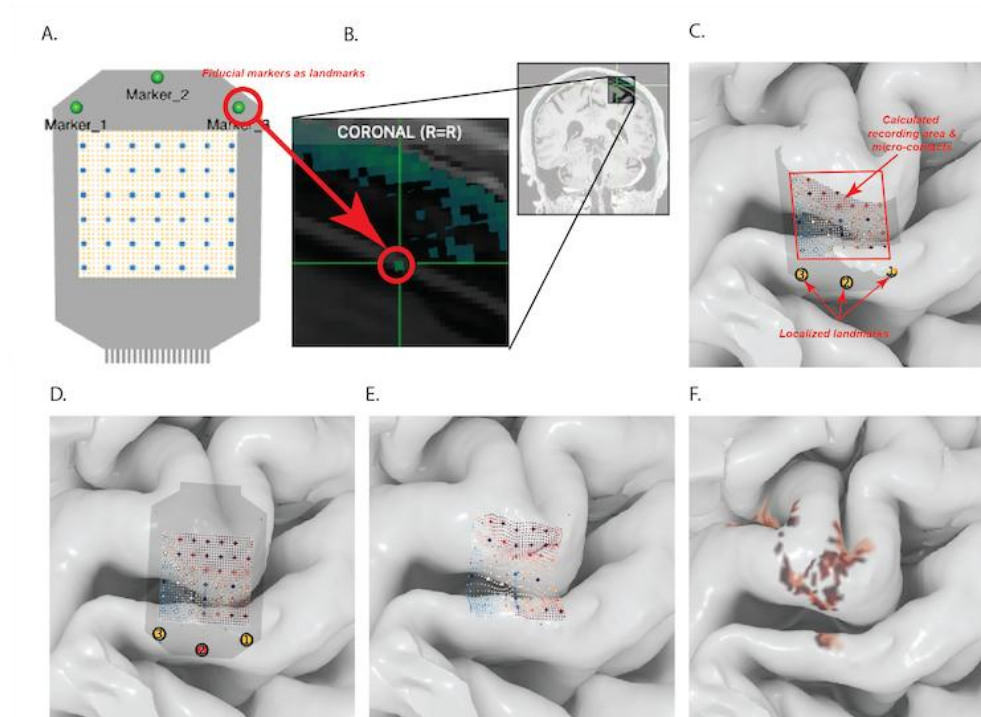
Title: Analyzing and visualizing data from human patients implanted with sEEG and ECoG electrodes in your web browser with RAVE

Authors: *Z. WANG, X. ZHANG, J. F. MAGNOTTI, M. S. BEAUCHAMP;
Univ. of Pennsylvania, Philadelphia, PA

Abstract: Intracranial electroencephalography provides a unique opportunity to record from small populations of neurons in the human brain using grid and strip (electrocorticography, ECoG) or shafts of stereoencephalographic (sEEG) electrodes. RAVE (Reproducible Analysis and Visualization of iEEG) is a comprehensive toolbox that includes YAEL (Your Advanced Electrode Localizer). RAVE and YAEL are open source and freely available from <https://rave.wiki>

New features of RAVE and YAEL include:

1. Support for micro-ECoG arrays: high-density electrode technologies are rapidly emerging, such as the Precision Neuroscience micro-array with 1024 contacts and the MXene micro-array with 126 contacts (see Averbek et al., SFN Abstracts 2025). Create fine grained anatomical analyses (e.g. arm, shoulder, finger representations) on cortical surface models to take advantage of the high spatial resolution of these arrays (see Figure 1).
2. Standalone 3D viewer for easy sharing: Patient imaging data, electrode locations and the results of iEEG analyses can be included in reports.
3. Support for fMRI, Diffusion MRI (tractography) and custom anatomical atlases (ROIs). Simply drag-and-drop any 2D or 3D dataset onto the 3D viewer.
4. Automatic localization of sEEG electrodes: Manually localizing sEEG contacts from a CT scan is time-consuming and error prone. YAEL streamlines this process with automated electrode localization. RAVE can create surface models of ROI (such as thalamic or other subcortical nuclei) and display them alongside sEEG shafts to allow for precise delineation of the location of each contact.
5. Report generation. Easily summarize the results from dozens of patients with HTML files that show trial-level, electrode-level, and experiment-level analyses. Reports can be opened by anyone with a web browser, without installing RAVE. This greatly simplifies collaboration and data sharing.



Localizing thinfilm ultra-density micro-ECoG and generating functional parcellation:
A. Electrode geometry containing the contact locations relative to fiducial landmarks; B. CT scans are aligned with MRI, and the user localizes each fiducial marker; C. RAVE-YAEL calculates the contact positions and displays them in 3D with cortical surface models; D. The user adjusts electrode positions to align predicted gyral-sulcal boundary with the anatomical structures; E. Contacts are projected onto the cortical surface models while preserving the electrode topology; F. Electrode data is mapped to the brain surface, resulting in fine-grained functional parcellation.

Disclosures: **Z. Wang:** None. **X. Zhang:** None. **J.F. Magnotti:** None. **M.S. Beauchamp:** None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

Time: Monday, November 17, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR198.28/ZZ15

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Title: SyncGenie: open-source hardware for stimulus synchronization and more

Authors: *L. ALKHOURY¹, S. A. SHAH², D. GUPTA³, J. HILL⁴, P. SWISSLER⁵, G. SCANAVINI¹;

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Abstract: The SyncGenie is a programmable synchronization device designed for a range of uses in neuroscience research. With its default firmware, it is a configurable stand-alone “trigger box” that enables neurophysiological data to be aligned with physical stimulus events. It can also be re-programmed for a wide range of other applications: for example, to support both hardware-triggered and software-triggered pulse synchronization, to measure audio or video latencies, to deliver trigger pulses on unique custom-programmed schedules, or even to serve as a cost-effective digitizer for real-time analysis of analog signals. In short, it is the neural engineer's "Swiss Army knife." The SyncGenie is an open-source hardware device, per OSHA certification number US002698. The printed circuit board design file, 3D-printable model for the enclosure, components list, assembly instructions, Arduino library, example firmware, and instruction manual are all disseminated via a dedicated repository on the Open Science Framework (<https://osf.io/r9pb6>). The repository now includes the circuit-board design and 3D-printable mount model for a SyncGenie-compatible photo-sensor. The sensor can be mounted easily on the corner of a screen to record visual triggers. We present performance data from a typical visual synchronization use case.

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Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

Location: SDCC Halls B-H

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Program #/Poster #: PSTR198.29/ZZ16

Topic: I.03. Decision Making

Support: NIH/NEI grant EY30155

Title: Universal dynamic nonlinearity in the neuronal kinetics underlying neurophysiological, electroretinographic, psychophysical and fMRI response dynamics

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Abstract: Introduction. It is well established that the typical neuronal response to a prolonged pulse stimulus is some version of an initial transient followed by a sustained plateau, with a roughly exponential decay at the stimulus offset. This form of response reflects a dynamic nonlinearity, since a linear system would show an Off response of the same transient form as the On response, though inverted in sign. The exponential decay that is typically seen at offset thus represents the operation of a dynamic nonlinearity that cannot be fit by the widely-used analytic approach of general linear modeling (GLM). Corresponding versions of this form of dynamic nonlinearity are found in the neurophysiological domains of temporal population receptive fields (tpRF), electroretinographic (ERG), psychophysical (PP) and functional Magnetic Resonance Imaging (fMRI). The analysis is structured under the assumptions of Tyler & Likova (2011), that the metabolic response kernel (MRK) that controls the BOLD function is largely defined by the metabolic functions of the cortical astrocytes and is uniform across the cortical areas, whereas the neuronal response function accounts for the variety of response behaviors across the cortex. Methods. We take a structured neuroanalytic approach of modeling the neuronal response dynamics with kernels consisting of a difference of gamma functions, the conventional solution to the molecular diffusion equation, convolved with the stimulus waveform. The novel aspect of this approach, however, is to precede the convolution with a saturating nonlinearity compressing the peak of the gamma function to a constant plateau, followed by adaptive gain control and sign-specific rectification with differential onset and offset gains. The sum of these two components provides the analytic predictor for the neuronal response in ERG and tpRF recordings, and PP probe paradigms, while a second convolution with a linear kernel for the metabolic/hemodynamic response function then provides the predictor for the cortical fMRI response dynamics. Results. This sign-specific nonlinear temporal modeling (SSNTM) approach provides an excellent characterization of the response waveforms at multiple levels of brain recording, from the single-cell to the whole-brain level, from sensory input to higher cortical responses. It can greatly reduce the residual error of the model fits relative to GLM, and captures significant aspects of the response that are completely missed by GLM. Conclusion: The SSNTM analysis provides a computationally tractable approach to characterizing the universal temporal nonlinearity of neural systems.

Disclosures: C.W. Tyler: None. L.T. Likova: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Topic: J.07. Data Analysis and Statistics

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Title: Promoting open science through community container registries

Authors: ***B. D. GRIER**^{1,2}, P. NUYUJUKIAN^{3,4,5,1};

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Abstract: Reproducibility is fundamental to scientific progress, yet widely acknowledged to be lacking. Issues with reproducibility are often discussed in the context of experiments, but they are endemic in data analysis as well. In an ideal world, researchers would be able to reproduce analyses simply by having access to data and the associated code. This is rarely the case however. Analysis code is typically dependent on additional software present in the computational environment, and this is the root of many reproducibility issues. Software libraries are difficult to build due to dependency conflicts and actively-maintained packages are not stable over time. Additionally, software libraries are difficult to port between operating systems. Containerization, recognized as an industry standard within the tech and IT sectors, directly addresses these issues. By providing isolated, consistent, and portable computational environments, containers ensure that analysis is reproducible and easily shareable. Here we introduce the “Community Container Depot”, a resource aimed at aggregating and disseminating containerized computational environments that are built and used by the neuroscience community. Users are able to submit containers used in their own research group and make use of containers submitted by others. A collection of containers developed by the community fosters collaboration and drives standardization of methods. Additionally, in conjunction with tools we have built to aid in creating custom containers, sharing containers reduces the barrier to entry for those wishing to replicate and build on previous findings. This positions the Community Container Depot as an effective tool for advancing neuroscience research and more broadly, promoting open science.

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Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Topic: J.07. Data Analysis and Statistics

Support: NIH U19NS118284

Title: Trusted Timestamping for Neuroscience

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Abstract: Digital data has become integral to neuroscience research, now commonly serving as the primary record. This makes data integrity critical to successful research and its rigor, reproducibility, and transparency. However, as dataset volumes continue to scale, so does the associated challenge of maintaining its integrity. Currently, researchers have limited tools to assert the integrity of digital data, particularly as large datasets are transferred from one storage location to another. This makes alterations to research data, regardless of intention, difficult to detect. In the rare cases of intentional scientific misconduct, publications arising from data manipulation can take years to uncover (if ever), derail progress, and significantly erode public trust in science. This presentation presents trusted timestamping, an open source and easy to use software framework to address the challenge of data integrity associated with scientific data generation. It leverages a well-established open standard, the Time-Stamp Protocol (IETF RFC 3161), ubiquitous in the information technology industry for providing integrity guarantees of software. This timestamping framework generates cryptographically secure assertions of any desired data file or directory of files, proving that a dataset existed in the exact version (down to the bit-level) at the time it was timestamped. This timestamp provably asserts that, if the underlying dataset hash matches, then the specific version of the data has not been altered, even years later. These assertions contain no information regarding the data, and can be publicly shared without any loss of privacy. The framework is available as a thin wrapper around the openssl software library and currently generates timestamps against several commercial timestamp authorities for each dataset. Additionally, an anonymous web API exists for convenience at timestamp.stanford.edu that records all timestamps into a public record ensuring the long-term integrity of the timestamps generated through the API. Finally, this framework also has hooks into git, facilitating easy and integrated timestamps of each git commit. In this manner, any git repository can be used as a free and legally defensible electronic lab notebook. If adopted broadly, approaches such as the framework presented here can help address the growing challenge of data integrity and help increase the public trust in scientific research.

Disclosures: P. Nuyujukian: None.

Poster

PSTR198: Techniques and Software for Imaging and Neural Analyses: In Human and Animal Models

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Topic: J.07. Data Analysis and Statistics

Title: Implementations of the ARTS open framework in neuroscience

Authors: *S. DASGUPTA¹, P. NUYUJUKIAN^{1,2,3,4};

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Abstract: The advancement of neuroscience research is reliant on the ability to clearly articulate analyses performed on data using code. While the way data is being stored and cataloged has become more standardized, the lack of sharable computing environments and fully accessible pipelines is a barrier to reproducing scientific findings. The archival, reproducible, and transparent science (ARTS) open framework incorporates containers, version control systems, and persistent archives through which all data, code, and figures related to a research project can be stored together and easily recreated. Example depositions relevant to neuroscience are presented which showcase how reproducibility and transparency of neuroscience workflows may benefit from platforms built around long-term sharing and validation.

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