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Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP001.01/LBP001

Topic: A.01. Neurogenesis and Gliogenesis

Support: NSF 2235566

Title: Cas adaptor proteins are required for cerebellar development

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Abstract: The cerebellum is responsible for motor coordination, balance, and posture as well as non-motor functions such as working memory, language, emotion processing, and executive function. Proper establishment of cerebellar circuitry is critical to cerebellar function and relies on the appropriate positioning of cells within the cerebellum. A coordinated series of events between granule cells, Purkinje cells, and Bergmann glia is hypothesized to contribute to the formation of cerebellar folia. However, the intracellular molecular mechanisms underlying cerebellar foliation remain to be elucidated. Using a *Cas* Triple Conditional Knock Out (Cas TcKO) model generated in our lab, we provide genetic evidence that Cas adaptor proteins are broadly required for cerebellar foliation. Genetic dissection of Cas TcKO mutants reveals a non-neuronal autonomous requirement of *Cas* genes in the formation of the Bergmann glial scaffold. Additional analyses show that Cas proteins are required for proper foliation patterning in a granule cell-autonomous manner. These findings build on previous research from our lab demonstrating that Cas proteins are key mediators of adhesion signaling during glial scaffold formation.

Disclosures: A.M. Treptow: None. **J.A. Estep:** None. **M. Riccomagno:** None.

Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP001.02/LBP002

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant NS002824-34

Title: Median Eminence Cues Influence Migration vs Axonal Targeting of GnRH Neurons

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Abstract: Migration of gonadotropin-releasing hormone (GnRH) neurons is critical for reproduction, with disruption in humans leading to delayed or absent puberty. GnRH neurons originate in the nasal placode and migrate into the forebrain. Once within the brain, like other neuroendocrine cells, GnRH axons target the median eminence (ME), where they release peptide into the portal capillary system, stimulating anterior pituitary cells. While molecules guiding GnRH neuronal migration have been identified, cues directing GnRH fibers to the ME remain unknown. To investigate factors within the ME, embryos were taken at E14.5 from WT mice, frozen immediately and stored until use (-80). Cryostat sections (150μm) were made, ME regions punched out, immediately placed in RIPA and protein concentration determined. Nasal explants containing primary GnRH neurons were prepared from E11.5 mice, prior to GnRH neurons leaving the proximity of the olfactory pit. Protein lysates (.33mg/ml) were placed in a well, mixed with 2% low-melting agarose to allow gradual release. Explants were positioned ~2 mm from the wells and cultured for 4 days in serum-free media. Explants were then fixed, stained for GnRH, and imaged. Analyses included: (1) distance GnRH cells migrated, (2) GnRH fiber length, and (3) orientation of GnRH cells/fibers relative to target well. Data were analyzed using unpaired Student's t-test or Chi-square with post hoc analysis. Preliminary analyses revealed that GnRH cells in the presence of ME protein lysate migrated shorter distances from the explant edge, indicating that the lysate slowed the overall rate of migration. However, despite reduced migration, GnRH neurons demonstrated clear directional orientation, with a significant proportion of GnRH cells and processes projecting toward the ME protein well relative to controls. Furthermore, GnRH fibers in ME-treated explants were markedly longer, suggesting that the protein lysate promotes axonal elongation in addition to directional guidance. Together, these results indicate that soluble factor(s) in the ME lysate create an attractive environment for GnRH fibers while simultaneously modulating the migratory behavior of GnRH neurons. This suggests that GnRH neurons respond to distinct molecular signals as they transition from a migratory to a fiber-targeting state. Such mechanisms may ensure that neurons in different brain locations project axons accurately to the ME for proper neuroendocrine function. Ongoing work is focused on fractionating protein lysates to identify the responsible molecule(s). Identifying these factors may reveal novel targets for therapeutic intervention in reproductive disorders.

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Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

Location: SDCC Hall B

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Program #/Poster #: LBP001.03/LBP003

Topic: A.01. Neurogenesis and Gliogenesis

Support: 1F31NS139663-01
ARCS Foundation Award

Title: Neonatal Hypoxic Injury Disrupts Arc Neuroblast Migration in the Human Infant Brain

Authors: *A. PODDAR[1], M. F. PAREDES[2];
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Abstract: The development of the infant brain is a dynamic, intricate process that, when disrupted, can lead to long-term neurological disability. In humans, new inhibitory neurons (IN) continue to be born and migrate into specific cortical destinations late in gestation and into the first six months of life. These neurons emerge from an expanded subventricular zone, termed the Arc, which is detectable on fetal and neonatal MRI. Neonatal Hypoxic Injury (HI) is a common and debilitating injury that occurs during late gestation and early infancy. Considering the growing awareness that INs migrate through the white matter along with the frequency and clinical outcomes of HI, it is critical to understand the impact of hypoxia on late migrating INs. To investigate these effects, we combined molecular and cellular profiling of postmortem human infant tissue from hypoxic-ischemic encephalopathy (HIE) donors with an in vitro piglet model. Analysis of human HIE tissue revealed disorganized migrating neuroblasts (DCX+ cells) with aberrant trajectories compared to those in neurotypical controls. To evaluate Arc structure globally, we analyzed T2 MRI sequences from the High-Dose Erythropoietin for Asphyxia and Encephalopathy (HEAL) Trial in neonates with suspected HIE. Arc volume on T2 MRI correlated inversely with injury severity, suggesting disrupted migration. To model this injury, we leveraged the neonatal piglet which shares key organizational and migratory features of Arc INs. Piglet organotypic slice cultures exposed to low oxygen recapitulated key features of human injury. Single-cell RNA sequencing revealed hypoxia-induced transcriptional adaptations in inhibitory neurons, including persistent changes that remained days after reoxygenation. Comparing these results to single-cell RNA sequencing of postmortem human tissue identified shared molecular pathways implicated in migration and injury response. Together, these results demonstrate that neonatal hypoxia disrupts postnatal IN migration and highlights potential molecular targets for therapeutic intervention in HIE.

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Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

Location: SDCC Hall B

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Program #/Poster #: LBP001.04/LBP004

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH Grant P20GM103443

Title: Investigating the role of microplastics in human neural cells

Authors: *C. OLSON[1], C. KIZILKAYA[1], H. K. SHOMUDRO[2], M. PAWLUS[1];
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Abstract: Current studies indicate the ubiquitous nature of microplastics in both external and internal environments, suggesting the possibility of these compounds in influencing many aspects of human health. Toxicity induced by exposure to polystyrene microplastics has been observed and shown to result from increased cellular accumulation of reactive oxygen species (ROS) in several human cell types, suggesting a causative role in a wide range of human pathologies. Currently a connection between microenvironmental plastic exposure and neural development and disease remain incompletely characterized. This project investigates possible mechanisms of cytotoxicity and tests the hypothesis that changes to important cellular signaling pathways are induced in human neural cells by polystyrene microplastics. We specifically investigate intracellular mechanisms relevant to oxidative stress, cell differentiation, and metabolism as these factors are known to be affected by cellular ROS accumulation and are implicated in the development of a range of human neural pathologies. To investigate a connection between plastic exposure and SH-Sy5Y toxicity we use cell functional assays, gene expression, microscopy, metabolic analysis and differentiation assays. Our work will characterize the connection between plastics in the internal microenvironment and human neural cells and investigate potential therapeutic strategies designed to disrupt the malfunctions driven by these compounds. The data collected from this study will form a basis for future studies which will investigate the effects of polystyrene microplastics on neurogenesis and development in zebrafish models.

Disclosures: C. Olson: None. **C. kizilkaya:** None. **H.K. Shomudro:** None. **M. Pawlus:** None.

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Topic: A.01. Neurogenesis and Gliogenesis

Support: National Research Foundation of Korea (NRF) grant funded by the Ministry of Education, Science and Technology (RS-2024-00431492)
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National Research Foundation of Korea (NRF) grant funded by the Ministry of Education, Science and Technology (RS-2023-00225239)

Title: Subgranular neural stem cells dynamics in vitromicrofluidic 3D spheroid culture platform

Authors: T. HUYNH[1], ***C. HEO**[2];
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Abstract: The hippocampus is a primary brain area responding for memory formation and severely affected by Alzheimer's disease. Although hippocampus is important to study Alzheimer's disease and drug development, pathophysiological mechanism of the malfunctional hippocampus is not fully understood because of the lack of proper *in vitro* models that faithfully recapitulate physiological and pathological features depending on the progress of diseases. Here, we introduce 2-layer hippocampus modeling using a microfluidic 3D spheroid culture platform. The 3D hippocampal spheroids were generated by 2 layered neurospheroid with adult subgranular zone-derived stem cells and hippocampal neurons subsequently with the microfluidic culture device. We proceed the spheroid culture for 3 weeks with over 90% of cell viability. The spheroids obtained from our platform exhibited high uniformity and the circularity of layered neurospheroids increased gradually overtime. The centric neural stem cells differentiated and migrated alongside the outer layered hippocampal neurons in 3D neurospheroid represented differently from 2D coculture. The centric neural stem cells showed differentiation ability in parallel to migration to give rise to newborn neuron and glial cells for the hippocampal model. In addition, the gene expression exhibited that gene sets related to neurogenesis, glial cell development and myelination, and neurotransmission significantly regulated during hippocampal spheroid development. Our advanced hippocampal model using the 3D microfluidic platform is a robust solution for translational medical research of recapitulate hippocampus region of the brain.

Disclosures: T. Huynh: None. **C. Heo:** None.

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Topic: A.01. Neurogenesis and Gliogenesis

Support: R01MH126195
T32HL166146

Title: A 3D bioprinted scaffold for generating in vitro morphogen gradients to pattern human cortical organoids

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Abstract: Brain organoids recapitulate key cellular and architectural features of native tissues, advancing our understanding of neural development and diseases. However, tools to pattern different brain regions within a single organoid are not well established. Previously, our group has developed the framework to use 3D bioprinted gelatin methacrylate (GelMA) scaffolds to support long term cortical organoid (hCOs) culture. The objective of this work is to develop functionally perfusable 3D bioprinted GelMA scaffolds that endow spatiotemporal control of morphogens to reproducibly polarize individual brain organoids into pallial and subpallial fates. Using digital light processing 3D bioprinting, we have designed a parallel two-channel scaffold to facilitate the perfusion of different medias compositions and generate a temporally stable morphogen gradient within our construct. Our optimized bioprinting parameters result in constructs with a percent error between 1-13% and coefficient of variation between 0.5-5.75% when compared to intended dimensions. To validate gradient formation within our perfused scaffolds, we use red and blue color additives within each channel and perform time course studies. Small molecular weight additives (~500 Da) readily diffuse through the hydrogel without maintaining a gradient and instead fully saturate the gel surrounding the organoid. However, larger (70kDa) dextrans demonstrate the formation of a stable gradient over a time course spanning at least 48 hours. We are now patterning embedded cortical organoids by perfusing the ventralizing molecule Sonic Hedgehog protein (SHH, MW=20-25kDa) through one channel to mimic the secretion from the floor plate during neural development. Ultimately, this platform will allow us to manipulate organoid differentiation by leveraging morphogen gradients to create more sophisticated and reproducible patterning phenotypes.

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Late-Breaking Poster

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Title: NeuroMeshoids: A scalable 3D nylon mesh-based platform for off-the-shelf hiPSC-derived neural organoid modeling

Authors: *K. AWASTHI[1], C. L. HOWE[2];
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Abstract: Background: Conventional 2D neural monolayer cultures exhibit limited structural complexity and functional connectivity. Although 3D neural organoid models overcome some of these issues, current models are often hindered by poor reproducibility, limited scalability, mechanical instability, and the need for complex hydrogels. To address these limitations, we developed NeuroMeshoids, a 3D culture platform that utilizes nylon mesh scaffolds to support the differentiation, maturation, and long-term maintenance of human induced pluripotent stem cell (hiPSC)-derived neural aggregates.
Methods: hiPSCs were differentiated into neural stem cells using dual SMAD inhibition and matured into mixed neuronal and glial populations using a growth factor cocktail. After 14 days, aggregated cultures were replated onto Geltrex-coated nylon mesh (40 and 70 μm pore sizes) to yield NeuroMeshoids. Morphological and functional characterization included immunofluorescence microscopy, scanning electron microscopy, cell viability assessment, qPCR, calcium imaging, and neurite tracing. NeuroMeshoids were compared with 2D cultures using gene expression and analysis of neurite complexity, synaptic density, and spontaneous neuronal activity.
Results: NeuroMeshoids exhibited robust attachment, extensive axonal outgrowth, and long-term viability on the mesh platform. Confocal microscopy and SEM revealed complex, fasciculated neurite networks spanning multiple z-planes and extending over long distances. qPCR showed >2-fold upregulation of neural (MAPT, MAP2, TUBB3) and synaptic (SYN1, DLG4, SLC17A6) markers in NeuroMeshoids relative to 2D cultures. Image-based analyses confirmed enhanced neurite length, branching, junction formation, and synaptic puncta density in the NeuroMeshoids. Calcium imaging revealed spontaneous, spatially distributed activity, indicating functional network formation. NeuroMeshoids also exhibited preservation of morphology and function after recovery from cryopreservation.
Conclusions: NeuroMeshoids represent a robust and scalable 3D neural culture system that facilitates accelerated neuronal maturation, synaptic connectivity, and long-term viability. The mechanically stable nylon mesh architecture supports complex neural network formation, advanced imaging, and functional analyses, and provides robustness to physical manipulation, cryopreservation, and recovery of the cultures. This platform holds promise as a reproducible and scalable “off-the-shelf” model for research and high-throughput drug screening.

Disclosures: K. Awasthi: None. **C.L. Howe:** None.

Late-Breaking Poster

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Title: Robust production of parvalbumin interneurons and fast-spiking neurons from human medial ganglionic eminence organoids

Authors: *M. P. WALKER[1], M. C. VARELA[2], J. BOK[3], E. L. CRESPO[4], T. THENSTEDT[4], L. GOLDSTEIN[4], A. M. TIDBALL[4], J. LI[5], Y. YUAN[6], L. L. ISOM[6], J. FU[3], M. D. UHLER[7], J. M. PARENT[4];
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Abstract: Parvalbumin (PV)-expressing cortical interneurons, which arise primarily from the medial ganglionic eminence (MGE), are critical regulators of cortical excitability and their dysfunction has been implicated in numerous neurodevelopmental disorders. While human pluripotent stem cell (hPSC)-derived brain organoids provide a promising platform to study human interneuron development and disease mechanisms, generating organoids that produce substantial levels of PV interneurons remains a significant challenge. We hypothesized that modulating WNT inhibition and Sonic Hedgehog (SHH) pathway activation would generate brain organoids that closely mimic human fetal MGE development and yield robust PV interneuron production. By systematically optimizing the timing and concentration of these morphogens, we successfully established a protocol that generates self-organizing single-rosette MGE organoids (MGEOs) that strongly express MGE lineage markers, including *LHX6, NKX2.1, PV,* and *SST*. To ensure reproducibility, we used female embryonic, female blood-derived, and male fibroblast-derived hPSC lines in our studies. Using immunostaining, RT-qPCR, and single-cell RNA sequencing, we found MGEOs closely resemble the transcriptomic profile of the developing human MGE and produce MGE derived cortical- and subpallial-fated interneurons, oligodendrocytes, and astrocytes. Our immunostaining revealed robust and stable expression of PV from 120+ days *in vitro,* along with expression of $K_v3.1$ and perineuronal nets. Using human cortical organoid-MGEO assembloids, we show that MGEO-derived interneuron progenitors rapidly migrate and integrate with excitatory cortically patterned organoid cells upon fusion. After long-term culture, these assembloids exhibited synchronous network activity on multielectrode arrays and showed abundant fast-spiking units upon spike sorting. Patch-clamp recordings in assembloid slices revealed spontaneous excitatory and inhibitory postsynaptic currents, further confirming functional synapse formation and integration. Our novel MGEO model provides a key human-specific platform for studying the development of PV and other MGE-derived cell types, and for modeling interneuron-related phenotypes in genetic epilepsies and related neurodevelopmental disorders.

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Late-Breaking Poster

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Program #/Poster #: LBP001.09/LBP009

Topic: A.01. Neurogenesis and Gliogenesis

Support: National Institute of Standards and Technology

Title: Palmitate-mediated impaired neuronal and glial differentiation of embryonic mouse neural progenitor cells

Authors: *S. KARMALI[1], S. DESAI[2], J. HERNANDEZ[3], M. BAQUEIRO[4], M. G. ROSS[3,5], M. DESAI[3,5];
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Abstract: Introduction:Both epidemiological and experimental models support theDevelopmental Origins of Health and Disease paradigm, which posits that environmental exposure—particularly during sensitive prenatal and postnatal windows—have durable consequences for neural architecture and cognitive function. Previous studies implicate palmitate-induced lipotoxicity in reduced dendritic complexity, synaptic density, and imbalanced neurogenesis-gliogenesis. Disruption of the neurogenesis and gliogenesis balance during development can lead to long-term deficits in brain function, yet the direct cellular mechanisms driving these developmental shifts remain underexplored. **Aim**:This study investigated the effects of palmitate exposure on mouse embryonic neural progenitor cells with focus on neuronal/astrocyte differentiation and morphology. **Methods**:Neural progenitor cells (NPCs) derived from the ganglionic eminence of E12.5C57BL/6 mouse embryos were treated with palmitate(0, 25, 100μM/48h) for 5 days during differentiation. Thereafter, cells were immunostained for neurons (MAP2n) and astrocytes (GFAP) and cell counts, and neurite length were assessed using the Keyence microscope. **Results**:NPCs exposed to palmitate demonstrated significant dose-dependent impairments in differentiation and morphological development. Treatment with 25μM palmitate modestly reduced neurogenesis (55.9%), whereas treatment with 100μM palmitate caused significant reduction in neurogenesis (22.9%) as compared to non-treated controls (59.6%). Astrogenesis was similarly affected with a decrease of 46.3% and39.3% at 25μM and100μM palmitate, respectively as compared to controls (54.5%). Morphological analysis revealed progressive reductions in neurite outgrowth, with shorter axon lengths in palmitate treated cells vs controls(25μM:55.8± 23.5μm;100μM:48.7± 23.3μm vs. 68.4± 21.7μm). Neurite lengths showed parallel reductions (35.8± 19.1, 35.1± 17.8vs. 46.9± 20.8μm), respectively.**Conclusion**:Thus, elevated palmitate concentrations significantly

compromise neuronal and glial differentiation while impairing neuronal maturation and connectivity. These findings demonstrate a potential cellular mechanism by which maternal obesity and high-fat diets may impair fetal brain development, contributing to long-term neurodevelopmental deficits.

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Topic: A.01. Neurogenesis and Gliogenesis

Support: Maryland Stem Cell Research Fund Launch Program 2024MSCRFL6374

Title: Substrate stiffness regulates iPSC-derived brain microvascular endothelial cell differentiation and maturation

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Abstract: Substrate stiffness regulates iPSC-derived brain microvascular endothelial cell differentiation and maturationEvan Newman, Li Yan Fischell Department of Bioengineering, University of Maryland, College Park, MD 20742, USAExtracellular matrix (ECM) stiffness is an important mechanical cue that influences neural and vascular development, but its contribution to blood-brain barrier (BBB) formation remains unclear. The BBB, formed by brain microvascular endothelial cells (BMECs) in close interaction with other neurovascular unit components, is highly sensitive to cell-ECM interactions. Mechanical cues, like stiffness, are known to regulate cell fate, signaling, and barrier function, yet the mechanistic role of ECM stiffness in BMEC differentiation and maturation has not been fully defined. We hypothesized that ECM stiffness regulates endothelial identity during BBB development. To test this, we engineered basement membrane hydrogels with tunable stiffness (1 kPa, 2.5 kPa, or 5 kPa) and differentiated iPSC-derived BMECs (iBMECs) on them. Gene expression was analyzed by RNA sequencing and quantitative PCR. Differential expression and Gene Ontology (GO) enrichment analyses were performed to identify biological processes regulated by stiffness at early and later stages of differentiation. GO enrichment at Day 4 showed that all stiffness conditions promoted developmental signaling, with distinct profiles. 1 kPa hydrogels enriched angiogenesis, mesenchyme development, and axon guidance; 2.5 kPa hydrogels highlighted forebrain development, neuronal projection guidance, and Wnt signaling; and 5 kPa hydrogels emphasized muscle tissue development, adhesion, and regulation of Wnt signaling. By Day 6, stiffness-dependent effects persisted relative to tissue culture plastic controls. iBMECs on 1 kPa gels

showed enrichment for cell fate specification and neuron differentiation, whereas 5 kPa hydrogels enhanced pathways related to mesenchyme development, junction assembly, and positive regulation of growth. Wnt-related pathways were more strongly represented in the stiffer condition, suggesting that mechanotransduction promotes endothelial identity and BBB specialization. These findings demonstrate that ECM stiffness dynamically regulates neurodevelopmental and barrier-associated gene programs in iBMECs. By shaping endothelial maturation through biomechanical signaling, stiffness provides a key determinant of BBB development and offers a strategy to create more physiologically relevant in vitro models for studying neurological disease.
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Late-Breaking Poster

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Topic: A.01. Neurogenesis and Gliogenesis

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Title: Absence of a microbiome results in variable perturbations on microglial morphology during postnatal swine brain development

Authors: B. A. LESTER[1], C. KELLY[2], S. HENRY[3], I. ELIAS[2], S. CEVENINI[2], M. HENDRICKSON[2], T. ASHLEY[2], J. MILNER[4], *A. M. PICKRELL[5], P. D. MORTON[6];
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Abstract: Communication between the gut microbiome and immune cells within the brain is essential for normal brain development. Specifically, microglia are known to play a crucial role in regulating and supporting the production of neural progenitor stem cells during brain development, and they are also sensitive to changes in the maternal microbiome during prenatal and early postnatal development. Here, we use a germ-free (GF) paradigm within a porcine (Sus scrofa) model to examine how the absence of a microbiome affects typical neurodevelopmental trajectories, looking specifically at microglial density and morphology across three developmentally significant regions: the subventricular/ventricular zone (VZ/SVZ), the prefrontal white matter (PFCWM), and layers II/III of the prefrontal cortex (PFCII-III) (n = 5-6 per group). Using automated image analysis software, we found that the GF paradigm results in no differences in microglial morphology or density in the SVZ/VZ or PFSCWM. In contrast, the PFCII-III of postnatal day (P16) piglets exhibited increased densities of microglia with activated

morphology, indicative of a more reactive phenotype. Supporting this, transcriptomic data revealed upregulation of genes related to neuroinflammation within this region, such as CD38 ($p < 0.001$, FC = 1.545). CD38 is a glial predominant receptor/enzyme that converts nicotinamide adenine dinucleotide (NAD) to nicotinamide mononucleotide (NAM), regulating the innate immune response. Notably, these effects were morphology-specific, with no changes in overall microglial density in any of the regions, suggesting changes in reactivity rather than overall microglial population numbers. Our findings reveal region-specific microglial and immune regulation in early postnatal development as a response to the GF paradigm. This work contrasts findings from GF mouse models, demonstrating increased overall microglial density and decreased expression of genes related to cell activation and immune system transduction. This expands our knowledge of gut-brain communication within a gyrified species and emphasizes the importance of the maternal microbiome in shaping early-life neurodevelopmental trajectories. Future studies will evaluate how germ-free conditions specifically affect the prefrontal cortex to determine if these morphological and transcriptomic changes have functional effects on other aspects of neurodevelopment, such as synaptic pruning.

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Title: Astrocytes respond to tensile cues to drive cortical folding: an in silico study

Authors: K. TANEJA[1], K. SAITO[2], H. KAWASAKI[2], ***M. HOLLAND**[1];
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Abstract: Cortical folding underlies higher-order brain function, yet the contribution of astrocytes—the most abundant glial cells—remains poorly understood. Astrocytes are especially concentrated beneath gyri, and their dysfunction has been linked to lissencephaly,

polymicrogyria, and other neurodevelopmental disorders. This study tested two mechanistic hypotheses for astrocytic involvement in gyrification: (1) a “pushing” model, where proliferating astrocytes push the cortex outwards, and (2) a “pulling” model, where astrocytes proliferate in response to tensile stresses generated by the buckling cortex.
Using a finite growth framework implemented in finite element simulations of ferret cortical development (E40-P16), we modeled isotropic and stress-driven white matter growth alongside tangential gray matter expansion. The model incorporated three developmental phases based on experimental timelines: germinal zone expansion, cortical growth, and astrocytic proliferation. Morphological outcomes were quantified using gyrification index (GI) and normalized sulcal depth (SD) and compared with ferret histology. Stress distributions were evaluated against *ex vivo* mechanical data. Multiple growth-rate ratios and proliferative zone configurations were simulated to test reproducibility and robustness.
Both hypotheses reproduced key morphological features, with folds initiating near proliferative regions and fold number generally matching the number of initial perturbations. GI and SD values from both models fell within ranges observed in ferret brains, demonstrating consistency with biological data. However, stress analysis distinguished the mechanisms: the pushing model predicted tangential compression in the deeper subcortex, inconsistent with *ex vivo* evidence, whereas the pulling model generated radial tension beneath gyri and tangential tension in deeper white matter, in agreement with experimental observations.
These results support the confirmatory hypothesis that astrocytes promote gyrification by responding to tensile cues, thereby redistributing stresses and deepening folds, rather than by mechanically pushing the cortex. The findings highlight the importance of relative white-to-gray matter growth rates, with deviations producing morphologies resembling human pathologies such as lissencephaly and polymicrogyria. This work provides a mechanistic basis for astrocytic involvement in cortical folding and suggests that altered astrocyte mechanosensitivity may underlie neurodevelopmental disorders.

Disclosures: K. Taneja: None. **K. Saito:** None. **H. Kawasaki:** None. **M. Holland:** None.

Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP001.13/LBP012

Topic: A.01. Neurogenesis and Gliogenesis

Support: NHGRI R01HG010634

Title: DNA Methylation and Structure Abnormalities Drive Glioma Heterogeneity

Authors: *M. WU[1], J. ZHOU[2], T. L. BEAUMONT[3], J. DIXON[4], J. R. ECKER[5];
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Abstract: Adult diffuse gliomas span astrocytoma and oligodendroglioma with IDH mutations and IDH-wildtype glioblastoma (GBM), the latter marked by extreme cellular plasticity. Bulk genomic studies from TCGA defined molecular subtypes, but how epigenetic programs coordinate state transitions within tumors remains unresolved. Previous studies found that GBM cell states recapitulates the development of normal human brain, including Oligodendrocyte progenitor like (OPC-like), astrocyte like (AC-like), Neural progenitor like (NPC-like), and mesenchymal like (MES-like) state. Cell states may transdifferentiate between each other. We applied joint single-nucleus methylome and 3D genome profiling (snm3C-seq) to 52 human gliomas and assigned DNA methylation and chromatin conformation (Hi-C) states to individual cells. Our results are as follows: 1) Cross-modal state mapping: Most tumors contain large fractions of OPC-like or Astro-like cells with strong concordance between methylation (mC) and Hi-C states. However, certain clusters of cells have discordant mC and Hi-C states, indicating transitional phenotypes. 2) Temporal discrepancy: We observe asynchronous remodeling, where chromatin architecture often shifts towards more differentiated states before DNA methylation during lineage transitions. For example, many cells are OPC-like in methylation and AC-like in chromatin conformation, suggesting 3D genome reorganization as an early indicator of fate change. 3) Early focal alterations: In some non-malignant cells we detect focal methylation alterations near oncogenes and low-level CNV mosaicism, yet their methylation profiles are more similar to normal cells than cancer cells. 4) Clonal evolution and SVs: Clonal analysis by CNV reveals that some new malignant clones arise with novel focal hypomethylation patterns or global methylation loss. Structural variants, including multi-break translocations that likely arising from one catastrophic event, are shared by large cancer cell fractions. Extrachromosomal DNA (ecDNA) are frequently found in WT GBM and they are associated with local epigenetic rewiring at amplified loci. These insights nominate epigenetic states as a biomarker of plasticity and a potential guide for patient-specific interventions.

Disclosures: M. Wu: None. **J. Zhou:** None. **T.L. Beaumont:** None. **J. Dixon:** None. **J.R. Ecker:** None.

Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP001.14/LBP013

Topic: A.01. Neurogenesis and Gliogenesis

Title: Glia are evolutionarily conserved regulators of critical period timing

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Abstract: Critical periods (CPs) are brief windows of heightened, experience- or environment-dependent neuronal plasticity that are believed to establish long-term, if not permanent neural

circuit architecture. Changes in CP duration are linked to neurodevelopmental disorders; yet the mechanisms that sculpt CP timing are loosely defined. Previously, we established a role for astrocytes, prominent peri-synaptic glia, in CP closure and thus motor circuit stability in *Drosophila*. In mammals, myelinating oligodendrocytes were also recently shown to instruct CP closure, prompting the question: how do two distinct populations of glia cooperate to shape CP timing? As *Drosophila* lack myelinating glia, we developed zebrafish, a model with all major glial cell types, to study the role of glial maturation and CP timing. Leveraging live imaging and a custom-build rig for optogenetic manipulation of motor neurons, the "OptoChamber", we first established that zebrafish exhibit a CP of structural plasticity that peaks at 3 days post-fertilization (dpf) but is limited at 4 dpf and beyond. Interestingly, loss of structural plasticity coincided with both astrocyte and oligodendrocyte maturation. Specifically, motor neurons lose plasticity as astrocytes make synaptic contact, and oligodendrocytes myelinate the spinal cord. To define a functional link between glial signaling and CP timing, we performed a mutant and CRISPR/Cas9-based genetic screen targeted each of the astrocyte-derived anti-plasticity molecules we defined in fly, as well as defined regulators of myelination. Our preliminary data suggest that loss of *slc6a1a/b* and *lrrc4a/b* genes can extend zebrafish motor plasticity. Together, these data uncover an evolutionarily conserved role for astrocytes in shaping CP timing across invertebrates and vertebrates.

Disclosures: S. Paul: None. **H. Jetter:** None. **J.P. Brandt:** None. **S. Ackerman:** None.

Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP001.15/LBP014

Topic: A.01. Neurogenesis and Gliogenesis

Support: NIH R01NS123165
Shriners Hospitals for Children 85410-NCA-24

Title: Dissecting the role of Myef2 in oligodendrocyte lineage progression

Authors: *Y. SONG[1], X. SHI[1], F. GUO[1], Y. WANG[2];
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Abstract: Dissecting the Role of Myef2 in Oligodendrocyte Lineage Progression
Multiple sclerosis (MS) is a chronic, immune-mediated demyelinating disease of the central nervous system (CNS) and a leading cause of neurological disability in young adults. A central pathological feature of MS is the failure of oligodendrocyte progenitor cells (OPCs) to differentiate into mature oligodendrocytes (OLs) and remyelinate damaged axons, leading to irreversible neurological deficits. While current therapies modulate immune activity, they do not address remyelination failure—a key driver of progressive disability. A critical unmet need in MS research is the identification of intrinsic molecular regulators of OL maturation and myelin

repair, which could serve as therapeutic targets to enhance endogenous remyelination and prevent neurodegeneration.Myelin expression factor 2 (Myef2) is a member of the family of DNA-binding transcription factors that recognize the CT-rich “GGTGT” consensus sequence. It functions primarily as a transcriptional repressor. Myef2 is known to involve direct binding to specific regulatory elements on target genes, where it recruits co-repressor complexes and histone deacetylases to condense chromatin structure and actively suppress gene expression. Our previous study showed that Myef2 is PARP1-regulated in PARylation, affecting myelinating gene expression. However, the role of Myef2 in the CNS, particularly in oligodendroglial biology, has remained elusive. Myef2-null mice die early postnatally hindering a detailed examination of OPC differentiation and myelination. Here, we utilize *Cre-loxP* approaches to generating lineage-specific Myef2 conditional knockout (cKO) mice and aim to test whether and how depleting Myef2 enhances myelin gene expression and promotes OPC differentiation and myelination *in vivo*. Our study revealed that cKO mice exhibited impaired motor function compared with control mice. This phenomenon is closely related to the impact of Myef2 on OPC differentiation in the brain, which in turn regulates the myelination process. In this regard, lHC and unbiased stereotaxic methods quantitatively analyzed the number of differentiated OLs (Sox10+CC1+) and OPCs (Sox10+PDGFRα+). Meanwhile, real-time quantitative PCR and Western blot analyses were employed to determine the expression levels of mRNAs and proteins associated with OPC differentiation and myelination.Our findings suggest that Myef2 may serve as a potential therapeutic target, as its depletion promotes the differentiation of OPCs into OLs, thereby enabling successful remyelination in chronic multiple sclerosis lesions characterized by OL loss.

Disclosures: Y. Song: None. **X. Shi:** None. **F. Guo:** None. **Y. Wang:** None.

Late-Breaking Poster

LBP001: A.01. Neurogenesis and Gliogenesis

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Title: A novel brain-specific MuSK isoform is localized in a subpopulation of hippocampal astrocytes and regulates BMP4-induced astrocyte differentiation from cultured neural stem cells

Authors: *J. LEE[1], A. Y. CHANG[1], C. XI[1], S. A. TWINNEY[2], J. K. HECKING[1,2], S. OH[3], A. S. PAYNE[4], A. E. WEBB[5], A. VALAT[2], J. S. PAGE[1,2], J. R. FALLON[1];
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MA; [3]Hallym University, Chuncheon-si, Korea, Republic of; [4]Department of Dermatology, Columbia University, New York, NY; [5]Buck Institute, Novato, CA

Abstract: The cell surface receptor MuSK (Muscle-specific kinase) binds both agrin/LRP4 and bone morphogenetic proteins (BMPs) and is established to play multiple roles in skeletal muscle including neuromuscular junction formation and excitability, muscle stem (satellite) cell quiescence, and regulating myofiber size. However, the role of MuSK in the brain is poorly understood. Here we show that >80% of the MuSK transcripts in adult rodent and human hippocampus encode a novel, truncated, brain-specific isoform, 'T2', that lacks both the Ig2 and the agrin/LRP4-binding Ig1 domains, but retains the BMP-binding Ig3 domain. Immunohistochemistry (IHC) shows that T2 MuSK is highly enriched in the neurogenic subgranular zone and in a subset of $SOX2^+$ astrocytes in the granule cell layer. As a first step to investigate T2 MuSK function in these glial cells, we cultured hippocampal neural stem cells (NSCs) in the presence of serum to induce astrocyte differentiation. NSCs expressed full-length ('T1') MuSK. Remarkably, under astrocyte differentiation conditions, MuSK was upregulated >1,000-fold, with only the T2 isoform detected. IHC showed that at 7 days in vitro (DIV) ~5-10% of the total cells were $MuSK^+/SOX2^+/Olig2^-$. Notably, a subpopulation of these $MuSK^+$ cells also expressed low levels of GFAP. However, MuSK was not detected in the majority of $GFAP^+/ALDH1L1^+$ astrocytes, which comprised ~70% of the culture. Together, these observations raised the possibility that the $MuSK^+$ cells are astrocyte progenitors. To test this idea, we treated the cultures for 24 hours with BMP4, which binds to the MuSK Ig3 domain and is a well-established inducer of astrocyte differentiation. As expected, BMP4 induced a robust increase in GFAP expression and changes in astrocyte morphology. Strikingly, BMP4 treatment also resulted in a >85% reduction in MuSK transcript levels, and $MuSK^+$ cells were no longer detected by IHC. Surprisingly, BMP4-induced MuSK downregulation was insensitive to the type I BMP receptor inhibitor LDN-193189, suggesting that BMP4-mediated T2 MuSK signaling may act by a novel pathway. To directly investigate the role of the MuSK Ig3 domain in astrocyte differentiation, we turned to ΔIg3-MuSK NSCs. At DIV 7, ΔIg3-MuSK cells displayed astrocyte-like morphology, but GFAP expression was ~30% lower than in wild-type. Taken together, these results indicate that T2 MuSK is expressed by a population of astrocyte progenitors where it regulates BMP4-induced astrocyte differentiation in a manner dependent on its BMP-binding Ig3 domain. Further, the selective expression of T2 MuSK in the subgranular zone suggests that it may function in a distinct hippocampal astrocyte lineage.

Disclosures: J. Lee: None. **A.Y. Chang:** None. **C. Xi:** None. **S.A. Twinney:** None. **J.K. Hecking:** None. **S. Oh:** None. **A.S. Payne:** None. **A.E. Webb:** None. **A. Valat:** None. **J.S. Page:** None. **J.R. Fallon:** None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP002.01/LBP016

Topic: A.02. Stem Cells and Reprogramming

Title: Aberrant Neuronal Synchronization Dynamics in iPSC-Derived Cerebral Organoids from Williams Syndrome in Dup7 Patients

Authors: *I. HWANG[1], K. S. KOSIK[2], J. YEO[1], M. ALMEIDA[3], D. C. CARRETTIERO[3]; [1]NRI, UC Santa Barbara, Santa Barbara, CA; [2]University of California Santa Barbara, Santa Barbara, CA; [3]Universidade Federal Do ABC, São Bernardo do Campo, Brazil

Abstract: Williams syndrome (WS) and Duplication7 (Dup7) syndrome are caused by reciprocal copy number variations (CNVs) of the7q11.23region, associated with contrasting cognitive and neurodevelopmental phenotypes. WS features hypersociability and microcephaly, whereas Dup7 presents with speech delay and macrocephaly. The affected region spans ~1.5Mb and includes up to 28 genes, yet how these gene dosage changes disrupt human cortical circuit development remains poorly understood. Here, we used induced pluripotent stem cell (iPSC)-derived cerebral organoids to model early cortical network development in WS and Dup7. We generated organoids from two independent iPSC lines per group (WS, Dup7, and controls), and used AAV9 to express GCaMP6s for longitudinal imaging of spontaneous calcium activity at days 90, 120, and150. For each line, four organoids were recorded per timepoint (n= 4), and all experiments were performed in two independent batches with consistent results. In control organoids, coordinated calcium activity emerged around day 120 and was maintained through day 150, reflecting typical maturation of cortical networks. In contrast, WS organoids displayed abnormally early synchrony at day 90, followed by a premature decline by day 120. Dup7 organoids, on the other hand, failed to exhibit coherent network synchrony at any timepoint. These findings were consistent across donor age and sex. Our results suggest that 7q11.23CNVs alter the developmental timing and stability of network synchronization. Because early synchronous activity plays a key role in establishing cortical modularity and mature desynchronization enhances neural efficiency, such disruptions may contribute to the atypical cognitive trajectories observed in these syndromes. This study may offer a powerful avenue to explore gene-gene interactions within the 7q11.23 region and serve as a model for targeted therapeutic screening.

Disclosures: I. Hwang: A. Employment/Salary (full or part-time); UC Santa Barbara. **K.S. Kosik:** A. Employment/Salary (full or part-time); UC Santa Barbara. **J. Yeo:** A. Employment/Salary (full or part-time); UC Santa Barbara. **M. Almeida:** None. **D.C. Carrettiero:** None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP002.02/LBP017

Topic: A.02. Stem Cells and Reprogramming

Support: NIMH R36 Grant 1R36MH136806-01

Title: Investigating mitochondrial protein dysregulation in an iPSC-derived neural model of the high-risk schizophrenia variant 22q11.2 deletion

Authors: *M. ROBINETTE[1], V. FAUNDEZ[2], R. PURCELL[3], G. J. BASSELL[4];
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Abstract: 22q11.2 deletion (22qDel) is the most common recurrent copy number variant and confers a >30x risk for developing schizophrenia. The deletion on the 22q11.2 locus results in the hemizygosity of six genes encoding mitochondrial-localizing proteins including one mitochondrial ribosome. Prior studies have reported impaired mitochondrial function in neural cells, but the mechanisms underlying dysregulated mitochondrial function and their contribution to human cortical development remain unclear. Recent findings suggest dysregulated mitochondrial translation in 22qDel, but this finding has yet to be assessed in neural cells and any mechanism involved remains unknown. We hypothesize that the loss of the mitochondrial-localizing proteins encoded by the 22q11.2 locus impacts mitochondrial translation, thereby affecting mitochondrial function in an induced pluripotent stem cell (iPSC) neural model. iPSCs from neurotypical study subjects were engineered into isogenic 22qDel lines using CRISPR/Cas9. Cortical organoids derived from the isogenic 22qDel iPSCs and their clonal controls were differentiated and matured to neural progenitor cells (NPCs) and to 50-, 100-, and 150-day cortical organoids. Tandem mass tagging (TMT) was used to quantify organoid proteomes across neurodevelopmental time points. Validation by western blot was performed to quantify the expression of specific mitochondrial proteins in NPCs and organoids. Analysis of the 22qDel organoid proteomes broadly points to dysregulated expression of mitochondrial proteins across all time points. Beyond the proteins directly encoded by the 22q11.2 locus, subunits that are part of the oxidative phosphorylation (OxPhos) Complexes in the electron transport chain (ETC) were downregulated. Complex reduction was verified using an OxPhos antibody mix that reports the expression of assembled complexes. Interestingly, mitochondrial translation was identified as the top pathway implicated among differentially abundant proteins in 22qDel cortical organoid proteomes. Further analysis revealed nearly half of human mitoribosomal proteins were dysregulated in 22qDel. This work provides new evidence that mitochondrial vulnerabilities emerge in 22qDel throughout cortical development and may lead to dysregulated mitochondrial translation and impaired OxPhos. The dysregulation of mitochondrial ribosomes could be responsible for the altered expression of these OxPhos subunit proteins in the ETC which could have functional consequences. Future directions of this project will use study participant 22qDel iPSCs to further investigate mechanisms related to mitochondrial translation.

Disclosures: M. Robinette: None. **V. Faundez:** None. **R. Purcell:** None. **G.J. Bassell:** None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP002.03/LBP018

Topic: A.02. Stem Cells and Reprogramming

Support: Japan Agency for Medical Research and Development (AMED)

Title: Single-cell multiome analysis of neural organoids derived from CGG repeat expansion disease iPSCs

Authors: *R. NAKAI[1,2], K. IMAMURA[2,1,3], M. SUGA[1,2], T. KONDO[2,1,3], K. ISHII[4], Y. IZUMI[5], H. INOUE[2,1,3];
[1]BRC, RIKEN, Kyoto, Japan; [2]CiRA, Kyoto Univ., Kyoto, Japan; [3]AIP, RIKEN, Kyoto, Japan; [4]Univ. of Tsukuba, Tsukuba, Japan; [5]Tokushima Univ., Tokushima, Japan

Abstract: Non-coding CGG repeat expansion is a genetic cause of neuronal intranuclear inclusion disease (NIID) and fragile X-associated tremor/ataxia syndrome (FXTAS). Both diseases share some pathological features and clinical manifestations, suggesting common molecular pathogenic mechanisms. Among the proposed pathogenic mechanisms, RNA toxicity has been implicated, in which repeat-derived RNAs sequester RNA-binding proteins into RNA foci and induce abnormalities in RNA metabolism. Furthermore, guanine-rich repeats form G-quadruplex (G4) structures, and G4 RNAs have been reported to drive neurodegeneration via phase separation.To investigate molecular changes associated with CGG repeat expansions, we performed single-cell Multiome analysis (scRNA-seq and scATAC-seq) using neural organoids derived from iPS cells of healthy controls, NIID patients, and FXTAS patients. We identified changes in gene expression and chromatin accessibility in glutamatergic neurons, GABAergic neurons, and astrocytes. Affected genes were significantly enriched in pathways related to synaptic function and cellular stress responses. Correlation analyses revealed regulatory relationships linked to these genes. Finally, based on the RNA toxicity hypothesis, we predicted upstream transcriptional regulators that could be interfered with by G4 RNA.These findings suggest a possible mechanism of transcriptional dysregulation mediated by CGG repeat expansion in iPSC-derived neural cells from patients with CGG repeat expansion diseases.

Disclosures: R. Nakai: None. **K. Imamura:** None. **M. Suga:** None. **T. Kondo:** None. **K. Ishii:** None. **Y. Izumi:** None. **H. Inoue:** None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP002.04/LBP019

Topic: A.02. Stem Cells and Reprogramming

Support: National Key Research and Development Program (2024YFC2707002)
Innovation Program of Shanghai Municipal Education Commission (2023ZKZD16)
National Natural Science Foundation of China (82071262)

Title: Novel Mechanism of CYFIP2 Involvement in The Pathogenesis of Developmental Epileptic Encephalopathy

Authors: *K. LI[1,2], L. JI[2], W. NIU[3], G. HE[2];
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Abstract: This study investigates a novel de novo *CYFIP2* nonsense mutation (p.Arg825Ter) identified in a developmental and epileptic encephalopathy (DEE65) family exhibiting milder clinical manifestations compared to patients with known gain-of-function (GoF) mutations, suggesting a distinct loss-of-function (LoF) pathogenic mechanism. Through generation of patient-derived induced pluripotent stem cells (iPSCs) and CRISPR/Cas9-engineered isogenic cell lines (including the severe GoF variant p.Arg87Cys and gene-corrected controls), we demonstrate that the p.Arg825Ter mutation significantly reduces CYFIP2 protein expression in both undifferentiated iPSCs and differentiated neuronal cultures ($p<0.001$), whereas the p.Arg87Cys mutation exhibits neuron-specific reduction with evident dosage dependence. Multi-electrode array (MEA) electrophysiological recordings revealed epileptiform activity across all mutant lines, with the p.Arg825Ter mutation demonstrating significantly attenuated discharge frequency compared to p.Arg87Cys ($p<0.01$, $n\geq6$ independent replicates). Immunocytochemical analysis confirmed corresponding phenotypic differences, with p.Arg825Ter neuronal cultures displaying reduced SYN1 immunoreactivity ($p<0.05$) and decreased dendritic spine density, consistent with the observed clinical severity gradient. Transcriptomic profiling identified mutation-dependent disruptions in axonal development and synaptic signaling pathways. Notably, the p.Arg825Ter mutation induced widespread mRNA dysregulation beyond these core pathways, suggesting broader transcriptional consequences. Mechanistic studies in HEK293T cells demonstrated that the p.Arg825Ter mutation impairs CYFIP2-WAVE1 protein-protein interactions (co-immunoprecipitation) while promoting aberrant nuclear localization. These findings establish the first human cellular models of CYFIP2 LoF pathogenesis and reveal fundamental differences between LoF and GoF disease mechanisms. The developed iPSC platform currently serves as a foundation for mechanistic investigation and therapeutic screening in DEE65, with promising implications for developing targeted treatment strategies.

Disclosures: K. Li: None. **L. Ji:** None. **W. Niu:** None. **G. He:** None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

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Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP002.05/LBP020

Topic: A.02. Stem Cells and Reprogramming

Support: GTP T32
CURE Sanfilippo
NIH

Title: Characterization of Peripheral Nervous System Dysfunction in Sanfilippo Syndrome Type A in Stem Cell-derived Sensory Neurons

Authors: *M. K. SHINN;
University of Georgia, Athens, GA

Abstract: Mucopolysaccharidosis Type IIIA (MPS IIIA), also known as Sanfilippo Syndrome Type A, is a rare autosomal recessive disorder that affects one in every 70,000 children worldwide, and currently there are no approved therapies. Patients with MPS IIIA are unable to catabolize a subtype of cellular polysaccharides, known as heparan sulfate (HS), due to inherited mutations in the gene encoding for the lysosomal enzyme, *N*-sulfoglucosamine sulfohydrolase (SGSH). Deficiency in this enzyme leads to intra-lysosomal storage and accumulation of HS, which results in severe neuropathology, including regression of intellectual and motor abilities, behavioral problems, hearing loss, and dementia. Children born with this disorder exhibit developmental abnormalities, organ failure, and neurodegeneration, which often result in death within the first two decades of life. To date, MPS IIIA neuropathologic and therapeutic studies have focused predominantly on changes in the central nervous system, especially in the brain, but little is known about the disease pathology in the peripheral nervous system (PNS). Intriguingly, both MPS IIIA patients and mouse models display symptoms of degeneration of the sensory and autonomic nervous system, including retinopathy, bowel issues, and cardiomyopathy. Yet, the molecular mechanisms triggering the underlying peripheral neuropathy are virtually unknown. The main goal of this project is to develop novel disease models to identify therapeutic targets to treat PNS issues in MPS IIIA patients. To do this, we utilized patient-derived induced pluripotent stem cells (iPSCs) to generate peripheral neural stem cell models to recapitulate PNS phenotypes and dysfunction found in MPS IIIA patients. iPSCs from MPS IIIA patients with an intermediate and severe clinical phenotype, respectively, were differentiated into neural crest cells and peripheral sensory neurons and were evaluated for disease pathology, cell morphology, and neural electrophysiology. MPS IIIA peripheral sensory neurons displayed substantial lysosomal accumulation of HS, as measured via mass spectrometry and fluorescence microscopy methods. Overall, this work will lead to the development of novel cellular models to improve our knowledge about the molecular underpinnings of PNS

dysfunction in MPS IIIA and will promote the discovery of new therapies by addressing the underlying cause of the disorder, lysosomal accumulation of heparan sulfate.

Disclosures: M.K. Shinn: None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP002.06/LBP021

Topic: A.02. Stem Cells and Reprogramming

Support: FDCT/0002/2023/RIB1
0010/2023/AKP

Title: Efficient induction of retinal pigment epithelium (RPE) under chemically defined conditions for the treatment of age-related macular degeneration (AMD)

Authors: Q. WANG[1], G. FAN[2], Y. ZHOU[3], W. LIU[4], J. WANG[1], ***G. CHEN**[5];
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Abstract: Age-related macular degeneration (AMD) is caused by the dysfunction of retinal pigment epithelium (RPE), which often leads to vision loss and blindness among elderly people. Because there is no curative therapy for AMD so far, RPE transplantation has become a promising approach to treat AMD by replacing damaged RPE. Human pluripotent stem cells (hPSCs) have the potential to generate an unlimited number of RPE cells to treat AMD patients. However, current differentiation methods are usually carried out under undefined conditions using animal products, and have problems with lengthy induction, manual isolation, and low efficiency. In order to effectively generate RPE cells from hPSCs for cell therapy, we examined the cell culture factors essential for RPE fate determination. We demonstrate that RPE can be effectively induced under chemically defined conditions without manual isolation when stagewise treatments are applied. Meanwhile, a novel RPE sphere method has been developed for transplantation. We hope these methods will be utilized in cell therapy to treat AMD in the near future.

Disclosures: Q. Wang: None. **G. fan:** None. **Y. Zhou:** None. **W. Liu:** None. **J. Wang:** None. **G. Chen:** None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

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Topic: A.02. Stem Cells and Reprogramming

Support: NIH Grant 1R21AG085428

Title: Swiftly to the Stars: Directed Chemical Reprogramming of Human Adult Fibroblasts to Astrocytes

Authors: *U. BHASKAR, E. SHRIMPTON, A. HURTADO, M. CARLESS;
University of Texas at San Antonio, San Antonio, TX

Abstract: Direct lineage reprogramming of terminally differentiated somatic cells allows the generation of clinically relevant cell types for modeling age-related neurological disorders. Most of these approaches predominantly focus on generating neuronal cells, with limited research on glial cell types. Previous studies using mouse and human embryonic fibroblasts suggest that the overexpression of three transcription factors, *NFIA, NFIB,* and*SOX9,* enables their conversion into induced astrocytes (iAs). However, these methods have poor efficiency with adult fibroblasts, are time-consuming, and present the possibility of genomic integration. Therefore, we devised a strategy that would allow direct reprogramming of human adult fibroblasts to iAs, using a small-molecule approach. Our method yields GFAP/S100B/ALDH1L1-positive cells at >20% efficiency across multiple cell lines, independent of age and sex of starting fibroblasts, which exhibit astrocyte-like glutamate uptake capacity, ATP-induced calcium signaling, and neuroinflammatory properties. We observe transcriptional changes that are indicative of a loss of fibroblast state, followed by acquisition of astrocyte-like fate, without the generation of a pluripotent intermediate state. Correlation to previously published datasets indicates a potential astrocytic population that resembles astrocytes from the adult brain. Comparison with iPSC-derived astrocytes from the same individual shows fibroblast-derived induced astrocytes to have higher oxidative stress and cellular senescence, indicative of an aging phenotype. Further studies are in progress to assess DNA methylation of these cells, which would help establish epigenetic markers of age, in addition to further validating astrocyte-cell specificity. This method will complement current *in vitro* models of neurons and other cell types, and therefore serve as a useful tool in improving our understanding of age and disease-related processes in the adult brain.

Disclosures: U. Bhaskar: None. **E. Shrimpton:** None. **A. Hurtado:** None. **M. Carless:** None.

Late-Breaking Poster

LBP002: A.02. Stem Cells and Reprogramming

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP002.08/LBP023

Topic: A.02. Stem Cells and Reprogramming

Support: Boehringer Ingelheim Fonds PhD Fellowship
NIH grant 5R35NS097305
Human Developmental Biology Resource (HDBR)

Title: Progenitor Cell Diversity in the Developing Human Ganglionic Eminences

Authors: *C.-V. SIEBERT;
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Abstract: The medial, lateral, and caudal ganglionic eminences (MGE, LGE, CGE) are transient embryonic brain structures that generate diverse neurons, including inhibitory neurons (INs) for the cortex. The MGE shows a distinctive cytoarchitecture, with vimentin^{+} progenitor clusters surrounding dense doublecortin-positive (DCX^{+}) nests (DENs), which may support expanded IN production in primates. The molecular heterogeneity of GE progenitors, their lineage links to basal ganglia and cortical neurons, and their similarity to other progenitor types remain unclear. Mitotic behaviors help define the identity and function of stem/progenitor cells, yet the division patterns of progenitors in the LGE, MGE, and CGE remain incompletely understood. We performed live imaging of developing LGE, MGE, and CGE during the second trimester. Among other divisions, we identified mitotic somal translocation (MST), a hallmark of cortical outer radial glia (oRG), across all GEs with distinct regional and temporal patterns. To define the molecular programs and lineage trajectories, we integrated paired single-cell transcriptomics and chromatin accessibility profiling. This revealed molecularly distinct populations of radial glia (RG), intermediate progenitor cells (IPCs), and neuroblasts (NBs) along with their lineage relationships and underlying gene regulatory networks. Using spatial transcriptomics integrated with immunostaining, we mapped defined progenitor populations onto the MGE cytoarchitecture. We identified migratory streams of striatal neurons, including a primate-enriched *CRABP1*+ interneuron population establishing a distinct domain within the MGE, capturing the dynamic migration of basal ganglia neurons to the developing striatum. To investigate the mechanisms underlying human MGE development, we generated MGE organoids that recapitulate MST and formed DEN-like structures. Using this model, we identified the protocadherin, PCDH19, as a candidate regulator of DEN formation. MGE organoids derived from *PCDH19* knockout and isogenic control iPSC lines revealed that PCDH19 is essential for the formation of DEN-like structures. This study provides new insights into interneuron development, revealing both conserved and region-specific features of molecular and mitotic programs. We further define the molecular pathways driving DEN formation, and establish MGE organoids as a faithful *in vitro* model for investigating developmental mechanisms.

Disclosures: C. Siebert: None.

Late-Breaking Poster

LBP003: A.03. Axon and Dendrite Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP003.01/LBP024

Topic: A.03. Axon and Dendrite Development

Support: NS112504
NS114247

Title: Leveraging optogenetic platforms to study the role of RNA granule transport in axon development

Authors: *S. KARTHIKEYAN[1], S. TYMANSKYJ[2], L. MA[1];
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Abstract: The formation of complex axonal morphologies depends on extracellular guidance cues, which can regulate growth cone dynamics and axon branching. In addition to modulating processes like cytoskeletal dynamics, these cues regulate translation of local mRNA transcripts, helping generate new protein to influence outgrowth. While mRNA transcripts are delivered to the axon as RNA granules bound to cytoskeletal motors and/or organelles, it is unclear how signaling cues govern RNA granule positioning *within* the axon to inform where nascent protein is synthesized. It is also unclear how RNA granules organize outgrowth and if their mobilization to a particular site is necessary for the response. Our lab has tackled these questions by leveraging two optogenetic platforms that confer precise spatiotemporal control over guidance signaling and granule transport, respectively. The first platform (Opto-Receptor) is adapted from Duan et al. 2018 and leverages the blue light sensitive CRY2/CIB1 system to recruit and cluster the intracellular domain of receptors at the cell membrane, triggering signaling at the site of illumination. When tested in embryonic sensory neurons, the TrkB version of this system (iTrkB-Opto) induced a branching response along locally illuminated segments of midaxon. Notably, the outgrowths were attenuated by the translation inhibitor cycloheximide, indicating a reliance on protein synthesis. To test if these local responses were associated with changes in RNA granule transport, we performed kymograph analysis on axons expressing fluorescently tagged RNA granules (e.g. FMRP and ZBP1) and observed increased granule entry and retention at the sites of induced growth. Local iTrkB-Opto stimulation was also performed at growth cones, which showed translation dependent increases in area and motility, and we are currently testing for associated increases in RNA granule delivery. Overall, our data support a model in which local cues reposition RNA granules to optimize the availability of translational substrates. To further assess the role of RNA granule positioning in axon development, we are currently employing a second optogenetic platform (Opto-Motor) adapted from Nijenhuis et al. 2020. By using the blue light sensitive iLID/SSPB system to transiently recruit kinesin or myosin motors to tagged RNA granules, we are able to manipulate their positioning and test how increasing or

decreasing their availability at a particular site affects local outgrowth dynamics. Overall, these optogenetic tools will help test how guidance cues regulate RNA granule transport to define sites of protein synthesis and local outgrowth.

Disclosures: S. Karthikeyan: None. **S. Tymanskyj:** None. **L. Ma:** None.

Late-Breaking Poster

LBP003: A.03. Axon and Dendrite Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP003.02/LBP025

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant R01 NS139060
NIH Grant R01 NS123439
NIH Grant T32 GM138826
NIH Grant T32 GM144292
NIH Grant F31 NS136004
NIH Grant R01 NS028182

Title: Structural Insights Into The Beat-Side Interactions Reveal Roles In Drosophila Neuromuscular Circuit Wiring

Authors: *R. ZHANG[1], J. PRIEST[1], A. M. OLECHWIER[1], A. LEBOVIC[1], J. ASHLEY[1], V. AHER[1], R. A. CARRILLO[2], E. OZKAN[3];
[1]University of Chicago, Chicago, IL; [2]Molecular Genetics and Cell Biology, University of Chicago, Chicago, IL; [3]Biochemistry & Molecular Biology, University of Chicago, Chicago, IL

Abstract: The precise control of animal behaviors depends on the appropriate assembly of neural circuits. The Drosophila larval neuromuscular system provides an ideal model to examine the mechanisms underlying circuit assembly. This ‘simple’ system consists of 33 motor neurons and 30 muscles with invariant connectivity patterns in each hemisegment. Cell surface proteins play critical roles in nervous system assembly. In Drosophila, Beaten Path (Beat) and Sidestep (Side) are two interacting cell surface protein families whose members have been described as axon guidance receptor-ligand pairs, in addition to roles in specifying synaptic connectivity. To understand the molecular basis and specificity of Beat-Side interactions, we report here the first Beat-Side structure, Beat-Vc bound to Side-VI. The structure showed a binding topology similar to other neuronal immunoglobulin superfamily receptors, including Nectins, SynCAMs, Dprs and DIPs, despite lack of established evolutionary relationships. Using a structure-based rational approach, we generated Drosophila larvae carrying mutations in the endogenous *side* locus that abrogate Beat-Ia binding: these mutants show a loss of ventral muscle innervation. Additionally, unlike overexpression of wild-type Side, overexpression of mutant Side in muscles does not alter motor neuron innervation of dorsal muscles. This gain-of-function phenotype can be rescued by co-overexpression of wild-type Beat but not Beat carrying mutations on the interaction interface.

These results suggest that the Side-Beat-Ia interaction is required for proper circuit assembly in the Drosophila neuromuscular system.

Disclosures: R. Zhang: None. **J. Priest:** None. **A.M. Olechwier:** None. **A. Lebovic:** None. **J. Ashley:** None. **V. Aher:** None. **R.A. Carrillo:** None. **E. Ozkan:** None.

Late-Breaking Poster

LBP003: A.03. Axon and Dendrite Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP003.03/LBP026

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant R15DA058203-01
Touro College and University System Seed Grant

Title: Beta-catenin hERG interactions regulate electrical activity and axon pathfinding in vivo,in vitro and in silico

Authors: S. KAUR, J. FANG, H. KAUR, A. MILLER, ***T. M. ELUL**;
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Abstract: Signaling pathways that modulate cell adhesion and cytoskeleton have been shown to localize potassium channels to the plasma membrane of neurons, which may in turn impact activity-dependent regulation of development of neuronal connectivity. However, the molecular and cellular mechanisms of potassium channel localization in relation to neuronal morphogenesis and activity are not well understood. We are testing whether Wnt and Cadherin factor, β-catenin, increases membrane localization of hERG channels to modulate electrical activity and axon pathfinding, *in vivo*, *in vitro* and *in silico*. Expression of a β-catenin mutant that disrupts its interaction with alpha-catenin in individual GFP expressing retinal ganglion cells (RGCs) in *Xenopus laevis* embryos resulted in fewer filopodia in, and more round and less complex (lower fractal dimension) growth cones, as well as more meandering axons, in whole brains. Still and timelapse imaging of primary cultures of RGCs from *Xenopus* embryos show growth cone filopodial and axonal dynamics, whereas voltage clamp electrical recordings of these cultured RGCs reveal channel activity. Computational modeling of the effects of changing numbers of potassium channels suggest differences in action potential parameters such as action potential duration, frequency and height. The next stages of this project include quantifying effects of gain of function of hERG, individually and together with loss-of-function of β-catenin, on morphological and electrical parameters of, as well as protein localization in, individual developing RGCs from *Xenopus laevis* tadpoles in whole brains and *in vitro*. This data will advance our understanding of molecular mechanisms that regulate activity dependent modulation of axon pathfinding during brain development, normally and in the context of neurodevelopmental disorders such as autism, epilepsy and intellectual disability

Disclosures: S. Kaur: None. **J. Fang:** None. **H. Kaur:** None. **A. Miller:** None. **T.M. Elul:** None.

Late-Breaking Poster

LBP003: A.03. Axon and Dendrite Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP003.04/LBP027

Topic: A.03. Axon and Dendrite Development

Support: PTEN Research Foundation UAB-24-001
NIH R01 MH097949 (BWL)
NIH R21 NS133670 (JMB)
NIH R01 NS110945 (MCW)

Title: PTEN Knockout Regulates Neuronal Growth Through mTORC1 and Alters Action Potential Firing Through mTORC2 Signaling

Authors: A. ABDULKAREEM[1], N. ELSTE[2], M. PRINA[3], M. C. WESTON[4], J. M. BARRY[5], ***B. W. LUIKART**[1];
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Abstract: PTEN is a phospholipid phosphatase that catalyzes the reverse reaction of PI3K to inhibit signaling downstream of growth factor receptor tyrosine kinases. *PTEN* mutations cause PTEN Hamartoma tumor syndrome (PHTS) with a variable presentation of phenotypes including macrocephaly, benign tumors, cancer, autism spectrum disorder (ASD), epilepsy, and hydrocephalus. PTEN loss-of-function results in the activation of downstream AKT, mTORC1, and mTORC2 signaling. In developing neurons, this results in neuronal hypertrophy including elaboration of dendrites, dendritic spines, and formation of excitatory synapses. Additionally, action potential properties including width and burst-firing probability are increased. Decreased mTORC1 function through genetic deletion of *Rptor* (aka *Raptor*) completely prevents neuronal hypertrophy and excitatory synaptogenesis of *Pten* knockout neurons. However, *Raptor* deletion alone does not prevent the development of epilepsy in *Pten* conditional knockout mouse models. Here we demonstrate that *Pten* knockout alters neuronal ion channel function independently of mTORC1. Knockout of *Akt1* and *Akt3* or *Rictor* demonstrates that AKT or mTORC2 are necessary for ion channel regulation and burst-firing. With silicon probe recordings, we find that changes in excitatory synapses, excitability, and burst-firing impact hippocampal network activity and associated spatial memory *in vivo*. Through selective pharmacological ion channel blockade we find that decreased voltage-gated potassium and calcium currents underly bursting of *Pten* knockout neurons. If the number of *Pten* knockout granule cells exceeds a threshold, the changes in network activity drive seizures which can only be prevented through loss of both

mTORC1 and mTORC2 function. Overall, these data support a model whereby neuronal hypertrophy and excitatory synaptogenesis is dependent on mTORC1 activation and the modulation of ion channel function is mTORC2 dependent. Both sets of phenotypes are sufficient to drive cognitive changes in mice and may model similar changes in patients with PHTS and ASD.

Disclosures: A. Abdulkareem: None. **N. Elste:** None. **M. Prina:** None. **M.C. Weston:** None. **J.M. Barry:** None. **B.W. Luikart:** None.

Late-Breaking Poster

LBP004: A.04. Transplantation and Regeneration

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP004.01/LBP028

Topic: A.04. Transplantation and Regeneration

Support: CNPq VTRR2018
Faperj VTRR2024

Title: Development and application of biofunctional surfaces for the study of axonal regeneration in the motor circuitry of rodents in vitro.

Authors: G. SARDELLA DA SILVA[1], J. SANTOS[2], ***V. RIBEIRO-RESENDE**[3];
[1]Carlos Chagas Filho Biophysics Institute, Universidade Federal Do Rio De Janeiro, Cidade Universitária, Brazil; [2]Federal University of Rio de Janeiro, Niteroi, Brazil; [3]Universidade Federal do Rio do Janeiro, Rio de Janeiro, Brazil

Abstract: The motor circuit involves communication between two populations of motor neurons. Primary motor neurons have somas in layer V of the motor cortex and project axons to the spinal cord. Secondary motor neurons, also known as motoneurons, have somas in the ventral horn of the spinal cord and innervate effector muscles via their axons. Multiple axonal injuries can affect both populations of neurons, resulting in debilitating consequences for affected patients, especially in cases involving primary motor neuron damage. Neuronal degeneration and regeneration differ between the central and peripheral nervous systems due to cellular and molecular differences in the microenvironments surrounding these neurons. Various strategies have been employed to promote regeneration, but individual therapies do not provide long-lasting results. One alternative strategy is to use surfaces coated with extracellular matrix elements, such as laminin or a modified version of this protein called polylaminin (laminin at pH 4). In this study, in vitro cultures of cortical and spinal neurons were examined under the following conditions: laminin at pH 7, laminin at pH 4 (polylaminin), and a control condition using Poly-D-Lysine. We developed a new culture system based on a rectangular silicone chamber filled with PCL filaments functionalized with laminin or polylaminin. Cortical or spinal tissue fragments were cultured in this system. The tissue fragments adhered well to the filaments and exhibited extensive cell migration and neuritogenesis. This process was enhanced by the

combination of PCL and laminin in both tissue types. Additionally, both monolayer cells and tissue fragments were characterized for the presence of the Lin28a protein, which was found to be expressed in neurons under all conditions and was also observed in spinal neurons from adult mice. Additionally, the presence of the Lin28a protein was characterized in both monolayer cells and tissue fragments. This protein was found to be expressed in neurons under all conditions and was also observed in spinal neurons from adult mice. Thus, the developed model indicated that PCL filaments biofunctionalized with laminin-modified surfaces promote adhesion, migration, and neuritogenesis. This represents a promising strategy for in vitro models studying neuronal regeneration.

Disclosures: G. Sardella Da Silva: None. **J. Santos:** None. **V. Ribeiro-Resende:** None.

Late-Breaking Poster

LBP004: A.04. Transplantation and Regeneration

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP004.02/LBP029

Topic: A.04. Transplantation and Regeneration

Support: CNPQ VTRR2018
FAPERJ VTRR2024
FAPERJ RCSG2022

Title: Investigating the Effects of Communication Between Sensory Neurons and Hepatic Tissue, with Potential Implications for Post-Hepatectomy Innervation.

Authors: *G. R. FREIRE[1], V. RIBEIRO-RESENDE[2], M. L. DIAS[3];
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Abstract: The relationship between the liver and the nervous system remains an underexplored area of research, particularly regarding hepatic innervation and its potential reinnervation following transplants. Hepatic innervation can significantly influence metabolism and immunogenicity, processes mediated by the autonomic nervous system. However, the mechanisms underlying this reinnervation, especially in bioengineered models, are still poorly understood. This study investigated the interactions between sensory neurons from the dorsal root ganglion (DRG) of embryonic rats (E14-E15) and liver fragments under different experimental conditions (intact (n=13), injured by steatohepatitis (n=4), and decellularized (n=11)), as well as a control condition without liver fragment (n=12). The goal was to evaluate the influence of the hepatic microenvironment on neuritogenesis and cell migration. In vitro co cultures were performed, where DRGs were placed on coverslips treated with poly-L-lysine and coated with laminin-1, surrounded by liver fragments in the mentioned conditions. The cultures

were incubated at 37°C and 5% CO_2 for 3 days in DMEM/F12 supplemented with 1% ITS, 10 ng/mL NGF, 1% P/S, and 100 µg/mL glutamine. Steatohepatitis was induced in rats via a high-fat diet and carbon tetrachloride (CCl_4) injection, while hepatic decellularization was achieved by perfusion with detergents (1% SDS and 1% Triton X-100). Histological analysis was performed using hematoxylin and eosin (H&E) to assess structural integrity and decellularization efficiency, as well as injury induction. Immunofluorescence was employed to label neurites (TUJ-1) and cell nuclei (DAPI), followed by observation under fluorescence microscopy. The culture medium was collected for future proteomic and ELISA analyses to identify trophic factors such as Hepatocyte Growth Factor (HGF). Quantitative analyses involved measuring neurite outgrowth, cell density, and migration extension. Results showed that healthy and decellularized livers promoted greater neurite extension and cell density, indicating a permissive environment for neuritogenesis and migration. In contrast, injured livers exhibited a significant reduction in these parameters, highlighting a detrimental effect on neuronal organization. The study underscores the crucial role of the hepatic microenvironment in modulating neuro-hepatic interactions, with important implications for tissue bioengineering and the development of therapeutic strategies for hepatic and neuronal regeneration.

Disclosures: G.R. Freire: None. **V. Ribeiro-Resende:** None. **M.L. Dias:** None.

Late-Breaking Poster

LBP005: A.05. Synaptogenesis and Activity-Dependent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP005.01/LBP030

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: RO1 grant from the National Institute of Neurological Disorders and Stroke (NS129555)

Title: EphB2 receptor forward signaling regulates PV interneuron inhibitory synapse development in hippocampus

Authors: *S. E. REYES-GARCÍA[1], S. SUTLEY-KOURY[2], V. SANTHAKUMAR[3], I. M. ETHELL[4];
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Abstract: Impaired excitatory-inhibition (E/I) balance is thought to underlie the development of hyperactive neuronal networks in neurodevelopmental disorders. EphB2 receptor tyrosine kinase is a major regulator of excitatory synapse development, but its role in inhibitory microcircuits is less understood. Parvalbumin (PV) interneurons provide perisomatic inhibition onto CA1 pyramidal cells (PC), where precise alignment of presynaptic vGAT with postsynaptic gephyrin clusters is critical for efficient inhibitory transmission. Understanding how EphB2 influences this

organization is essential for clarifying mechanisms of E/I balance. We previously found an increase in the number of PV/vGAT presynaptic sites, and the enhanced strength of PV→PC functional connectivity in the CA1 hippocampus of mice lacking EphB2 in PV cells, indicating that EphB2 may negatively regulate PV activity and PV→PC connectivity. Here, we utilize genetic approaches to assess the role of EphB2 forward signaling in functional and structural PV→PC connectivity through whole-cell patch-clamp electrophysiology, immunohistochemical analysis, and behaviors in mice. We used gain and loss-of-function approaches to inhibit EphB2 forward signaling with EphB2 point mutants: F620D (kinase-hyperactive) and K661R (kinase-dead). Confocal microscopy and quantitative image analysis were used to measure puncta density, nearest-neighbor distance, and colocalization coefficients between PV/vGAT and vGAT/Gephyrin. PV/vGAT colocalization was significantly increased in kinase-dead K661R mutant, with higher density of PV-positive vGAT puncta in SP area of CA1 hippocampus, suggesting enhanced perisomatic inhibitory innervation of PCs. Conversly, kinase-hyperactive F620D mutant showed decreased PV/vGAT overlap and lower vGAT puncta density. Parallel analyses of vGAT/Gephyrin colocalization revealed a similar finding: EphB2K661R mice exhibited stronger presynaptic–postsynaptic alignment, while EphB2F620D mutants showed reduced overlap and more dispersed puncta organization compared to wild-type controls. Analysis of sIPSCs on PCs was done to assess functional connectivity. In addition, we showed that deletion of EphB2 receptors from PV cells protects against PTZ induced seizures. Our findings demonstrate that EphB2 kinase activity in PV cells negatively regulates the organization of PV-positive inhibitory synapses in CA1 hippocampus. These results suggest that EphB2 plays a critical role in tuning inhibitory circuit architecture, with implications for disorders linked to PV cell dysfunction and altered E/I balance, such as autism and epilepsy.

Disclosures: S.E. Reyes-García: None. **S. Sutley-Koury:** None. **V. Santhakumar:** None. **I.M. Ethell:** None.

Late-Breaking Poster

LBP005: A.05. Synaptogenesis and Activity-Dependent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP005.02/LBP031

Topic: A.05. Synaptogenesis and Activity-Dependent Development

Support: NIH R21 206800

Title: Transgenic expression of chimeric NMDA receptor GluN2 subunits reveals that ionotropic signaling links novelty exposure to hippocampal Arc expression

Authors: *H. E. ZIKRIA-HAGEMEIER[1], G. D. KLETTER[2], D. A. GUTEMA[3], M. S. RAFIE[4], T. C. DUMAS[5];
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[2]Interdisciplinary Program in Neuroscience, George Mason University, Fairfax, VA;

[3]Intersciplinary Program in Neuroscience, George Mason University, Fairfax, VA; [4]George Mason Unversity, Fairfax, VA; [5]Psychology, George Mason Univ, Fairfax, VA

Abstract: N-methyl-D-aspartate receptors (NMDARs) are glutamatergic receptors that enable activity dependent synaptic plasticity which subserves learning and memory. In the hippocampus, NMDAR activation leads to expression of the Immediate early gene (IEG) for activity regulated cytoskeletal protein, Arc/Arg3.1 (Arc), which serves as a marker for contextual engram formation. Recently, it was shown that NMDARs produce postsynaptic signals via ionotropic and non-ionotropic signaling. However, the links between these separate NMDAR signaling pathways and Arc expression have not yet been investigated. Therefore, we created transgenic mice that express chimeric glutamatergic NMDAR 2 (GluN2) subunits [where carboxy terminal domains (CTDs) are swapped between GluN2A and GluN2B; GluN2A-B^{ctd} and GluN2B-A^{ctd}] in order to separate the ionotropic and the non-ionotropic contributions to synaptic plasticity and thereby learning and memory. We exposed transgenic mice at different developmental stages (with different background content of GluN2A and GluN2B) to a novel Barnes maze environment for five minutes of free exploration and then immediately examined hippocampal Arc expression via *in situ* hybridization staining on tissue in the regions of interest, area CA1 (Cornu ammonis 1) pyramidal cells and dentate gyrus (DG) granule cells. In the animals under three weeks of age (P17-19) having a predominantly GluN2B background, the mice expressing GluN2A-B^{ctd} subunits displayed increased Arc expression levels compared to age-matched wildtype (WT) controls in both area CA1 and the DG. Conversely in animals over three weeks of age (P22-24 and P57-60) having a predominantly GluN2A background, mice expressing GluN2B-A^{ctd} subunits exhibited lower levels of Arc expression compared to WT controls. However, baseline levels of Arc expression in the home cage controls who were not exposed to the novel environment differed across genotypes with GluN2B-A^{ctd} expressing mice having more Arc expression compared to the WT home cage controls. These results suggest that the NMDAR ionotropic signaling regulates Arc expression. Additionally, excessive baseline Arc expression in mice expressing GluN2B-A^{ctd} subunits might explain impaired spatial learning in these animals while greater activity driven Arc levels may help explain superior long-term memory in mice expressing GluN2A-B^{ctd} subunits. A better understanding of the signaling pathways between environmental experience and contextual engram formation provides more therapeutic targets and perhaps better treatments for disorders involving spatial memory impairments, including Alzheimer's disease and schizophrenia.

Disclosures: H.E. Zikria-Hagemeier: None. **G.D. Kletter:** None. **D.A. Gutema:** None. **M.S. Rafie:** None. **T.C. Dumas:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.01/Web Only

Topic: A.06. Developmental Disorders

Support: ProMedica Health System Foundation
NIH grant P50MH100023
NIH grant P51OD11132
NIH grant TR002378

Title: Generating Autism Spectrum Disorder Subtypes using Machine Learning approaches

Authors: *G. VENTO[1], J. K. RILLING[2], L. J. YOUNG[3], E. ANDARI[1];
[1]Department of Neurosciences and Psychiatry, University of Toledo, Toledo, OH; [2]Department of Anthropology, Emory University, Atlanta, GA; [3]Center for Translational Social Neuroscience, Emory University, Decatur, GA

Abstract: Autism spectrum disorder (ASD) is a heterogenous disorder that is characterized by a spectrum of deficits in social interaction and empathy. The preeminent issue with ASD is its wide phenotypic variation and the challenge therefore to find effective treatments. Current operationally defined subdivision of ASD is not biologically or clinically relevant. The objective of this study is to generate subtypes of ASD using behavioral and personality traits measures and validating these predicted clusters with clinical and biological measurements. Our hypothesis was that if we analyzed ASD in this way, then we would be able to propose new biologically relevant subtypes. A total of 114 adult men 18-45 years old, including 74 neurotypical (NT) and 40 ASD were recruited at Emory University and completed a series of behavioral tasks (such as the personality test (NEO-PI-R), reading the mind in the eyes (RMET), Symptom Checklist 90-revised questionnaire (SCL-90), intelligence quotient (IQ), and Broader Autism Phenotype Questionnaire (BAPQ)); diagnostic tests such as Autism Diagnosis Interview-Revised (ADI-R) and use biological measures such as resting-state functional connectivity (rs-fMRI). For the machine learning analysis, we used random forest tree algorithm to classify ASD and NT. We included NEO-PI-R and RMET in the main classifier. The resulting model feature contribution was described using SHapley Additive exPlanations (SHAP). ASD subtypes were then derived based on the SHAP values for the individual data points utilizing K-means clustering. Subtypes were then validated using the other behavioral, clinical and brain function data, and utilizing t-tests and Cohen's D effect sizes. The random forest tree model classified ASD and NT with an average accuracy of 80%. Top features included personality domains such as extraversion and neuroticism. The resulting k-means clustering derived 3 different subtypes. T-tests indicated significant differences in the following measures: ADI-R repetitive behaviors, BAPQ, IQ, SCL-90, neuroticism, extraversion, RMET, and rs-FC between the brain areas with theory of mind and empathy processing. Our results suggest that one of the subtypes of ASD is characterized by high neuroticism, lower positive emotions, higher IQ, and lower rsFC between networks involved in social cognition. Another subtype is also characterized by high levels of neuroticism, higher ADI-R scores on repetitive behaviors, and lower rsFC networks involved in social salience. These results are very promising, and the next step is to examine whether these putative subtypes are biologically relevant and respond to treatment.

Disclosures: G. Vento: A. Employment/Salary (full or part-time); University of Toledo Department of Neurosciences and Psychiarty. **J.K. Rilling:** None. **L.J. Young:** None. **E. Andari:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.02/LBP032

Topic: A.06. Developmental Disorders

Support: NSF Grants 1640909 (JVJ) and 1735095 (CM)
DOE Grant P200A240132 (CM)

Title: Further Analysis of A.I. Fast Diagnostics Plus Severity Assessments of Neurodivergent disorders From Millisecond Kinematic Motor Data

Authors: K. P. DOCTOR[1], C. L. MCKEEVER, Ms.[2], ***J. V. JOSE**[3];
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Abstract: Neurodevelopmental disorders (NDD) are a major health concern in the US. Based on CDC statistics, there are 1/36 children with autism spectrum disorder (ASD), 9.4%, with Attention-Deficit/Hyperactivity Disorder (ADHD), and about 70% of ASD have comorbid ADHD. This leads to a lack of providers able to provide timely diagnosis for these disorders. In a recent paper (1) we started to address this problem by using high-definition Bluetooth sensors measuring the motor data generated by NDD and neurotypical (NT) participants carrying out the reaching protocol. We selected a subset of all kinematic variables measured to use for training within a Long Short-Term Memory (LSTM) of a Deep Learning (DL) protocol. In (1) we found that we could quickly diagnose unseen reaching trials from NDD participants with an accuracy of over 70% plus having the Area Under the curve (AUC) of the Receiver Operating Characteristic (ROC) with up to 86% values and above 90% for NT participants. By looking at the millisecond extrema fluctuations in the noise filtered data sets we identify trends in the degree of severity for each NDD. We have tested the validity of the DL results of (1) to mitigate the possibility of overfitting. We first preformed random label swaps before DL showing reduced performance with an increase in randomization. Next, we use other A.I. techniques and analysis on the data measured sets to compare with the DL results: (a) SHapley Additive exPlanations (SHAP) and saliency analysis. (b) Random Forest. *(c)* Support Vector Machine calculations. These data alternatives analysis adds further support to the strength of the movement-based prediction analysis (1). We also looked at the severity of each NDD based on a statistical analysis of the millisecond kinematic fluctuations. Two biomarkers were identified characterizing the probability distributions of the millisecond fluctuations. The Fano Factor (FF), and the Shannon Entropy (SE) giving the amount of randomness present in the movements of each participant. A stability analysis was also done to ensure that an appropriate number of trials were completed to make sure that the SE and FF biometrics were constant and stable. The results described above provide extra support for the LSTM results reported in (1), further that the biometrics are also stable as a function of trials. Nonetheless, further testing in larger cohorts will

be needed as well as doing the studies as a function of time to further test the results of Ref. (1). K. Doctor, et al. Deep Learning Diagnosis Plus Kinematic Severity Assessments of Neurodivergent Disorders . Sci Rep 15, 20269 (2025).

Disclosures: K.P. Doctor: None. **C.L. McKeever:** None. **J.V. Jose:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.03/LBP033

Topic: A.06. Developmental Disorders

Support: KAKENHI 25K10855
AMED 24lk0310098h0001

Title: Maternal transcutaneous auricular vagus nerve stimulation exerts preventive effects on maternal immune activation-induced behavioral deficits in offspring mice.

Authors: *H. KUNIISHI[1,3,2], M. XIE[1,3,2], H. MATSUZAKI[1,3,2];
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Abstract: The fetal period represents a critical window for brain development, during which excessive maternal immune activation (MIA) is associated with an elevated risk of neurodevelopmental disorders, including autism spectrum disorder and schizophrenia. Maternal pro-inflammatory cytokines, particularly interleukin-6 (IL-6), are known to disrupt key neurodevelopmental processes in the offspring brain. Cervical vagus nerve stimulation (VNS) has been shown to attenuate peripheral inflammation through activation of the efferent vagal pathway. More recently, transcutaneous auricular VNS (taVNS), a non-invasive method targeting the auricular branch of the vagus nerve (ABVN) in the external ear, has been demonstrated to suppress inflammatory cytokines in both clinical and preclinical settings. In the present study, we investigated whether taVNS could modulate maternal inflammatory responses and mitigate MIA-induced neurodevelopmental abnormalities in offspring. Pregnant mice received lipopolysaccharide (LPS) to induce MIA, with taVNS administered concurrently. Maternal IL-6 levels were quantified, and behavioral as well as neuropathological outcomes were evaluated in the offspring. Our results revealed that taVNS significantly reduced maternal IL-6 levels two hours after LPS administration. Furthermore, adult offspring of taVNS-treated dams were protected from MIA-induced deficits, including impaired social interaction, increased repetitive behaviors, and heightened microglial activation. These findings suggest that maternal taVNS during acute infection may serve as a promising strategy to reduce the risk of neurodevelopmental disorders in offspring through suppression of maternal inflammatory signaling.

Disclosures: H. Kuniishi: None. **M. Xie:** None. **H. Matsuzaki:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.04/LBP034

Topic: A.06. Developmental Disorders

Title: Educational intervention on the neurodevelopment of a preschooler with autism spectrum disorder: case study

Authors: *E. RAMÍREZ MORENO[1], G. HERNÁNDEZ-HERNÁNDEZ[2], J. ARIAS-RICO[3], R. BALTAZAR TELLEZ[4], L. RIVERA-RAMIREZ[4], I. MORENO-VITE[4], Z. CALDERÓN-RAMOS[5];
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Abstract: The objective of this study was to evaluate the impact of an educational and care intervention on the neurodevelopment of a preschool child with ASD (Autism spectrum disorder), using the Montessori approach and the TEACCH therical models. This case study employs a qualitative and observational approach, wherein an educational intervention was implemented utilising the Montessori and TEACCH (Treatment and Education of Children with Autism and Associated Communication Problems) models. The primary focus of the programme was the organisation of the school environment, with specific emphasis on the visually defined spaces designated for work, play, and rest, in addition to visual routines (TEACCH). The programme utilised pictograms, gestures, and cards to facilitate the expression of fundamental needs, such as the need to use the bathroom, satisfy hunger, rest, and engage in play. Furthermore, it incorporated manipulative activities involving sensory materials, including stringing, sorting, classifying, and transferring liquids. The Autism Rating Scale (CARS) was utilised to ascertain the type of autism before and after the intervention. CARS is a tool designed to evaluate the behaviour of children with suspected ASD. Scores of 15-29 indicate Non-Autistic behaviour, 30-36 indicate Moderately Autistic behaviour, and 37-60 indicate Severely Autistic behaviour. The results demonstrated enhancements in adaptation to the school environment, augmented tolerance for routine, enhanced attention, autonomy, and participation. The intervention led to enhancements in fine motor coordination, classroom participation, emotional connection with the adult supervisor, and functional communication, while concurrently reducing isolation behaviours. Furthermore, an enhancement in the domain of social skills and emotional self-regulation was observed. Consequently, the Childhood Autism Rating Scale (CARS) score was 39, indicating severe autism. Following the intervention, the participant obtained a score of 30, indicating a moderate stage of autism. In conclusion, the combination of

Roy's Adaptation Model with Montessori and TEACCH strategies promoted the adaptive development of children with ASD. The structured and humanised nursing intervention is highly relevant for neurological development in children, promoting autonomy, communication, and socialisation. This reaffirms the role of the professional in creating individualised care plans and in facilitating school-family collaboration to ensure the continuity of the adaptive process.The authors have no conflicts of interest regarding the publication of these findings.

Disclosures: E. Ramírez Moreno: None. **G. Hernández-Hernández:** None. **J. Arias-Rico:** None. **R. Baltazar Tellez:** None. **L. Rivera-Ramirez:** None. **I. Moreno-Vite:** None. **Z. Calderón-Ramos:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.05/LBP035

Topic: A.06. Developmental Disorders

Support: NICHD R01 HD042182
Seale Innovation fund
Red Gates Foundation

Title: 22q11 deletion selectively alters progenitor states and projection neuron identities in the developing cerebral cortex.

Authors: *T. M. MAYNARD[1], S. RUKH[2], D. W. MEECHAN[2], C. SIGGINS[2], Z. ERWIN[2], A.-S. LAMANTIA[2];
[1]Fralin Biomedical Research Institute, Virginia Tech Carilion, Roanoke, VA; [2]Fralin Biomedical Research Institute at Virginia Tech Carilion, Roanoke, VA

Abstract: Heterozygous deletion of chr22q11.2 (22q11 deletion syndrome, 22q11DS) is associated with a broad range of neurodevelopmental disorders (NDDs), including autism spectrum disorder (ASD) and schizophrenia (Scz), in part due to disrupted generation of Layer 2/3 projection neurons that are central to association cortical networks. We used a multi-faceted approach, including bulk- and single-cell transcriptomics, neuronal birthdating, and quantitative cellular assays to probe the state of a subpopulation of cortical progenitors: basal progenitors (bPs), which contribute to the expansion of L2/3 cortical neurons in the *LgDel* model of 22q11DS. Deletion selectively disrupts bPs, but not the primary stem cell pool - apical progenitors (aPs)/radial glia - which preferentially generate lower-layer excitatory neurons and also produce bPs. This disruption is also temporally selective, peaking at E14.5 when bP output is highest, while later bP cohorts are less affected. scRNAseq analysis and quantitative cellular analysis suggest that deletion does not cause a complete gain or loss of either progenitor or neuroblast subtypes, but instead alters the frequency and dynamics of bP and NB subpopulations, without significantly disrupting aPs. These bP-targeted changes prefigure the generation of a

diminished L2/3 PN cohort with altered times of genesis, molecular identities, and laminar positions—well before the emergence of L2/3 cortical circuit dysfunction that is thought to underlie NDD pathologies such as ASD and Scz.

Disclosures: T.M. Maynard: None. **S. Rukh:** None. **D.W. Meechan:** None. **C. Siggins:** None. **Z. Erwin:** None. **A. LaMantia:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

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Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.06/LBP036

Topic: A.06. Developmental Disorders

Support: NIH Grant R01 MH125516
UC LEADS

Title: Distribution of PV+ Neurons in the SCN2A+/- Mouse Model

Authors: *L. J. G. BATTIN[1,2];
[1]Neurosurgery, University of California, San Francisco, San Francisco, CA; [2]Neurobiology, Physiology, and Behavior, University of California, Davis, Davis, CA

Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental condition that is characterized by social impairment, increased sensory sensitivity, delayed learning, and increased seizures. Prior work links ASD development to an imbalance in the ratio of excitatory/inhibitory (E/I) neurons in the brain. However, the interactions between E/I imbalance and ASD among precise brain regions and neuronal populations remain unclear. To investigate this, we immunoassayed for a variety of inhibitory neurons in wild-type and SCN2a+/- mice, a genetic ASD model. Brain sections were imaged, regions of interest were traced based on the Allen Mouse Brain Atlas, and cells were counted manually. Here we show cell density across different brain regions for the inhibitory neuron marker, parvalbumin (PV). We discovered greater PV+ neuron density in SCN2a+/- mice in the Cornu Ammonis Areas 1-3 (CAs 1-3), a neuron-dense subregion of the hippocampus. Our results demonstrate E/I imbalance may be region-specific for the SCN2a+/- model, suggesting upstream altered circuitry in the hippocampus that gives rise to ASD symptoms. Moreover, the role of CAs 1-3 is heavily implicated in epileptic seizures, and further investigation may support the development of anticonvulsants.

Disclosures: L.J.G. Battin: None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.07/LBP037

Topic: A.06. Developmental Disorders

Support: NIH NIAA R01AA027075

Title: A serendipitous discovery in a Rett mouse model implicates dietary lipids in disease progression

Authors: *D. H. YASUI[1], J. M. LASALLE[2,3,4];
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Abstract: The vast majority of Rett syndrome (RTT) cases are caused by heterozygous mutations in *MECP2* in females. RTT symptoms include severe motor defects, impaired breathing, and altered metabolism. Loss of MeCP2e1 encoded by *MECP2* underlies motor, breathing and metabolic defects in RTT patients and MeCP2e1 deficient mice. To address the hypothesis that microglia contribute to RTT symptoms in brain we ablated brain microglia in MeCP2e1 deficient mice by chronic administration of PLX3397 in purified chow through 23 weeks of age. To track disease, we performed gait analysis by measuring foot placement on paper and neuro phenotype scoring based on mobility, body shape, grooming, and response to tail hang weekly in *Mecp2e1*$^{-/+}$ and *Mecp2e1*$^{-/y}$ and wild type *Mecp2e1*$^{+/+}$ and *Mecp2e1*$^{+/y}$ littermate control mice. Surprisingly, chronic microglial ablation had insignificant effects on neuro and motor phenotypes in *Mecp2e1*$^{-/+}$ and *Mecp2e1*$^{-/y}$ deficient mice. Serendipitously, we discovered that the change in from standard to purified vehicle chow alone was able to significantly reverse, neuro-phenotype scores in *Mecp2e1*$^{-/+}$ females at 10 weeks of age and 8 weeks of age in *Mecp2e1*$^{-/y}$ male mice. Purified chow normalized body weight in *Mecp2e1*$^{-/+}$ female mice for the full 23-week treatment and body weight in *Mecp2e1*$^{-/y}$ males up to 10 weeks. Interestingly, purified chow normalized gait defects in *Mecp2e1*$^{-/+}$ female mice but not *Mecp2e1*$^{-/y}$ male mice. The standard chow that correlated with higher disease scores had a significantly different long chain fatty acid (LCFA) composition than the PLX3397 purified vehicle chow that correlated with lower disease scores. In conclusion, we hypothesize that defects in LCFA metabolism impair mitochondrial function neuronal signaling in MeCP2e1 deficient mice and RTT patients. This may result in the gradual loss of normal neuronal signaling balance followed by long term hypoactive neuronal function as observed in RTT brain. However, the implication from these results suggests that a diet with an optimized LCFA composition may counteract these disease phenotypes.

Disclosures: D.H. Yasui: None. **J.M. LaSalle:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

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Program #/Poster #: LBP006.08/LBP038

Topic: A.06. Developmental Disorders

Support: 1R21NS137061-01A1

Title: PP2A B' subunit regulates synaptic development and cognition - A fly model to study intellectual disability (ID).

Authors: *S. KALA BHATTACHARJEE[1], C. WU[2];
[1]Neuroscience Center of Excellence, LSU Health, New Orleans, LA; [2]Neuroscience Center, LSU Health Sciences Center, New Orleans, LA

Abstract: Objective: Intellectual disability (ID) affects up to 3% of the population, yet its molecular underpinnings remain poorly understood. Recent genetic studies have identified *de novo* mutations in the PP2A B56 regulatory subunits - PPP2R5C and PPP2R5D as contributors to ID. We investigated the role of the PP2A B' subunit in synaptic development and cognitive function using *Drosophila melanogaster*, where the single orthologous gene *well-rounded* (*wrd*), encodes the sole fly homolog of both B56 subunits - to elucidate how these mutations impair synaptic development and cognition. Methods: We generated transgenic flies expressing wild-type and ID-linked mutant forms of mCherry-tagged Wrd *(UAS-mCherry-Wrd)* mimicking ID-linked mutations in PPP2R5C/D. These were expressed in *wrd* null flies using tissue-specific Gal4 drivers. Synaptic morphology was assessed at larval neuromuscular junctions (NMJs) via immunohistochemistry. Rescue experiments were conducted in *wrd* null backgrounds to assess synaptic morphology at larval neuromuscular junctions (NMJs), activity-dependent remodeling at photoreceptor synapses, and gustatory learning in adults. Activity-dependent synaptic remodeling was evaluated at adult photoreceptor synapses under light/dark paradigms. Gustatory learning was tested using a proboscis extension response (PER) assay. Results: Loss of *wrd* disrupted active zone (AZ) stability at NMJs, impaired light-induced AZ remodeling in photoreceptors, and caused aversive taste memory deficits. Wild-type Wrd rescued all phenotypes, while mutant *Wrd* transgenes failed to restore AZ opposition, remodeling, or learning, despite rescuing distal axon vesicle accumulation. These findings suggest that ID-linked mutations in the conserved acidic loop of Wrd selectively impair synaptic functions and cognition. Conclusion: Our study establishes *Drosophila* Wrd as a genetically tractable model to investigate PP2A B' subunit function in synaptic development and cognitive processes. ID-linked mutations in PPP2R5C/PPP2R5D disrupt specific aspects of Wrd-mediated phosphatase activity, providing mechanistic insight into PP2A-related intellectual disability. This model offers a platform for future therapeutic exploration targeting phosphatase regulation in neurodevelopmental disorders.

Disclosures: S. Kala Bhattacharjee: None. **C. Wu:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

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Program #/Poster #: LBP006.09/LBP039

Topic: A.06. Developmental Disorders

Support: T32HD07489
P50HD105353
R01HD094715

Title: Developing techniques for neuroinflammation detection in autism spectrum disorder

Authors: *N. COTTAM[1], J. GUERRERO-GONZALEZ[1], L. VAZQUEZ[2], J.-P. YU[2], A. ALEXANDER[3], D. DEAN III[3], L. OESTREICH[4], B. TRAVERS[3];
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Abstract: Autism spectrum disorder (ASD) is defined by impaired social cognition and repetitive/restricted behaviors, with diagnosis typically occurring in early childhood. Inflammation and microglial activation have emerged as two critical components in the pathogenesis of ASD. However, there are no reproducible methods for non-invasively investigating the presence of these structural states in the brain. In this work, we explore whether diffusion weighted imaging (DWI) imaging models can detect inflammation in the form of activated microglia in the brain. The relationship of extracellular volume fraction (EXVF) to volume fraction of isotropic diffusion compartment (FISO) is variable depending on a state of chronic or acute inflammation, where more EXVF can be indicative of chronic and FISO can be indicative of acute. Here, we compared this ratio across a typically-developing and autistic pediatric population. We found that EXVF was higher in both the frontal and visual cortices of autistic children, and that cerebrospinal fluid had higher FISO in typically developing children. We also compared the proportion of neurons and microglia in the hippocampus, motor cortex and cerebellum. These regions have vastly different cell-type proportions, and our results in typically developing children replicate these findings. Our data coincide with the literature in suggesting that inflammatory processes in the ASD pediatric population deviate from the typically developing pediatric population and that microglia are relevant in these differences. While these results coincide with gross findings in the literature, it is important to validate these findings with the aim of developing rigorous and reproducible inflammation detection techniques.

Disclosures: N. Cottam: None. **J. Guerrero-Gonzalez:** None. **L. Vazquez:** None. **J. Yu:** None. **A. Alexander:** None. **D. Dean:** None. **L. Oestreich:** None. **B. Travers:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.10/LBP040

Topic: A.06. Developmental Disorders

Title: Elevated ALFF in the inferior temporal gyrus of children with autism: Evidence from ABIDE resting-state fMRI

Authors: *Y. MA[1,2,3], L. JI[3], B. CHEN[3], M. E. THOMASON[3,4];
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Abstract: Autism spectrum disorder (ASD) is a complex neurodevelopmental condition that affects approximately 1 in 31 children aged 8 years (3.2% of the population; Centers for Disease Control and Prevention, 2022). Symptoms of ASD include deficits in social interaction and communication, alongside restricted interests and/or repetitive behaviors (American Psychiatric Association, 2013). Resting-state functional MRI (fMRI) studies have revealed early alterations in neural connectivity in children with ASD, particularly in networks involved in social cognition, sensory processing, and executive functions (e.g., Uddin et al., 2013). In this study, we analyzed resting-state fMRI data from the multi-site, open-source Autism Brain Imaging Data Exchange (ABIDE) dataset (Di Martino et al., 2014). A total of 231 participants aged 6-12 years (children with ASD: N=118; typically developing children: N=113) were included, targeting the critical period for early diagnosis and intervention. We used the Autism Diagnostic Observation Schedule (ADOS) total score to assess ASD symptoms and the amplitude of low-frequency fluctuations (ALFF) as a measure of the spontaneous neural activity of a brain region during rest (Lord et al., 2000; Zang et al., 2007). To investigate the association between ASD symptoms and ALFF, we conducted mixed linear regression analyses using the lmerTest package in R (Kuznetsova et al., 2017). Results showed elevated ALFF in the bilateral inferior temporal (IT) gyrus among children with ASD compared to typically developing children (Fig. 1). Given the IT's role in visual perception and recognition, heightened spontaneous neural activity in this region aligns with sensory sensitivities found in prior ASD studies (e.g., Miyashita, 1993). These findings contribute to the growing understanding of atypical sensory and visual processing in ASD. Future work could explore the effectiveness of neural-based interventions, such as neurofeedback and transcranial direct current stimulation (tDCS), to modulate IT activity and improve sensory processing in children with ASD.

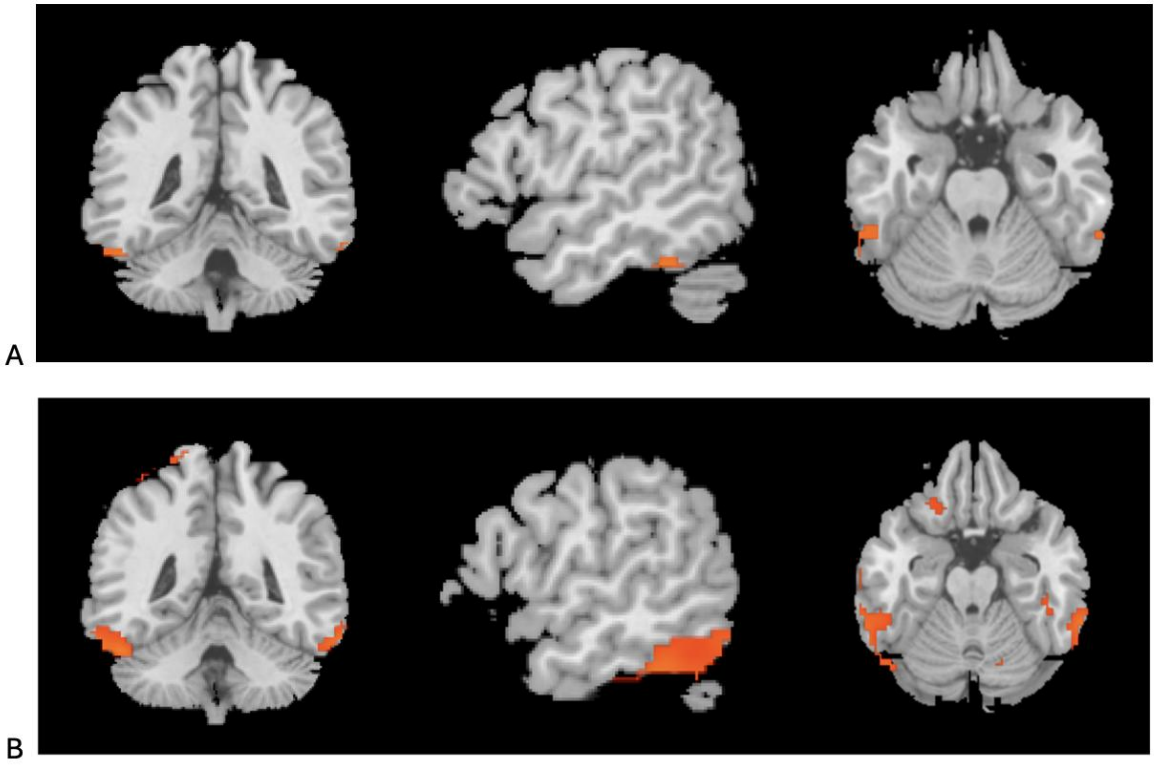

Figure 1. Regions showing ALFF differences between children with ASD and typically developing children. Children with ASD had increased resting-state neural activity in the bilateral inferior temporal gyrus compared to typically developing children at both $p < .001$ (A) and $p < .005$ (B) significance levels.

Disclosures: Y. Ma: None. **L. Ji:** None. **B. Chen:** None. **M.E. Thomason:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.11/LBP041

Topic: A.06. Developmental Disorders

Support: SFARI Autism Rat Models Consortium 2.0 grant 903332

Title: Disrupted sensory integration in a rat model of Fragile X Syndrome

Authors: *A. J. DUSZKIEWICZ[1], A. RÅSTEDT[2], E. R. WOOD[2], A. PEYRACHE[3], P. A. DUDCHENKO[4];
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Abstract: Autism spectrum disorder often involves atypical sensory processing, including hypersensitivity and difficulties with combining information across sensory streams. Fragile X Syndrome (FXS), caused by mutations in the *FMR1* gene, is a common inherited form of autism. Although rodent models have advanced our grasp of neural mechanisms underlying sensory hypersensitivity in FXS, the circuit-level origins of impaired multisensory integration remain largely unexplored. Here, we provide the first evidence that ablation of the *FMR1* gene disrupts sensory integration in the cortical circuits underlying spatial orientation. Spatial orientation in mammals depends on the ability to integrate information across sensory modalities. Central to this process are head-direction (HD) cells, each tuned to a specific heading direction of the animal, together creating an internal compass. This compass is updated by vestibular signals that encode angular head velocity (AHV) and is anchored to the external world via visual input. Taking advantage of the HD system's experimental accessibility, we examined how these two information streams interact in *Fmr1*$^{-/y}$ rats, a model of FXS. To that end, we simultaneously recorded populations of neurons from postsubiculum (PoSub; 30-115 cells/session) and retrosplenial cortex (RSC; 52-171 cells/session) using silicon probes in adult *Fmr1*$^{-/y}$ (n = 7) and wild-type (WT, n = 8) rats. During a visual-vestibular mismatch task, rats explored an elevated platform while a prominent visual landmark was displayed on a portion of the 360° LED screen surrounding the arena. When this landmark was rotated by 45° or 90°, HD neurons in WT rats shifted their preferred firing directions only partway, consistent with integration of visual and self-motion inputs. In contrast, HD cells in *Fmr1*$^{-/y}$ rats rotated exactly with the visual landmark, indicating a lack of vestibular contribution to reorientation. This was further reflected in reduced AHV tuning across both brain regions and greater instability of the HD signal in darkness. Finally, to establish whether this disruption of sensory integration is specific to the FXS rat model, we tested the rat model of SYNGAP1-related intellectual disability (*Syngap1*$^{-/+}$ rats) on the same experimental protocol, and found that *Syngap1*$^{-/+}$ rats (n = 6, n = 5 WT littermates), in contrast to *Fmr1*$^{-/y}$ rats, exhibit intact sensory integration and AHV tuning in the HD system. Further experiments will determine whether disrupted sensory integration and AHV tuning in *Fmr1*$^{-/y}$ rats translates to impairments in behavioural tasks that critically rely on self-motion signals.

Disclosures: A.J. Duszkiewicz: None. **A. Råstedt:** None. **E.R. Wood:** None. **A. Peyrache:** None. **P.A. Dudchenko:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

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Program #/Poster #: LBP006.12/LBP042

Topic: A.06. Developmental Disorders

Support: NIH Grant U54HD082008
NIH Grant U54HD104461

Title: Alpha rhythms are dysrhythmic and unstable during resting state EEG in FXS

Authors: *P. SIEKIERSKI[1,2], E. PEDAPATI[3,4];
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Abstract: Fragile X syndrome (FXS) is the most common inherited cause of autism spectrum disorder and intellectual disability, arising from *Fmr1* gene silencing that results in thalamocortical dysrhythmia characterized by reduced alpha oscillatory power. However, such traditional spectral analysis approaches may obscure important temporal dynamics of neural rhythms. We applied cycle-by-cycle analysis to source-localized resting-state EEG data from 70 individuals with FXS and 71 age- and sex-matched typically developing controls to characterize alpha oscillatory dysfunction beyond conventional power metrics. Using generalized linear mixed-effects models, FXS participants exhibited three distinct alpha abnormalities: (1) reduced burst occurrence specifically in males ($z = -4.23$, $p < 0.001$), while females showed no significant difference ($z = 0.65$, $p = 0.518$); (2) prolonged cycle periods across both sexes ($z = 6.65$, $p < 0.001$), indicating slower alpha frequencies; and (3) elevated burst amplitudes in both groups ($z = 2.78$, $p = 0.005$), with males showing higher amplitudes than females ($z = -5.00$, $p < 0.001$). Regional analysis revealed distinct patterns: temporal dysfunction (reduced bursts, prolonged periods) was most pronounced in cognitive control regions (cingulate, central, parietal cortices), while amplitude increases were strongest in sensory areas (temporal cortices: RT: $t = -7.05$, $p < 0.001$; LT: $t = -6.88$, $p < 0.001$). Within the FXS group, hierarchical regression models revealed that alpha burst amplitude significantly correlated with hyperactivity symptoms ($R^2 = 0.193$, $p = 0.002$), social communication difficulties ($R^2 = 0.095$, $p = 0.017$), and obsessive-compulsive behaviors ($R^2 = 0.068$, $p = 0.047$). These findings reveal that alpha dysfunction in FXS encompasses complex temporal dynamics and regional specificity beyond simple power reductions. The sex-specific burst count reduction in males, universal period prolongation, and amplitude elevation suggest distinct underlying mechanisms involving altered interneuron circuit balance, potentially reflecting an increased SOM/PV interneuron ratio due to reduced PV+ cell density in FXS. These quantifiable biomarkers bridge circuit-level pathophysiology with clinical phenotypes, offering targets for precision therapeutic interventions and objective metrics for clinical trials in FXS.

Disclosures: P. Siekierski: None. **E. Pedapati:** A. Employment/Salary (full or part-time); Psychiatry and Behavioral Neuroscience, University of Cincinnati College of Medicine.

Late-Breaking Poster

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Topic: A.06. Developmental Disorders

Support: NIH Grant R01EY025627

Title: Determining the ethology of visual circuit disruption in the superior colliculus of fragile X mice

Authors: *T. N. KEOPRASERT[1,2], J. W. TRIPLETT[2,1];
[1]George Washington University, Washington, DC; [2]Center for Neuroscience Research, Children's National Hospital, Washington, DC

Abstract: Fragile X syndrome (FXS) is the leading inherited cause of intellectual disability and autism spectrum disorder. Sensory processing deficits are commonly co-morbid with FXS; however, our understanding of the etiology of sensory dysfunction is limited. Given its role in linking sensory input to directed head and eye movements, we previously interrogated circuits in the superior colliculus (SC) of FXS mice (Fmr1-/y) and found that visual circuit organization and function were disrupted. Specifically, visual receptive fields are larger and inputs from primary visual cortex (V1), but not the retina, are disorganized. However, it remains unclear if these circuit disruptions impact behavior. To fill this gap, we assessed prey capture behavior as a robust readout of SC function in Fmr1-/y mice and their littermate controls. Surprisingly, we found that knockout mice captured crickets more quickly than wild-type controls (mean latencies 94s vs. 311s; p=0.049). Intriguingly, while wild-type mice showed clear evidence of training, with capture latency significantly decreasing from day 1 to day 3 (p=0.0014), Fmr1-/y mice did not. Knockout mice maintained stable latencies throughout training, which were consistently shorter than controls. Together, these data suggest that circuit disruptions in the SC of Fmr1-/y mice confer enhanced performance in prey capture and provide new insights into how SC dysfunction contributes to sensory processing abnormalities in FXS. Furthermore, these data suggest that V1 inputs to the SC may negatively regulate prey capture behavior.

Disclosures: T.N. Keoprasert: None. **J.W. Triplett:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.14/LBP044

Topic: A.06. Developmental Disorders

Title: Development of a Human IPSC-Based Neural Microphysiological System to Model Down Syndrome

Authors: *M. F. GRISALES[1], X. GUO[2], J. J. HICKMAN[3,4];
[1]College of Medicine, University of Central Florida, Orlando, FL; [2]University of Central Florida, Oviedo, FL; [3]University of Central Florida, Orlando, FL; [4]Hesperos, Inc., Orlando, FL

Abstract: Down syndrome (DS) is a complex aneuploidy genetic disorder caused by trisomy of chromosome 21 that affects 1 in 700 live births in the United States. This genetic disorder is clinically characterized by intellectual disability and developmental deficits that are connected with cellular changes linked to neurogenesis, gliogenesis, and reduced cortical volume. The increasing prevalence of DS has led to the necessity to identify phenotypic alterations and cellular/molecular mechanisms in the neural deficits in DS patients. To reduce limitations in current in vivo and in vitro studies and to address the pathophysiology of DS, we aimed to develop a human-based high-throughput neural microphysiological system to model DS utilizing human-induced pluripotent stem cells (iPSC). The differentiation of human iPSC-DS cell lines into human iPSC-DS cortical neurons followed a specific published protocol [1]. Cellular characterization of the differentiated cell lines by flow cytometry and immunocytochemistry showed a decreased differentiation of neuronal populations. To evaluate neural network activity particularly synaptic plasticity, human iPSC-DS cortical neurons were cultured on patterned microelectrode array (MEA) surfaces, and the capacity for the induction of long-term potentiation was evaluated. The MEA analysis combined with additional phenotypic analysis showed cellular and synaptic changes that contribute towards the neuropathology and clinical characteristics of DS. The establishment and validation of this human-based DS model can be applied to understanding neurodevelopmental disorders and advancing preclinical therapeutic discoveries.
Reference:1.Autar K., Guo X., Rumsey JW, et al. (2022). Stem Cell Reports 17, 96-109. doi: 10.1016/j.stemcr.2021.11.009.

Disclosures: M.F. Grisales: None. **X. Guo:** None. **J.J. Hickman:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

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Program #/Poster #: LBP006.15/LBP045

Topic: A.06. Developmental Disorders

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UCLA Jonsson Comprehensive Cancer Center and Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research Ablon Scholars Program

Title: A single cell multi-omic analysis identifies molecular and gene-regulatory mechanisms dysregulated in the developing Down syndrome neocortex

Authors: *C. K. VUONG[1], A. WEBER[2], M. SEONG[2], N. MATOBA[3], B. SHAFIE[2], P. ZHANG[2], S. NICHTERWITZ[2], S. YOUNESI[2], M. J. GANDAL[4], D. H. GESCHWIND[5], J. L. STEIN[6], L. DE LA TORRE-UBIETA[2];
[1]University of California, Los Angeles, Los Angeles, CA; [2]Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA; [3]UNC-Chapel Hill, Chapel Hill, NC; [4]Psychiatry and Genetics, University of Pennsylvania, Philadelphia, PA; [5]Psychiatry and Human Genetics, University of California, Los Angeles, Los Angeles, CA; [6]Genetics and Neuroscience Center, UNC-Chapel Hill, Chapel Hill, NC

Abstract: Down syndrome is the most common genetic cause of intellectual disability, presenting with cognitive, learning, memory, and language deficits. The cellular and molecular mechanisms driving this disorder remain unclear, limited by a lack of systematic studies in the developing human brain. Here, we leveraged single-nucleus multi-omics to profile the mid-gestation neocortex in a cohort of 26 donors. We observed a reduction in neural progenitors and corticothalamic neurons and concomitant increase of intratelencephalic neurons, accompanied by accelerated time to neuronal specification. We uncovered widespread changes in gene expression, chromatin accessibility and cell interaction networks impacting neurogenesis, specification and maturation and gene-regulatory networks directing these processes, including those downstream of transcription factors encoded in chromosome 21. Finally, we identified cell-specific molecular pathways shared with other neurodevelopmental disorders as well as heritability enrichment of GWAS signals in altered chromatin. Together, our data revealed a cascade of molecular dysregulation outlining the earliest steps in Down syndrome, providing a foundation for future therapeutic targets.

Disclosures: C.K. Vuong: None. **A. Weber:** None. **M. Seong:** None. **N. Matoba:** None. **B. Shafie:** None. **P. Zhang:** None. **S. Nichterwitz:** None. **S. Younesi:** None. **M.J. Gandal:** None. **D.H. Geschwind:** None. **J.L. Stein:** None. **L. De La Torre-Ubieta:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.16/LBP046

Topic: A.06. Developmental Disorders

Title: Type V CRISPR-Cas mediated gene editing of UBE3A-ATS as a therapy for Angelman Syndrome

Authors: R. BENDRIEM[1], ***A. BUBNYS**[1], I. NWOLAH[2], A. PARK[3], T. PANICO[1], J. E MURPHY[1], C. CHUNG[1];
[1]Arbor Biotechnologies, Cambridge, MA; [2]Biomedical Engineering, University of Virginia, Charlottesville, VA; [3]Pennsylvania State University, Horsham, PA

Abstract: Angelman Syndrome is caused by the loss of maternal *UBE3A*. Reactivation of the paternal *UBE3A* allele, normally silenced by the expression of the *UBE3A* antisense transcript (UBE3A-ATS) in mature neurons, has been extensively pursued as a therapeutic treatment for Angelman syndrome. Here, we describe a gene editing strategy using a Type V CRISPR-Cas enzyme to potently disrupt *UBE3A-ATS* and restore UBE3A mRNA and protein levels in *in vitro* Angelman patient neurons. We first screened multiple type V CRISPR nucleases and guides, spanning a 60,000 base pair region from the SNORD115 clusters to the 3' end of the *UBE3A* coding region, in HEK293 cells. Approximately 100 nuclease/guide pairs with efficient indel formations from the initial HEK293 screen were then tested in wild-type human iPSC-derived cortical neurons using a lentivirus-based delivery for the nuclease and lipofectamine-based delivery for the associated guides to identify pairs that were capable of robustly disrupting *UBE3A-ATS* and recovering *UBE3A* mRNA and protein levels. We identified 8 guides which, when paired with two nucleases (ABR-001v and ABR-004v), demonstrated UBE3A recovery equal to or greater than that of a benchmark ASO in Angelman patient neurons, including 5 guides that reached UBE3A levels equivalent to neurotypical controls. To demonstrate the functional impact of the UBE3A-ATS locus disruption, we developed an assay for measuring neuronal network activity of human iPSC-derived cortical neurons on a multi-electrode array (MEA). We identified a network hyperexcitability phenotype in Angelman patient-derived neurons. Our nuclease/guide pairs that robustly restored *UBE3A* expression were able to reverse this hyperexcitability phenotype and this degree of rescue was correlated with guide potency. Taken together, these results demonstrate the feasibility of using a Type V CRISPR-Cas enzyme to durably treat Angelman Syndrome.

Disclosures: R. Bendriem: A. Employment/Salary (full or part-time); Arbor Biotechnologies. **A. Bubnys:** A. Employment/Salary (full or part-time); Arbor Biotechnologies. **I. Nwolah:** None. **A. Park:** None. **T. Panico:** A. Employment/Salary (full or part-time); Arbor Biotechnologies. **J. E Murphy:** A. Employment/Salary (full or part-time); Arbor Biotechnologies. **C. Chung:** A. Employment/Salary (full or part-time); Arbor Biotechnologies.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.17/LBP047

Topic: A.06. Developmental Disorders

Title: Elucidating Common Genetic Variation in a Multi-Ancestral Population of Children with ADHD

Authors: *S. WANG[1], J. B. WILLIAMS[2];
[1]The State University of New York at Buffalo, Buffalo, NY; [2]University At Buffalo, Buffalo, NY

Abstract: Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by inattention and hyperactivity, affecting brain development. Genetics plays a major role in the risk for ADHD, but the exact factors involved are not fully understood. In our study, we examined genetic associations to ADHD in around 10,000 children aged 9-10. Using genome-wide association study (GWAS) analysis, we identified 2.3 million single nucleotide polymorphisms (SNPs), five of which showed significance. Importantly, GWAS was ancestrally stratified, and European ancestry clusters were meta-analyzed with publicly available childhood ADHD summary statistics from a European population (15,338 childhood ADHD cases vs. 45,398 controls). Additionally, we used transcriptome-wide association study (TWAS) analysis and found that the genes linked to these SNPs are associated with brain development. We have discovered novel SNPs linked to ADHD and identified how they impact gene expression in the brain.

Disclosures: S. Wang: None. **J.B. Williams:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

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Program #/Poster #: LBP006.18/LBP048

Topic: A.06. Developmental Disorders

Support: Roy J. Carver Charitable Trust (Grant #23-5683)
Startup Funds to AMA

Title: From mother to offspring: tracking neurodevelopmental and behavioral consequences of gestational influenza

Authors: *A. KAUSHIK[1], F. J. RIGAL[2], I. CHALEN[3], A. M. ANTONSON[3];
[1]Neuroscience, University of Illinois, Urbana-Champaign, Urbana, IL; [2]Physics, University of Illinois, Urbana-Champaign, Urbana, IL; [3]Animal Sciences, University of Illinois, Urbana-Champaign, Urbana, IL

Abstract: Maternal immune activation (MIA) is an established risk factor for neurodevelopmental disorders (NDDs) such as schizophrenia and autism spectrum disorder in offspring. In the US, about 63% of pregnant women experience at least one infection during pregnancy, nearly half of which are respiratory. This is important because maternal viral infections, such as influenza, can interfere with fetal brain development, potentially increasing

the risk of NDDs by up to threefold. Most MIA studies employ pathogen mimetics like Poly(I:C). However, no study has shown the postnatal cortical and behavioral effects of gestational influenza A virus (IAV). To address this gap, we employed a translationally relevant model using a mouse-adapted H3N2 strain of IAV (X31), which engages both innate and adaptive immune responses. On gestational day 9.5, pregnant C57BL/6NTac dams were intranasally inoculated with IAV (X31; 10^4 $TCID_{50}$) or a vehicle control (Saline). To separate the effects of prenatal insult from postnatal maternal care, pups were cross-fostered to lactating Swiss Webster dams at postnatal day (PD) 0.5. Cross-fostering was highly successful, with 17 of 18 litters adopted. Dams were monitored daily for weight gain. Dams were also scored post-inoculation for sickness behaviors, including ptosis, lethargy, huddling, eye/nose discharge, shivering, labored breathing, piloerection, and hunched posture. Compared to controls (n=12), X31-infected dams (n=15) showed weight loss beginning at 3 days post inoculation (dpi), resolving by 9 dpi (Time × Treatment $p<0.0001$, mixed-effects ANOVA). Sickness behavior scores were also significantly elevated (Time × Treatment $p<0.0001$, mixed-effects ANOVA) in X31 dams (n=13) versus controls (n=9), peaking at 2 and 3 dpi ($p<0.0001$, Šidák post-hoc test). At parturition, no group differences were observed in spleen weight ($p=0.8446$) or colon length ($p=0.138$), suggesting recovery from acute systemic effects observed earlier in infection (X31 n=13, Saline n=9; Mann-Whitney U test). Ongoing work will examine PD21 offspring brains for cortical excitatory neuron markers SATB2 and TBR1 to assess persistence of previously documented prenatal cortical disruptions. Behavioral assays modeling anxiety-like and repetitive behaviors, including marble burying, Y-Maze, open field, and elevated plus maze, are currently underway. All outcomes will be compared across sexes. Together, these novel findings will not only improve our understanding of the utility of live IAV infection as a clinically relevant MIA model, but also advance our understanding of how maternal influenza shapes offspring neurodevelopment and behavior.

Disclosures: A. Kaushik: None. **F.J. Rigal:** None. **I. Chalen:** None. **A.M. Antonson:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.19/LBP049

Topic: A.06. Developmental Disorders

Support: ANRF, New Delhi (grant no. SUR/2022/001671)

Title: Altered physical and sensorimotor developmental trajectory in rat offspring prenatally exposed to valproic acid as a model of autism spectrum disorder

Authors: *S. RAHI[1], S. P. SAH[2];
[1]Pharmacology Division, University Institute of Pharmaceutical Sciences, Panjab University, Chandigarh, Chandigarh, India; [2]Pharmacology Division, University Institute of Pharmaceutical Sciences, Chandigarh, India

Abstract: Autism spectrum disorder (ASD), is a neurodevelopmental disorder that normally begins before the first 3 years of life. As per the CDC report 2023, 1 in 36 children had ASD, with boys having 3.8-fold higher incidence than girls. Research demonstrates that children with ASD experience early delays in sensorimotor development, communication, and social relation which predict subsequent cognitive and behavioural outcomes. Exposure to antiepileptic drug valproic acid (VPA) during the gestation period is linked with developmental and physical malformations in the children. So far, the effect of VPA on early-developmental deficits and postnatal growth is not yet well discussed. In our study, we aimed to explore the influence of prenatal exposure to VPA in pregnant dams at two different doses (500 mg/kg and 600 mg/kg) on physical and sensorimotor development in rat offspring. Physical landmarks including body weight, tail malformations, pinnae unfold, and fur appearance were examined in the offspring in early postnatal days. Impairment in any of these landmarks was recognised as early developmental irregularities. While for sensorimotor landmarks, ten different developmental milestones including negative geotaxis, righting reflex, and grasping ability were examined. The findings of the study indicated a delayed physical and sensorimotor development in VPA exposed offspring as compared to normal offspring, with higher impacts seen in 600mg/kg than in 500mg/kg. Overall, the current work highlights a range of tests as a reliable way to assess the early developmental delay in the prenatal VPA model of autism and as a possible outcome measure for early intervention studies

Disclosures: S. Rahi: None. **S.P. Sah:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.20/LBP050

Topic: A.06. Developmental Disorders

Title: Gene therapy restores visual cortical function in a mouse model of CDKL5 deficiency disorder

Authors: *S. E. BENEZRA[1,2], B. HARVEY[3,2], E. MOROZOVA[4,2], A. GHOSHAL[2], A. BRENNECKE[2], A. DI NARDO[2];
[1]Biomarkers, Biogen, Cambridge, MA; [2]Biogen, Cambridge, MA; [3]Cambridge Neurophysiology Solutions, Mansfield, MA; [4]Neuroscience, Smartlabs, Cambridge, MA

Abstract: Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) is a rare neurodevelopmental condition caused by mutations in the X-linked *CDKL5* gene, which is essential for normal brain development and function. Patients typically present with early-onset seizures and profound developmental delays, including cortical visual impairments. Since CDD is a monogenic disorder, delivering the wildtype *CDKL5* gene to the brain is hypothesized to provide clinical benefit. To this end, we developed an AAV-based gene therapy for *CDKL5* and evaluated its efficacy in a genetic mouse model of CDD.

As a first step, we aimed to identify a phenotype in the mouse model that could be translated to the clinic. Given the visual impairments commonly seen in CDD patients, we assessed visual evoked potentials (VEPs) in freely moving mice undergoing tethered EEG recording. We discovered a novel phenotype in the mouse model, where visually-related gamma power was elevated in both hemizygous males and heterozygous females. This finding was replicated across four independent cohorts.
We then tested three dose levels of our gene therapy and observed dose-dependent increases in *CDKL5* protein expression and corresponding improvements in the gamma phenotype. Importantly, cortical *CDKL5* protein levels were strongly correlated with normalization of gamma power, suggesting a close link between target engagement and functional rescue.
These results demonstrate that gene replacement can restore cortical visual processing deficits in a model of CDD and support further investigation of visually-related gamma as a treatment response biomarker in CDD patients.

Disclosures: S.E. Benezra: None. **B. Harvey:** None. **E. Morozova:** None. **A. Ghoshal:** None. **A. Brennecke:** None. **A. Di Nardo:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

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Topic: A.06. Developmental Disorders

Support: NIH Grant 1R01NS109358-01
NIH Grant 1R01NS111029-01A1
Sundry startup 238748

Title: PIK3R2 variants drive cranio-cerebellar disproportion in a mouse model of Chiari I malformation

Authors: *Q. LI[1], D. PHAN[1], E. DENNIS[2], K. MEKBIB[3], K. KAHLE[1];
[1]Neurosurgery, Massachusetts General Hospital, Boston, MA; [2]National Institute on Alcohol Abuse and Alcoholism, Brookline, MA; [3]Yale University School of Medicine, New Haven, CT

Abstract: Chiari I malformation (CM1), the most common congenital anomaly of the hindbrain, is characterized by cerebellar tonsil herniation through the foramen magnum. The developmental mechanisms underlying CM1 remain poorly understood. Here, we investigated the role of PI3K signaling in CM1 pathogenesis by modeling a patient-associated *PIK3R2* mutation in mice. Constitutive activation of *PIK3R2* resulted in enlargement of both the cerebellum and posterior cranial fossa, consistent with cranio-cerebellar disproportion observed in CM1 patients. Conditional deletion of *PIK3R2* in *Atoh1+* granule cell precursors selectively induced tonsillar extrusion, demonstrating that overgrowth of the cerebellum relative to the cranial vault is sufficient to drive hindbrain herniation. Histological and developmental analyses revealed that

PIK3R2-driven hyperactivation of PI3K signaling promotes proliferation of glutamatergic progenitors and alters posterior fossa growth. These findings identify *PIK3R2* as a causative driver of CM1-like pathology in vivo, highlight cranio-cerebellar disproportion as a central pathogenic mechanism, and suggest that modulation of PI3K signaling could provide new therapeutic strategies for CM1.

Disclosures: Q. Li: None. **D. Phan:** None. **E. Dennis:** None. **K. Mekbib:** None. **K. Kahle:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.22/LBP052

Topic: A.06. Developmental Disorders

Support: Foundation for Prader Willi Research
Dr. Franciose Muscatelli's lab

Title: Feeding and swallowing deficits in a Prader-Willi syndrome mouse model

Authors: *S. SHAIKH[1], K. OSMAN[2], C. HAXTON[2], F. MUSCATELLI[3], T. E. LEVER[2]; [1]University of Missouri - Columbia, Columbia, MO; [2]Otolaryngology - Head and Neck Surgery, University of Missouri, Columbia, Columbia, MO; [3]NMDA/IBDM, Marseille, France

Abstract: Prader-Willi syndrome (PWS) is a congenital neurodevelopmental disorder caused by disruption of imprinted genes on chromosome 15q11-q13. Altered hypothalamic oxytocinergic circuits are implicated in the pathogenesis of PWS, contributing to hallmark neonatal dysphagia (feeding/swallowing deficits) and, via maladaptive pathways, to hyperphagia and obesity in later childhood. While several mouse models have been used to study PWS, dysphagia has not been objectively defined. The Madin KO mouse model, in which both *Magel2* and *Necdin* genes are deleted, is considered one of the most robust and genetically representative pre-clinical models of PWS. It recapitulates key features of human PWS, including failure to thrive: ~40% of Madin KO mice die within 24 hours after birth, without a visible milk spot. Survivors show lower body weights before weaning, which normalize in females by postnatal day 21 (P21) but persist in males. These findings suggest postnatal dysphagia in this model that may differ by sex, which has not yet been confirmed using objective assays. To evaluate feeding/swallowing physiology in this model, we conducted longitudinal phenotyping of 20 Madin KO and 20 wild-type (WT) mice (both sexes) from P21 (DOB = 0) through P42, using our custom videofluoroscopic swallow study (VFSS) protocol and analysis software (JawTrack). Preliminary findings from our Madin KO colony indicated ~40% reduction in Madin KO mice across multiple litters, as expected. VFSS revealed that female KOs had faster lick rate and swallow rate at P21 compared to WT females, which may explain their normalized body weights post-weaning at P21, suggesting a transient hyperphagic phenotype in female KO mice. Male KOs maintained reduced

body weights at P21 and P42, without significant differences in VFSS-related feeding/swallowing outcome measures.
This work highlights sex-specific differences in feeding/swallowing physiology in the Madin KO model. While consistent sex differences are not clearly established in human PWS, clinical studies report hyperphagia variability across both genotype and sex. Building on these findings, our future studies with this model will include additional translational VFSS measures relevant to PWS, such as esophageal transit and swallow-breathing coordination. To capture the earliest emergence of feeding/swallowing deficits, we are currently adapting our VFSS methods to study pre-weaned mice. Importantly, these preliminary results link gene loss to altered maturation of feeding and swallowing behaviors, providing an opportunity to investigate neural mechanisms and therapeutic targets for PWS and related neurodevelopmental disorders.

Disclosures: **S. Shaikh:** A. Employment/Salary (full or part-time); University of Missouri, Foundation for Prader-Willi Research. **K. Osman:** None. **C. Haxton:** None. **F. Muscatelli:** None. **T.E. Lever:** None.

Late-Breaking Poster

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Program #/Poster #: LBP006.23/LBP053

Topic: A.06. Developmental Disorders

Support: Emory Undergraduate Independent Research Grant
NIH R01-NS114253

Title: Characterization of KIF1C disease-associated variants reveals disrupted RBP interactions

Authors: *E. ZHOU[1], A. JANUSZ-KAMINSKA[1], G. J. BASSELL[2];
[1]Department of Cell Biology, Emory University, Atlanta, GA; [2]Emory University School of Medicine, Atlanta, GA

Abstract: Kinesin motor proteins are essential for intracellular transport and function. This process is especially important in neurons due to their polarity and complex morphology. KIF1C is a neuronally enriched kinesin involved in transporting vesicles and RNA granules along microtubules. While KIF1C mutations are genetically linked to neurological disorders such as Hereditary Spastic Paraplegia (HSP), the molecular consequences of patient-derived variants remain poorly characterized. In this study, we expressed five disease-associated KIF1C variants in mouse neuroblastoma (N2A) cells and analyzed their expression using immunoblotting. We found that a truncation mutation at Arginine 731 (Arg731*) led to increased protein levels relative to wild-type KIF1C. Co-immunoprecipitation assays revealed that wild-type KIF1C interacted with several RNA-binding proteins (RBPs) associated with RNA transport granules, including FMRP, Staufen-1, and MBNL1. Interestingly, the C-terminus truncation variant exhibited significantly reduced interaction with these RBPs, which suggests a disruption in their

proper transport. These results suggest that KIF1C mutations may differentially disrupt neuronal RNA transport pathways. These disruptions provide insight into potential mechanisms of RNA transport dysregulation in neurological disease.

Disclosures: E. Zhou: None. **A. Janusz-Kaminska:** None. **G.J. Bassell:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.24/LBP054

Topic: A.06. Developmental Disorders

Support: NICHD 1F30HD117624-01

Title: Prenatal stress induces transcriptomic alterations enriched for neurodevelopmental disorder risk genes in the fetal mouse brain

Authors: *B. VEROSKY[1], T. L. GUR[2];
[1]The Ohio State University, Columbus, OH; [2]Department of Psychiatry & Behavioral Health, The Ohio State University, Columbus, OH

Abstract: Maternal stress during pregnancy is associated with increased risk for neurodevelopmental disorders in the offspring. Using mouse models, we and others have shown that prenatal stress elevates inflammatory gene expression in the fetal brain and leads to long-term social and anxiety-like behavioral deficits. Microglia, the resident innate immune cells of the brain, are critical regulators of brain development and consequently well-positioned to mediate these effects, yet it remains unclear how prenatal stress alters microglial states relative to disruptions in developing neuronal populations. To evaluate how the different microglial and neuronal populations are altered by prenatal stress, pregnant C57BL/6 mice underwent two hours of daily restraint stress from gestational day (GD) 10.5 to 16.5, and whole fetal brains were collected immediately after stress (GD16.5) or one day later (GD17.5) for single-cell RNA sequencing (scRNAseq). Whole brain samples (one male and one female per dam; n=3 dams/group) and microglia-enriched samples (n=3 dams/group, fetal brains pooled from whole litter) were analyzed. Cell proportion analysis revealed no changes in neuronal progenitor, excitatory neuron, inhibitory neuron, or microglial subpopulations. Differentially expressed genes (Bonferroni-corrected p-value < 0.05) in each microglial subpopulation showed a significant enrichment (Fisher's Exact Test with Benjamini-Hochberg correction, $p < 0.05$) for Autism spectrum disorder, schizophrenia, and bipolar disorder risk genes at E16.5. The same analysis on the neuronal cell populations revealed a similar enrichment a day later at E17.5, particularly in apical progenitors, intermediate progenitors, and migrating neurons. The differentially expressed genes in neurons were significantly enriched for gene ontology terms involving axonogenesis, synaptogenesis, and energy regulation across most neuronal cell types. Our results suggest that prenatal stress initiates a microglial response that may shape neuronal

developmental transcriptomic programs enriched for neuropsychiatric risk genes. This sequential disruption offers mechanistic insight into how maternal stress could program vulnerability to psychiatric disorders.

Disclosures: B. Verosky: None. **T.L. Gur:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.25/LBP055

Topic: A.06. Developmental Disorders

Support: R01MH130441
R01MH12012
R43MH133521

Title: GxE in a dish: common genetic variants altering neurodevelopment in response to valproic acid, an environmental risk factor for autism

Authors: *A. B. MARQUEZ GONZALEZ[1], N. MATOBA[2], A. BELTRAN LOPEZ[1], B. LE[3], J. VALONE[4], J. PARK[1], R. SINGLA[1], D. COWEN[1], M. LOGISA[1], M. ELIAS[1], J. PIVEN[5], M. D. SHEN[6], J. GIRAULT[6], J. L. STEIN[7];
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Abstract: Prenatal exposure to Valproic Acid (VPA), a widely used antiepileptic and mood-stabilizing drug, disrupts neurodevelopment and is the strongest known environmental risk factor for autism spectrum disorders (ASD). Yet, not all exposed individuals develop ASD, emphasizing the need to understand how brain-specific responses to VPA are shaped by genetic background.
To model these neurodevelopmental effects, we generated human cortical organoids (hCOs) from 134 genotyped individuals with diverse ASD risk profiles, including participants with longitudinal cognitive assessments and brain MRI data. hCOs were exposed to two clinically relevant concentrations of VPA for two durations, 48 hours to capture acute transcriptional responses and 7 weeks to model sustained prenatal exposure. We combine single-cell RNA seq, brightfield imaging, multielectrode array (MEA)-based electrophysiology, and individuals' clinical profiles to assess the impact of VPA on ASD risk and identify genetic variants more susceptible to this.
Preliminary results revealed the effects of VPA on neuronal development and function. In hCOs

from 4 donors, VPA perturbed 328 genes after short-term exposure and 147 genes after long-term exposure. Notably, SLC17A7 (VGLUT1), which encodes the vesicular glutamate transporter critical for excitatory neurotransmission, was upregulated after 48h but downregulated after 7 weeks. Prolonged VPA exposure consistently reduced spontaneous neuronal firing, aligning with the observed downregulation of SLC17A7.
Additionally, brightfield imaging across all participants revealed a clear dose-dependent reduction in organoid size; however, when examined at the individual level, organoids showed highly variable responses, with some donors exhibiting strong reductions, others only modest effects, and some showing little to no change, suggesting variable VPA susceptibility.
Our approach aims to connect in vitro cellular responses with in vivo neurodevelopmental outcomes, advancing our understanding of the genetic and environmental ASD risk mechanisms, how genetic background modulates vulnerability to environmental insults, how VPA perturbs cortical circuit formation, and identify pathways that may underlie ASD risk. These experiments may yield translationally relevant understanding of gene by environment interactions in neurodevelopment and inform safer clinical decisions regarding VPA use during pregnancy when other treatments are not optimal.

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Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.26/LBP056

Topic: A.06. Developmental Disorders

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Title: Early developmental origins of cortical disorders modeled in human neural stem cells

Authors: X. MATO BLANCO[1], S. KIM[2], A. JOURDON[3], F. M. VACCARINO[4], N. SESTAN[5], C. COLANTUONI[6], P. RAKIC[7], G. SANTPERE[8], ***N. MICALI**[5];
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Abstract: The implications of the early phases of human telencephalic development, involving neural stem cells (NSCs), in the etiology of cortical disorders remain elusive. Here, we explore the expression dynamics of cortical and neuropsychiatric disorder-associated genes in datasets generated from human NSCs across telencephalic fate transitions in vitro and in vivo. We identify risk genes expressed in brain organizers and sequential gene regulatory networks throughout corticogenesis, revealing disease-specific critical phases when NSCs may be more vulnerable to gene dysfunction and converging signaling across multiple diseases. Further, we simulate the impact of risk transcription factor (TF) depletions on neural cell trajectories traversing human corticogenesis and observe a spatiotemporal-dependent effect for each perturbation. Finally, single-cell transcriptomics of autism-affected patient-derived NSCs in vitro reveals recurrent expression alteration of TFs orchestrating brain patterning and NSC lineage commitment. This work opens perspectives to explore human brain dysfunction at early phases of development.

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Late-Breaking Poster

LBP006: A.06. Developmental Disorders

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Topic: A.06. Developmental Disorders

Support: NIH Grant R15 GM140472
Kennesaw State University Funds to Sustain Research Excellence
Kennesaw State University Mentor Protege Program
Kennesaw State University Summer Undergraduate Research Program

Title: Describing the regulatory network of the homeobox gene ceh-27/Nkx2.1 in nervous system development

Authors: *L. KNIGHT[1], E. MOSER[2], M. L. HUDSON[3];
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Abstract: Attention Deficit Hyperactivity Disorder (ADHD) affects approximately 3% of adults and 8% of adolescents worldwide. The ADHD-associated gene *Nkx2.1* codes for the homeodomain transcription factor NKX2-1 and serves a critical role in regulating nervous system formation and function. Heterozygous mutations in *Nkx2.1* have been linked to the development of ADHD and related neurodevelopmental disorders, but the regulatory environment surrounding this gene is largely undescribed. *Nkx2.1* is strongly conserved across

phyla, allowing us to examine it in a simple model organism, such as the nematode *Caenorhabditis elegans*, which has a well characterized genome, fully mapped nervous system, and invariant cell lineage. The *C. elegans* ortholog of *Nkx2.1* is *ceh-27*, a homeobox gene found in many neuron subtypes. Currently, the role of *ceh-27* in neural development remains uncharacterized. By employing genetic approaches and 4D timelapse confocal microscopy, we found that animals with a homozygous *ceh-27* mutation undergo a ventral rupture during mid-embryogenesis, indicating *ceh-27* is required for normal embryogenesis. Using the AIY interneuron terminal fate marker *ttx-3::GFP*, we determined that *ceh-27* null mutants completely lack *ttx-3* expression in the AIY neurons, supporting the idea that *ceh-27* is also required for AIY interneuron fate specification. In addition, expression of *ngn-1*, the *C. elegans* ortholog of human Neurogenin, is lost in the AIY and SMDD neurons in *ceh-27* null mutants, suggesting that *ceh-27* may regulate *ngn-1* expression in this cell lineage. Relative intensity of a *ceh-27* promoter-driven fluorescent reporter revealed that animals with a homozygous *ceh-27* deletion allele display a two-fold increase in *ceh-27* transcriptional activity compared to control animals, indicating *ceh-27* auto-represses its transcriptional activity. Finally, we have used single-cell RNA sequencing data to identify candidate genes under *ceh-27* transcriptional regulation involved in neuron and pharyngeal cell development. Together, these findings illustrate a broad regulatory role of *ceh-27/Nkx2.1* in the developing *C. elegans* nervous system.

Disclosures: L. Knight: None. **E. Moser:** None. **M.L. Hudson:** None.

Late-Breaking Poster

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Kennesaw State University Mentor-Protégé grant
Aditya Birla Carbon Scholars Program

Title: The ADHD associated gene*ceh-27*/Nkx2.1 is required for normal pharyngeal development and pharyngeal motor neuron fate specification in Caenorhabditis elegans

Authors: *E. MOSER[1], L. KNIGHT[2], M. L. HUDSON[3];
[1]Molecular and Cellular Biology, Kennesaw State University, Sandy Springs, GA; [2]Kennesaw State University, Lawrenceville, GA; [3]Molecular and Cellular Biology, Kennesaw State University, Marietta, GA

Abstract: Attention Deficit Hyperactivity Disorder (ADHD) affects roughly 250 million people worldwide. Evidence of a genetic component to ADHD comes from heterozygous mutations in

the transcription factor *Nkx2.1*, which are linked to the development of benign hereditary chorea, which also presents as ADHD in adults. *Nkx2.1* codes for a homeobox transcription factor, which plays a critical role in regulating gene expression by binding to specific DNA sequences and controlling the transcription of target genes. Understanding the gene regulatory environment around *Nkx2.1* is critical for characterizing its downstream effects on neural development and can help identify other genes that contribute to ADHD. *Nkx2.1* is highly conserved across phyla, allowing the use of model organisms to better understand *Nkx2.1* function. The nematode *Caenorhabditis elegans* can be used to study *Nkx2.1* through its orthologous homeobox gene *ceh-27*. *C. elegans* has an invariant cell lineage, well defined nervous system, and fully mapped genome which makes it ideal for characterizing the role of *ceh-27*. We used timelapse video microscopy, along with genetically encoded pharyngeal neuron and muscle specific marker genes, to observe pharyngeal organogenesis and neuronal development of the M4 motor neuron in wildtype and *ceh-27* null mutant embryos. Our data suggests *ceh-27* is required for normal pharyngeal development, suggesting that *ceh-27* has a critical role in pharynx organogenesis. Additionally, *ceh-27* plays a role in M4 motor neuron specification through downregulation of ceh-28: a gene required for the fate specification of the M4 motor neuron. Our findings indicate a significant role in *ceh-27/Nkx2.1* in nervous system and organ development.

Disclosures: E. Moser: None. **L. Knight:** None. **M.L. Hudson:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP006.29/LBP059

Topic: A.06. Developmental Disorders

Title: Genetic and neuroanatomical correlates of intellectual disability in children

Authors: *D. WANG, R. PATEL, T. TSUI, J. B. WILLIAMS;
Department of Psychiatry, Jacobs School of Medicine and Biomedical Sciences, State University of New York at Buffalo, Buffalo, NY

Abstract: Intellectual Disability (ID) involves deficits in intellectual functioning and adaptive behavior, primarily influenced by genetics. This study conducted a genome-wide association study (GWAS) on ~ 11,000 children aged 9-11, identifying no genome-wide significant loci, attributing to ID's complex genetic basis dominated by rare variants burden which is undetectable through common variant analysis. On the other hand, the cross-trait analysis using MiXeR revealed strong genetic correlations between ID and neuropsychiatric disorders such as Attention Deficit/ Hyperactivity Disorder (ADHD), Autism Spectrum Disorder, and Major Depressive Disorder. Structural Magnetic Resonance Imaging (sMRI) analysis identified significant alterations linked to ID in cortical thickness, surface area, and volume, primarily within Pars Opercularis, Lingual, and Rostral Anterior Cingulate regions, with Pars Opercularis showing the highest effect sizes. Regression analysis showed that these structural measures

significantly predict cognitive abilities, especially vocabulary, overall cognition, and working memory, with notable involvement of the Pericalcarine, Middle Temporal, and Pars Opercularis regions. Lastly, by meta-analyzing this GWAS dataset with the DDD and GEL datasets and performing functional annotation and mapping analysis using FUMA, we identified two significantly associated genes. These findings collectively highlight cortical biomarkers that are essential for understanding the cognitive differences seen in ID. Combining genetic and neuroimaging methods provides functional insights into the pathophysiology of ID, offering new mechanistic understanding.

Disclosures: D. Wang: None. **R. Patel:** None. **T. Tsui:** None. **J.B. Williams:** None.

Late-Breaking Poster

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Program #/Poster #: LBP006.30/LBP060

Topic: A.06. Developmental Disorders

Support: DA023999

Title: Piercing nuclear hernias suggest role of endocannabinoid signaling in the cytoskeleton functionality in migrating neurons

Authors: *Y. M. MOROZOV[1], P. RAKIC[2];
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Abstract: A fraction of neurons migrating through developing brain are known to show nuclear envelope (NE) rupture and herniation of the chromatin in cytoplasm. We are reporting powerful streams of chromatin rupturing NE together with the plasma membrane in migrating cerebral neurons in mouse embryos. Such chromatin streams represent a novel form of cell pathology, which we named ‘piercing nuclear hernia’ (PNH). Simultaneous piercing of the nuclear and plasma membranes exposes nucleoplasm and cytoplasm to the intercellular space and may be a reason of accidental cell death that, in contrast to the programed cell death mechanisms, are not detectable using biochemical or immunochemical markers for apoptosis, autophagy, or necrotic type of cell death. We also showed that disfunction of the endocannabinoid system increases the probability of nuclear membrane rupture and chromatin herniation in migrating neurons. Indeed, about 40% of migrating neurons in cannabinoid type 1 receptor knock-out ($CB_1R^{-/-}$) mouse embryos and wild type embryos exposed to two different CB_1R agonists show NE ruptures or/and PNHs. This indicates that deviations from optimal functioning of the endocannabinoid system in under- or over-activity may trigger analogous mechanisms increasing the membranes vulnerability and chromatin herniation. Role of increased intranuclear pressure and cytoskeleton malfunction in the mechanism of NE rupture is documented and commonly accepted. In accord, our results provide evidence that optimal endocannabinoid signaling participates in the

cytoskeleton functionality in migrating neurons. Catastrophic rupture of the nuclear and plasma membranes provokes ultrastructural pathology of mitochondria and other organelles in a fraction of neurons. At the same time, other neurons with PNH showed generally normal ultrastructure that may indicate a mechanism of neuronal cell body reparation. Further study of neuronal cell bodies recovery may discover yet unknown molecular mechanisms and become instrumental for increasing regenerative capacity of neurons after traumatic brain injury, ischemic conditions and during neurodegenerative diseases. On the other hand, demonstrated novel pathology of migrating cells and technique of its upregulation may be in perspective applied for inducing breaks of the plasma membrane and death of metastatic tumor cells.

Disclosures: Y.M. Morozov: None. **P. Rakic:** None.

Late-Breaking Poster

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Topic: A.06. Developmental Disorders

Support: NIH Fellowship F31NS139645
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Title: RNA exosome gates Purkinje maturation in human cerebellar organoids

Authors: *N. A. BARR[1], J. J. GADA[1], R. E. KANG[1], M. J. WADE[1], E. TJOA[1], V. LEE[1], D. J. MORTON[1,2];
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Abstract: Accurate cellular differentiation relies on precise regulation of RNA processing and decay that coordinates transcript maturation and turnover across developmental transitions. RNA surveillance machinery safeguards the transcriptome to ensure these transitions proceed correctly. Although many RNA surveillance systems are ubiquitously expressed, their dysregulation often causes tissue-specific neuropathology. At the center of this control is the RNA exosome, an essential 3'-5' ribonuclease complex implicated in stem cell differentiation. Recessive mutations in *EXOSC3*, a structural subunit gene of the RNA exosome complex, cause Pontocerebellar Hypoplasia Type 1b (PCH1b), a severe neurodevelopmental disorder characterized by degeneration of the pons and cerebellum. The role of RNA surveillance in human cerebellum development, and the specific contribution of *EXOSC3*, has remained unclear. Here, we establish a human *in vitro* model of PCH1b by CRISPR-editing human induced pluripotent stem cells (hiPSCs) to introduce patient-derived *EXOSC3* alleles spanning mild and severe disease, and differentiated into cerebellar organoids in 3D culture. Immunofluorescence and single-cell transcriptomics benchmarked to the human fetal cerebellar atlas show that our organoids recapitulate the expected cell-state landscape and developmental gradients, thus

providing a platform to study RNA exosome-linked cerebellar phenotypes. Our findings reveal that pathogenic EXOSC3 variants do not broadly collapse lineages; instead, the principal effect is selective: the Purkinje trajectory is perturbed. Cells initiate the Purkinje trajectory but fail to consolidate late maturation features, accumulating at intermediate states. These results are consistent with a maturation checkpoint on the Purkinje branch, while other lineages progress comparatively well. The magnitude and direction of these alterations track with allelic severity, consistent with a graded requirement for RNA exosome function during high-flux developmental transitions. Together, these findings define the RNA exosome as a gatekeeper of Purkinje maturation, clarify the cellular basis of PCH1b, and establish a platform to study how RNA quality control shapes brain development and disease.

Disclosures: N.A. Barr: None. **J.J. Gada:** None. **R.E. Kang:** None. **M.J. Wade:** None. **E. Tjoa:** None. **V. Lee:** None. **D.J. Morton:** None.

Late-Breaking Poster

LBP006: A.06. Developmental Disorders

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Program #/Poster #: LBP006.32/LBP062

Topic: A.06. Developmental Disorders

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Title: Mutations in the spliceosomal gene SNW1 disrupt RNA splicing and cause primary microcephaly through impaired neural stem cell proliferation

Authors: *L. JI[1,2], K. LI[2], G. HE[2];
[1]Shanghai Jiao Tong University, Shanghai, China; [2]BioX Institution, Shanghai Jiao Tong University, Shanghai, China

Abstract: The spliceosome is a fundamental cellular machinery required for pre-mRNA splicing, and mutations in its components are increasingly implicated in neurodevelopmental disorders (NDDs), particularly primary microcephaly. Here, we uncover the critical role of SNW domain-containing protein 1 (SNW1), a spliceosomal scaffold protein, in neurodevelopment. Through international data sharing and cohort analyses, we identified nine heterozygous SNW1 mutations in patients presenting with severe microcephaly, intellectual disability, seizures, brain malformations, and facial dysmorphisms. Functional assays demonstrated that these variants impair SNW1 expression, localization, or binding to core spliceosomal partners (PPIL1, PLRG1, PRPF8), resulting in disrupted splicing activity. Patient mutations led to exon skipping and nonsense-mediated decay, consistent with loss-of-function effects. To assess biological consequences, we used *Drosophila melanogaster* and human embryonic stem cell-derived

cerebral organoids. Neural stem cell-specific knockdown of the fly ortholog Bx42 caused reduced brain lobe volume and loss of proliferation, phenotypes rescued by human SNW1, indicating functional conservation. In cerebral organoids, heterozygous SNW1 deletion caused significant size reduction, reduced neural stem cell proliferation, and increased apoptosis without affecting neuronal survival. RNA sequencing revealed widespread transcriptional alterations and splicing defects, with exon skipping as the predominant event. Notably, critical neurodevelopmental genes including *CENPE*, *MEF2C*, and *NRXN2* exhibited aberrant exon skipping and altered expression. Together, our findings establish SNW1 as a novel spliceosomal gene underlying microcephaly-associated NDDs. Mechanistically, SNW1 dysfunction compromises spliceosomal integrity, leading to defective neural progenitor proliferation and brain development. These results highlight the essential role of spliceosome fidelity in human neurodevelopment and expand the spectrum of spliceosomal disorders.

Disclosures: L. Ji: None. **K. Li:** None. **G. He:** None.

Late-Breaking Poster

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Topic: A.06. Developmental Disorders

Support: GR089263

Title: Dissecting Craniofacial Development: Loss of DCHS1 Intracellular Domain Recapitulates Van Maldergem Syndrome in Mice

Authors: *K. BYERLY[1], C. WOLFE[1], S. FISHER[1], H. PARRIS[1], A. ALSTON[1], M. BREI[1], H. DONG[2], T. PETRUCCI[1], S. PATEL[1], R. NORRIS[1];
[1]Medical University of South Carolina, Charleston, SC; [2]Clemson University, Clemson, SC

Abstract: Van Maldergem syndrome (VMS) is a rare autosomal recessive disorder characterized by craniofacial dysmorphisms and neuronal heterotopia. Mutations in *DCHS1* disrupt *DCHS1-FAT4* signaling, a key regulator of planar cell polarity and Hippo pathway activity during neural development. While global *Dchs1* knockout mice recapitulate VMS phenotypes, the required signaling domain of DCHS1 has not been explored. To address this, we generated a novel *Dchs1* mutant murine model (*Dchs1-dICD-V5*) lacking the ICD via CRISPR-Cas9 editing and compared it with a conventional *Dchs1* knockout. Constructed using Cre-LoxP mouse genetics. Similar gross skeletal abnormalities were observed in both murine models: corkscrew tail, rib malformations, abnormal snout morphology, etc. This lead to our central hypothesis that mice with homozygous mutations for *Dchs1-dICD-V5*$^{-/-}$ will exhibit phenotypes similar to the global knockout *Dchs1*$^{-/-}$ mice and human patients with Van Maldergem Syndrome. Homozygous affected mice from both models, along with wild-type littermates in a minimum n = 3, were analyzed for gross craniofacial abnormalities using micro-computed tomography (micro-CT) as

well as standard histological stains (hematoxylin & eosin, alizarin red, alcian blue, etc.) and changes in subcellular pathways were analyzed via western analyses and immunohistochemistry. All studies were analyzed by scientists blinded to genotype. Strikingly, homozygous mutant mice lacking the DCHS1 intracellular domain exhibited hallmark VMS phenotypes, including craniofacial dysmorphisms and aberrant Hippo pathway signaling and increased proliferation of neurons. These findings demonstrate that the intracellular domain of DCHS1, previously uncharacterized in the context of VMS, is indispensable for proper DCHS1-FAT4 signaling and craniofacial development in mammals. Our novel model provides a valuable tool for dissecting the molecular mechanisms underlying VMS and highlights the functional significance of the DCHS1 intracellular domain in mammalian organogenesis.

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Late-Breaking Poster

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Topic: A.06. Developmental Disorders

Support: CIRM Grant DISC4-16295

Title: Single Cell Functional Genomics of Autism Risk Genes :A Calcium Imaging and scRNA-seq Approach

Authors: *S. FU[1], C. WHITE[2], C. T. BAEZ BECERRA[3], O. F. VILA[4], A. NATARAJAN[4], M. BEHRENS[5], X. JIN[2], J. R. ECKER[6];
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Abstract: Neuronal functional alterations and gene expression dysregulation are implicated in the pathophysiology of autism spectrum disorder (ASD). However, profiling both aspects in the same neuron at scale has been technically challenging. To address this, we are developing a high-throughput CRISPR-based functional genomics platform combining calcium imaging and single-cell RNA sequencing (scRNA-seq) using the Cellanome's R3200 system - a multi-modal cell biology platform. In our pilot study, we loaded thousands of primary mouse neurons into Cellanome flow cells alongside lentiviruses encoding guide RNAs (gRNAs) targeting NeuN, Dnmt3a (two independent gRNAs), or safe-targeting controls. The lentiviral constructs co-express mKate2, enabling identification of infected neurons. Calcium imaging was performed off-instrument at DIV5 using the CQ3000 high-content imager. We identified that primary neurons infected with gRNA targeting Dnmt3a exhibited decreased spontaneous activity. We then selectively enclosed individual mKate2+ neurons in permeable hydrogel compartments,

called CellCage™ enclosures (CCEs) in the Cellanome instrument. After cells were enclosed, cultured within CCEs, and longitudinally imaged, cells were lysed for cDNA synthesis, and RNA-seq library preparation. In parallel, we are establishing a human iPSC-derived neuron model carrying the ASD-associated DNMT3A p.Arg736His mutation. These neurons exhibit increased soma size compared to isogenic controls. We aim to apply the same calcium imaging and scRNA-seq workflow to this model to link functional phenotypes with transcriptomic changes. Together, we aim to perform large-scale perturbation of ~72 high-confidence ASD risk genes, providing integrated insights into how specific gene disruptions impact both neuronal function and gene expression, with the long-term goal of elucidating ASD disease mechanisms.

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Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP007.01/LBP065

Topic: A.07. Development of Neural Systems

Title: Adolescent exercise alters dopaminergic axon morphology in dorsal striatum of adult mice

Authors: *D. SAHIN[1], R. FELSHER[2], I. LOTIA[3], C. J. AOKI[2];
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Abstract: Exercise (EX) activates dorsal striatum's dopaminergic system, yet whether EX during adolescence has long-term impact on the dopaminergic function remains unknown. We examined adolescent EX's effects on morphological features of tyrosine hydroxylase-immuno-labeled dopaminergic axons (LA) in dorsal striatum by electron microscopy (EM). Four groups of mice were analyzed: CONCON (no fixed or freely movable wheel during adolescence or adulthood), CONTOY (fixed wheel “toy” in adulthood, no wheel in adolescence), CONEX (no wheel in adolescence, wheel access in adulthood), and EXEX (wheel since adolescence). ImageJ was used to measure LA’s perimeter, area, circularity, density in neuropil, and density of mitochondria in LA (MITO). Perimeter shows the vesicle fusion potential. Circularity shows LA’s perimeter/LA’s area, with 1.0 representing minimal vesicle fusion potential. MITO shows the energy production potential. One-way ANOVA showed that CONCON and CONTOY lacked differences in these measurements. Thus, CONCON and CONTOY were combined, then compared to CONEX and EXEX (now, comparisons across 3 groups). Density did not differ across the groups. Circularity of EXEX was significantly higher than CONCON/TOY and CONEX’s. Perimeter of all three groups were significantly different from one another, with CONCON/TOY being the highest, the EXEX being the lowest and CONEX’s being intermediate. LA areas were the highest for CONCON/TOY and lowest for EXEX. MITO of CONCON/TOY was higher than EXEX’s. These results suggest that adolescent EX increases the

efficiency of energy production (indicated by the decresed MITO for the EXEX group) and consumption (indicated by the lowered MITO for the EXEX group), vesicle production (indicated by the decreased LA area for the EXEX group) and transport for vesicular release (indicated by the decrease of Perimeter, Circularity for the EXEX group). The lack of differences between CONCON and CONTOY in all of these measurements indicate that novelty of the "toy" did not contribute towards the morphological changes in LA. Possibly, the dorsal striatum adapts to increased physical activity and, thus, energy demand during adolescence but not during adulthood, leading to the observed ultrastructural changes in LA. If so, then CONEX's LA may be at an efficiency level that is in between those of the other two. EXEX could be more efficient by storing greater amounts of dopamine in each vesicle, thereby requiring less vesicular fusions events, compared to the CONEX and CONCON/TOY.

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Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

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Program #/Poster #: LBP007.02/LBP066

Topic: A.07. Development of Neural Systems

Title: Transthyretin as a Novel Marker for Retinal Pigment Epithelium Induction in Human Pluripotent Stem Cells

Authors: *L. HAN, G. FAN, Y. HU, W. LIU, G. CHEN;
Faculty of Health Sciences, University of Macau, Macau, China

Abstract: The retinal pigment epithelium (RPE) provides essential support for photoreceptor functions in retina. Dysfunction of the RPE is a hallmark of degenerative conditions such as age-related macular degeneration (AMD), the leading cause of vision loss among older adults. It is a promising approach to treat AMD with RPE induced from human pluripotent stem cells (hPSC). In order to improve RPE induction methods, we try to identify RPE-specific genes to guide hPSC differentiation. We identified a set of genes with relatively higher expression levels in RPE cells using the whole mouse expression dataset MOE430 from the BioGPS database. Besides the well-known RPE-specific genes, our RPE-specific set also includes transthyretin (*TTR*), a gene involved in the transport of retinol-binding protein and thyroxine. Because of TTR's roles in Alzheimer's and heart diseases, we further examined its expression using scRNA-seq datasets from the eye and various other tissues. scRNA-seq of mouse organogenesis further showed that TTR displayed tissue-specific expression during the early stages of embryogenesis. We then examined TTR in human embryonic stem cells (hESCs), and observed basal level expression of TTR in undifferentiated cells. We further examined pathways that could potentially affect TTR expression in different lineages during differentiation. Our findings show that TTR could serve as a novel marker to guide lineage-specific induction, and its role remains to be explored in differentiation as well as in the production of RPE for disease treatment.

Disclosures: L. Han: None. **G. fan:** None. **Y. Hu:** None. **W. Liu:** None. **G. Chen:** None.

Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

Location: SDCC Hall B

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Program #/Poster #: LBP007.03/LBP067

Topic: A.07. Development of Neural Systems

Support: NSF Crest HRD2112556
NIH R25 2R25GM107754-06A1

Title: Characterization of BTB/POZ-containing protein in dopaminergic neurons to understand its role in neuronal function in C. elegans

Authors: *A. GONZALEZ, W. CHANDLER, B. NELMS;
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Abstract: The dopaminergic system modulates cognitive and motor functions in the central nervous system. In humans, problems with dopamine production and signaling are linked to serious physiological and psychiatric disorders, such as but not limited to Parkinson's, Alzheimer's, schizophrenia, and major depressive disorder. In recent decades, the nematode Caenorhabditis elegans (*C. elegans*) has become a valuable model organism for studying the genetic and molecular mechanisms of the dopaminergic system, with conserved functional orthologs in mammals. RNA-seq analysis of the *C. elegans* dopaminergic system has uncovered numerous new genes with unknown roles in neuronal development, synaptic maintenance, and signal transduction. Among these, F59F3.6 shows high selective expression in dopaminergic neurons, although its function remains unclear. Structural analysis reveals that the gene product of F59F3.6 shares the *BTB/POZ* domain with its human orthologs, the potassium channel tetramerization domain-containing (KCTD) proteins. This conserved domain is linked to transcription regulation and protein-protein interactions that influence receptor ubiquitination and synaptic plasticity, indicating a possible functional role for F59F3.6 in neuronal signaling. To explore its function, we created a F59F3.6 deletion to assess dopamine-dependent motor behaviors and neurological defects. Understanding the role of F59F3.6 enhances our knowledge of both conserved and species-specific mechanisms of synaptic plasticity, laying the groundwork for a better understanding of synaptic dysfunction in neurodegenerative and psychiatric disorders.

Disclosures: A. Gonzalez: None. **W. Chandler:** None. **B. Nelms:** None.

Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP007.04/LBP068

Topic: A.07. Development of Neural Systems

Title: Dynamic changes in choroid plexus and ventricular volumes during pregnancy: evidence from longitudinal MRI

Authors: *S. CANGE[1], O. PRUDEN[1], D. MERCADO[1], A. MIRMAJLESI[2,3], J. STEARNS[2,3], B. SZEKELY[4,3], R. J. RUSHMORE III[5,6], C. HELLER[7,8], H. ARCINIEGA[9,3];
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Abstract: Pregnancy is accompanied by profound physiological, hormonal, and neuroanatomical changes, yet the maternal brain remains understudied in neuroscience. Emerging evidence suggests that cerebrospinal fluid (CSF) dynamics and immune regulation play a key role in supporting these adaptations. To explore this, we examined fluid-regulating structures in the maternal brain, focusing on the choroid plexus (ChP) and ventricles. These structures are central to CSF production and brain waste clearance. Variations in their volume may reflect pregnancy-related immune responses and physiological changes, offering new insight into maternal neuroanatomy.We analyzed open-access longitudinal MRI data from a 38-year-old primiparous female who conceived via in vitro fertilization and underwent 26 scans spanning the pre-gestational period through postpartum. To quantify volumetric changes, the ChP was manually segmented by three independent raters following a standardized protocol. Ventricular structures, including the lateral, third, and fourth ventricles, were also segmented by three raters, using the Harvard-Oxford atlas as an initial guide and refined with semi-automated correction to ensure anatomical accuracy. Inter-rater reliability was high, with Dice coefficients >0.85 across raters, confirming segmentation accuracy and consistency. Using a generalized additive model, we found that lateral and third ventricle volumes increased progressively throughout gestation and returned to baseline postpartum. To assess relationships with the ChP, we performed Spearman correlations between ChP volume and ventricular volumes. In all cases, ventricular volumes were significantly positively associated with ChP volume, indicating coordinated structural changes in fluid-regulating brain regions across pregnancy.This longitudinal MRI case study demonstrates that the ChP and ventricular system undergo coordinated volumetric changes across pregnancy, with lateral and third ventricles enlarging during gestation and returning to

baseline postpartum. The strong positive associations between ventricular and ChP volumes suggest dynamic adaptations in fluid-regulating brain structures that may support maternal physiology. These findings provide novel in vivo evidence of pregnancy-related neuroanatomical plasticity and establish a foundation for future studies investigating brain health during pregnancy and postpartum.

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Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP007.05/LBP069

Topic: A.07. Development of Neural Systems

Support: Funded by Société des Produits Nestlé SA

Title: Neural flexibility of visual network is associated with better cognitive flexibility and executive functioning: preliminary findings from a Chinese cohort

Authors: *J. HAUSER[1], Y. LU[2], Y. GUI[3], X. MA[3], G. WANG[3], M. HARTWEG[4], T. SAMUEL[5], D. BRKIC[6], F. JIANG[7];
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Abstract: Brain and cognitive flexibility are predictive of intelligence, especially early in development. Previous studies have shown how magnetic ressonance-derived neural flexibility measured in infancy is associated with later cognitive skills and executive functioning (EF), but very little has been done in typically developing older children (e.g., toddlers and school age). Here, we report preliminary results of anongoing first-ever neuroimaging observational study in Chinese toddlers. We applied Yin et al's (2020) method to measure fMRI-derived neural flexibility, at the whole brain level and in seven canonical resting state networks (Frontoparietal, Medial frontal, Motor, Subcortical, Visual I, Visual II, and Visual association). Toddlers completed the entire fMRI scanning in a comfortable and safe natural (non-sedated) sleep state. We then used Dimensional Change Card Sorting task (DCCS) to assess cognitive flexibility, Behavior Rating Inventory of Executive Function (BRIEF-P) to measure EF, and Wechsler

Preschool and Primary Scale of Intelligence (WPPSI) for cognitive skills. The preliminary results (N=11, mean age=2.88 y.o.) indicate neural flexibility of Visual I (VI) network is correlated with better DCCS performance, or lower cost of switching ($\rho = -0.82$, $p < 0.01$). Visual network I neural flexibility was also associated with better EFs, or Global EF Index ($\rho = 0.47$, $p < 0.03$). These promising yet preliminary results, show how neural flexibility of visual areas is significantly associated with better cognitive flexibility and executive functioning in toddlers. This outcome complements and extends previous research that showed how early visual network's neural flexibility at 3 m.o. negatively correlated with cognitive ability assessed later on, at 5-6 y.o. Overall, current findings suggest that neural flexibility in toddlerhood presents a much different pattern when compared to early infancy and is highly correlated with the emerging neurodevelopmental skills, such as cognitive flexibility and executive functions. Therefore, it is important to continue the mapping of maturation trajectories across higher and lower functional domains in the brain, to better understand how changes in neural flexibility are linked to cognitive flexibility and executive functioning in pre-school age and beyond.

Disclosures: J. Hauser: A. Employment/Salary (full or part-time); Employee of Société des Produits Nestlé SA. **Y. Lu:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research funded by Société des Produits Nestlé SA. **Y. Gui:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research funded by Société des Produits Nestlé SA. **X. Ma:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research funded by Société des Produits Nestlé SA. **G. Wang:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research funded by Société des Produits Nestlé SA. **M. Hartweg:** A. Employment/Salary (full or part-time); Employee of Société des Produits Nestlé SA. **T. Samuel:** A. Employment/Salary (full or part-time); Employee of Société des Produits Nestlé SA. **D. Brkic:** A. Employment/Salary (full or part-time); Employee of Société des Produits Nestlé SA. **F. Jiang:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research funded by Société des Produits Nestlé SA.

Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP007.06/LBP070

Topic: A.07. Development of Neural Systems

Support: RO1 NS088479

Title: A novel role for NMDA receptors in neural crest development

Authors: *C. APREA[1,2], A. J. NAPOLI[2,1], S. HAFEEZ[3,1], K. MORGAN[1], S. LAKHANI[1], S. CADOLINO[1], J. KWAK[1], B. MARTIN[4,1], H. SIROTKIN[2,1], L. P. WOLLMUTH[2,1];
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Abstract: The neural crest (NC) is a vertebrate-specific developmental tissue composed of transient, multipotent stem cells that migrate extensively and differentiate into over thirty neural and non-neural derivatives including divisions of the autonomic nervous system (sympathetic, parasympathetic, enteric), pigmentation, craniofacial cartilage, smooth muscle, adipose tissue, somatosensory neurons, adrenal medulla, parts of the heart, and more. NMDA receptors (NMDARs) are glutamate-gated ion channels best known for mediating excitatory synaptic transmission but also contribute to early brain development in non-synaptic contexts. Given that NC and the brain develop from a common stem cell pool and NMDARs are involved in early brain development, we considered whether NMDARs might also be involved in NC development. To study the role of NMDARs in NC development, we capitalized on a mutant zebrafish line lacking all NMDAR-mediated signaling (*grin1* $^{-/-}$). In zebrafish, neural crest stem cell (NCSC) fate is influenced by position along the rostro-caudal axis, subdivided into cranial, vagal, and trunk lineages. We therefore assayed each lineage to assess any role of NMDARs. Interestingly, we found using behavioral and histological approaches that *grin1* $^{-/-}$ fish display hyperpigmentation (cranial & trunk), craniofacial abnormalities (cranial), enteric glia hyperproliferation (vagal), elevated resting heart rate (vagal), and other dysregulated NC lineages, all suggesting a hyperproliferative phenotype. This broad effect suggests an early role of NMDARs in NC development. To test this we used MK-801 a non-competitive NMDAR antagonist, to temporally regulate NMDAR activity and identified an early requirement for NMDARs, prior to 48 hours post fertilization. These findings suggest that NMDARs regulate NCSC proliferation. To validate this, we used immunohistochemistry to label NCSCs (SOX10) and proliferation (PCNA) and observed a marked increase in proliferating NCSCs. Furthermore, using a CDK biosensor crossed to a SOX10 reporter line, we found that MK-801 treatment increased the proportion of cycling NCSCs, indicating defective cell cycle regulation. We hypothesized this dysregulation results from insufficient activation of the p53/p21 pathway, which promotes cell cycle exit. Consistent with this idea, treatment with Trichostatin A, a p21 activator, rescued the hyperproliferation phenotype across multiple NC-derived tissues in *grin1* $^{-/-}$ fish. Collectively, our findings demonstrate that NMDAR signaling regulates NC cell cycle, and thereby NC proliferation in early development and is essential for proper development of diverse NC lineages.

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Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP007.07/LBP071

Topic: A.07. Development of Neural Systems

Title: Prenatal stress induces transient developmental alterations in distinct GABAergic populations and leads to long-lasting behavioral abnormalities

Authors: *K. SHOSHANI-HAYE[1], G. FRIEDLANDER[1], S. ALMEIDA-CORREA[2], Y. SHEMESH[3], A. CHEN[1];
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Abstract: Prenatal stress (PNS) is a well-established risk factor for psychiatric disorders, yet the underlying neurobiological mechanisms remain unclear. Here, we demonstrate that PNS induces long-term behavioral abnormalities, including increased anxiety- and depressive-like behaviors specifically in adult male mice. To investigate potential neurodevelopmental disruptions, we analyzed the medial prefrontal cortex (mPFC) at key postnatal stages. RNA sequencing at postnatal day 1 (P1) revealed significant transcriptional changes, particularly in genes associated with neuronal migration and differentiation, with a diminished effect by P14. Histological analysis identified a transient imbalance in inhibitory neuron subpopulations, PNS decreased the density of early-born neurons derived from the medial ganglionic eminence (MGE) while increasing late-born neurons derived from the caudal ganglionic eminence (CGE) at P1. EdU labeling confirmed that these shifts were time- and subtype- specific, affecting inhibitory neuron proliferation at distinct embryonic stages. By P15, these neuroanatomical alterations largely resolved, yet behavioral abnormalities persisted into adulthood. Our findings suggest that PNS disrupts inhibitory neuron development during a critical early window, leading to lasting behavioral consequences despite the transient nature of anatomical changes. This study highlights the selective vulnerability of inhibitory neuron subtypes to early-life stress and provides insight into potential mechanisms underlying stress- related psychiatric disorders.

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Late-Breaking Poster

LBP007: A.07. Development of Neural Systems

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Program #/Poster #: LBP007.08/LBP072

Topic: A.07. Development of Neural Systems

Support: R01MH134004
R01NS120954
5P01HD033113-18

Title: A developmental balance between hemispheric specialization and interhemispheric connectivity in the human infant brain

Authors: S. VENKADESH[1], I. BA GARI[2], N. JAHANSHAD[3], F.-C. YEH[4], ***J. R. KORENBERG**[5];
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Abstract: Hemispheric specialization is a hallmark of human brain organization, but the developmental origins of lateralization remain poorly understood. Foundational models propose that hemispheric specialization reflects an adaptive interplay with interhemispheric connectivity, whereby specialized regions minimize reliance on callosal transfer to mitigate conduction delays and optimize capacity[1,2]. Prior MRI studies of callosal morphology and volume asymmetries hinted at such trade-offs[3,4], yet direct evidence for how lateralization and callosal connectivity interact in early human development has been lacking.We leveraged the Baby Connectome Project dataset[5] (n≈80, ages 0-60 months) to quantify hemispheric organization at the tract-to-region[6] level. For each infant, we computed the proportion of gray matter volume in each cortical parcel[7] overlapped by tracts from 12 major association pathways and by corpus callosum (CC) projections. Lateralization indices (Li) were defined from interhemispheric asymmetries in association pathway overlaps. This tract-to-region framework yields a connectivity-based measure of asymmetry that is more mechanistically grounded than volumetric indices. Theil-Sen robust regression[8] estimated the slope of the |Li|-CC relationship across cortical regions within each infant, yielding an individual marker of hemispheric balance. Nearly all infants exhibited negative slopes (Fig. 1A-B), indicating that more lateralized regions had weaker callosal overlap. Importantly, these slopes became more negative with age (Fig.1C), consistent with a developmental consolidation of balance between specialization and interhemispheric dependence. This provides the first infant-level evidence for a dynamic balance mechanism underlying the emergence of lateralized function. These findings bridge longstanding theory with developmental data, highlight tract-to-region mapping as a marker of hemispheric organization, and suggest new avenues for probing altered asymmetry in genetic and clinical populations.

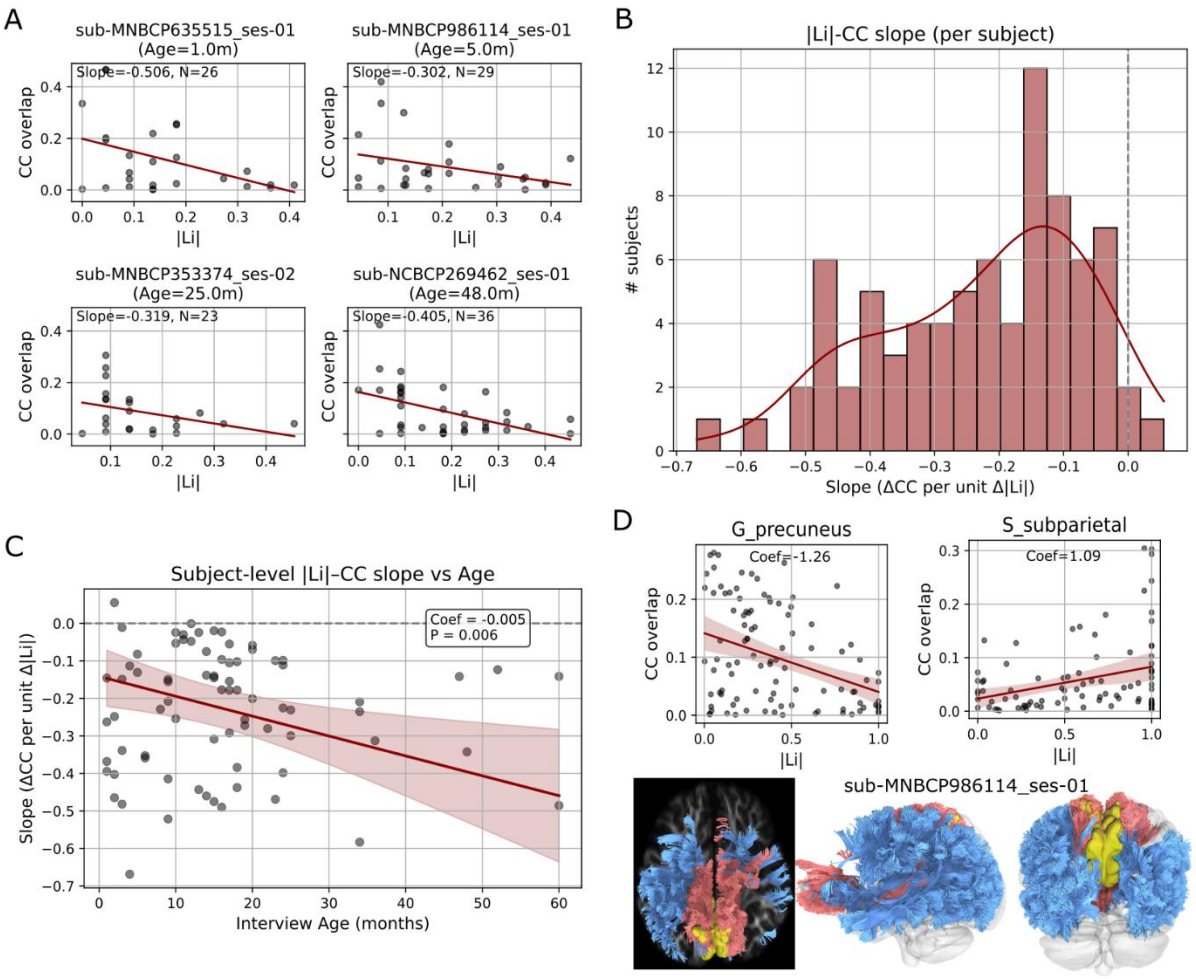

Figure 1. Analyses of hemispheric balance. **(A)** Example infants show consistently negative slopes of |LI| versus callosal overlap across cortical regions. **(B)** Histogram of subject -level slopes reveals a robust negative skew across the cohort. **(C)** Slopes become more negative with age, indicating a developmental strengthening of hemispheric balance. **(D)** Scatterplots (age-corrected) show opposite LI–CC relationships for adjacent precuneus (negative) and subparietal (positive), with tractography visualizations illustrating association (blue) and callosal (red) pathways.

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Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.01/LBP073

Topic: A.08. Adolescent Development

Support: Hope College Neuroscience Program

Title: Early postnatal homocysteic acid exposure leads to sex-dependent changes in rat pup ultrasonic vocalizations in an animal model of bipolar disorder

Authors: *A. FIGURSKI, L. A. CHASE;
Hope College, Holland, MI

Abstract: Many neuropsychiatric disorders, such as Bipolar Disorder (BPD), are developmental in nature, with behavioral phenotypes presenting at the onset of puberty. Previous work within the Chase lab demonstrated that rat pups injected with homocysteic acid (HCA) display a mixed behavior state, exhibiting manic and depressive behaviors that do not develop until after puberty. Interestingly, however, HCA-treated females tend to exhibit a more depressive phenotype while males tend to exhibit a more manic phenotype. Furthermore, these behaviors can be reversed by treatment with lithium and involve changes in gene expression in the prefrontal cortex that are also improperly regulated in BD, further validating this model's relevance to BPD. This study aims to identify prepubescent developmental changes in HCA-exposed pups through ultrasonic vocalizations (USVs). Commonly used, USVs assess affective and communicative behaviors before behavioral phenotypes are detectable. Sprague Dawley rat pups received either saline or HCA (0.8 mmol HCA/kg rat) i.p. injections daily from postnatal day 3 (P3) to P19. USVs were recorded on P6 and P12 during a three-minute maternal separation. Recordings were analyzed using Avisoft Bioacoustic software, and a two-way ANOVA revealed sex/HCA interaction effects within the P12 pups, indicating neurodevelopmental changes do occur prior to puberty despite the fact that few behavioral changes have been observed at this time point in this animal model. Specifically, HCA treatment diminishes the number of calls made by female pups and increases the number of calls made by male pups relative to their respective controls, especially during the first minute of separation. In addition, HCA-treated females call for shorter durations while HCA-treated males call for a longer duration compared to their relative controls. Finally, HCA appears to reduce the number of calls at a frequency greater than 48,000 Hz for females and increase the number for males in addition to altering the types of calls made by isolated rat pups. Given that children who are eventually diagnosed with bipolar disorder often exhibit communication differences relative to peers, these findings provide additional face validity for this animal model for BPD enhance the model's utility for understanding early developmental changes associated with the disorder.

Disclosures: A. Figurski: None. **L.A. Chase:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.02/LBP074

Topic: A.08. Adolescent Development

Support: data collection for this project was funded in part through the NIH ECHO program, UH3 ODD022313
Preclinical data collection was funded by Société des Produits Nestlé SA

Title: Nutrition, brain, cognition and learning in childhood and adolescence: identification of key nutrients using clinical and preclinical data modelling

Authors: *D. BRKIC[1], E. PISA[2], E. GEBARA[1], S. C. DEONI[3], S. MACRI[2], J. HAUSER[4]; [1]Nestlé Institute of Health Sciences, Lausanne, Switzerland; [2]Centre for Behavioural Sciences and Mental Health,, Istituto Superiore di Sanità, Rome, Italy; [3]Advanced Baby Imaging Lab, Rhode Island Hospital, Providence, RI; [4]Nestec - Nestlé Research Center, Lausanne, Switzerland

Abstract: Healthy nutrition supports optimal brain and cognitive development in early life (<5 years old). However, how nutrition contributes to optimal brain functioning and development, cognition and learning in school age is still elusive. Here in a data-driven approach, we first used the RESONANCE study cohort to establish, via mediation analysis, the most important nutrients coming from regular diet contributing to myelination, structural connectivity (DTI), cognitive and learning skills in typically developing school age children (N=282, mean age 7.5). Then, via predicting modelling, we identified the most significant nutrients for predicting increase in myelination and structural connectivity. Second, we tested this nutritional blend in a preclinical developmental model of cognition and learning. Specifically to investigate the role and mechanisms of action of the most relevant brain-related nutrients (i.e., lipids) in cognition and learning, we exposed male and female CD1 mice to a control diet, enriched diet (ED) composed of the mix of nutrients resulting from mediation analysis, and to an enriched diet (ED+) with the most significant brain-related lipids. We focused on postnatal days (PND) 28-56, a time corresponding to puberty and adolescence (n=8-10 per sex per group). Adolescent (PND 42-56) mice were then tested for executive functions via the attentional set shifting task (ASST), and for spatial learning via the Barnes maze task (BMT), including reversal learning in the days following acquisition. Results show that both enriched diets resulted in improved cognitive flexibility, whereby ED and ED+ mice required fewer trials ($F_{2,44}$=3.574, $p<0.05$) and committed fewer errors ($F_{2,44}$=3.491, $p<0.05$) than controls to acquire the criterion in extradimensional shift stage of the ASST ($p<0.05$ in post hoc tests). Additionally, while all groups learned and retained the escape-box location in the BMT at similar rates, only ED+ mice exhibited significantly faster reversal learning ($p<0.05$). Furthermore, ED+ group reached the relocated escape box with reduced latency on reversal day 2 ($p<0.05$), whereas ED group did so on day 3 ($p<0.05$) and control mice showed no reversal learning. This is the first study to use a data-driven approach to identify nutritional impact on brain, cognition, and learning in typically developing school-age children. Combined with the use of age-matched developmental preclinical model, it also unravels the underlying causative effects on cognition and learning. Together, these findings highlight how a combination of specific nutrients promotes optimal brain maturation and connectivity, cognition and learning in development.

Disclosures: D. Brkic: A. Employment/Salary (full or part-time); Société des Produits Nestlé SA, Société des Produits Nestlé SA. **E. Pisa:** None. **E. Gebara:** A. Employment/Salary (full or part-time); ciété des Produits Nestlé SA. **S.C. Deoni:** None. **S. Macri:** None. **J. Hauser:** A. Employment/Salary (full or part-time); Société des Produits Nestlé SA.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.03/LBP075

Topic: A.08. Adolescent Development

Title: Object Orientability and Proximal Spatial Cues Influence Object Location Memory Across Rodent Development

Authors: *E. G. WILLIAMSON[1,2,3], L. N. SOLANO[4], C. A. LAMBERT[4], A. G. DEFINA[3], A. SCHECHTMAN-TAYLOR[3], P. A. ROBINSON-DRUMMER[4,3];
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Abstract: Memory for objects' location and identity are essential to learning and survival. These processes rely on the maturation of recognition memory networks. Rodents prefer to explore novel objects (NOR) or familiar objects in novel locations (NOL). Young rats likely depend on distinct object- and environment-based visual cues to support their spatial navigation and learning before their cortical spatial mapping systems mature. Our prior research found that juveniles (PD21±1) and adults (PD62±3) show stronger spatial recognition memory when orientable (Ori, ones with features that denote a specific orientation in space), rather than non-orientable (NonOri) objects were used. We extended these findings by exploring how object- and environment-based visual cues influence male and female Long-Evans rats' exploratory behaviors (including rearing and mounting) and examining neural data from adult NOL testing. We also analyzed how proximal cues' distance from objects during training may influence spatial learning. We found that juveniles prefer to explore Ori objects more than NonOri, a less pronounced preference in adults. During short-term (5min) spatial recognition memory testing, juveniles showed increased rearing when presented with NonOri objects but increased mounting with Ori, while adults showed consistent behavior regardless of object type. Despite these exploratory differences, both adults and juveniles showed stronger spatial discrimination (i.e. location memory) for Ori than NonOri objects. Initial analyses of cFos activation in adult brains suggest that the PRH and dHPC are more reactive to learning with NonOri objects than Ori objects, regardless of task type (NOR v NOL). Trending effects suggest that the pRSC may also differentially respond to object orientation, indicating a potential circuit interaction that supports recognition of specific object features. When proximal cue distance from the objects was manipulated, location discrimination was not evident at either age, and the effect of object orientability on performance was inconsistent. Additional examination of proximal cue effects is required to differentiate performance decrements from actual impairments in learning. Together, these data demonstrate a clear developmental shift in exploratory behavior during recognition memory testing that may reflect ongoing maturation of learning and memory circuits. Additional analyses of cortical (e.g. mPFC) contributions to learning, especially in juvenility and

adolescence, would highlight the neurobiological underpinnings of the ontogeny and function of object and spatial recognition and short-term memory processes.

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Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

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Program #/Poster #: LBP008.04/LBP076

Topic: A.08. Adolescent Development

Support: NSERC RGPIN-2023-04656

Title: Learning to learn from others: developmental onset of social selectivity in food preference learning in juvenile rats

Authors: *S. N. SMITH, M. R. HOLAHAN;
Dept Neuroscience, Carleton University, Ottawa, ON, Canada

Abstract: Social-olfactory learning is one of the earliest cognitive abilities to develop, supported by olfactory circuits which are functional at birth. Social transmission of food preference (STFP) is a well-established procedure for assessing social learning. A shift from generalized to selective learning has been shown to occur during preadolescence. This period coincides with the maturation of connectivity between olfactory regions and later-developing hippocampal-amygdala circuits. The identification of social selectivity in STFP provides insight to sensitive periods of social neurodevelopment. In the current study, male and female Sprague-Dawley rat pups underwent STFP testing on post-natal day (p)21, 24, 28, or 35. Rats were assigned to either a 30-minute social (demonstrator rat fed cumin diet) or non-social (cumin diet-dusted surrogate) interaction. Access to both a cumin- (familiar) and thyme-flavored (novel) diet was then provided for 1 hour to evaluate diet preference. Effect of age, sex, and social condition on percentage of cumin consumed relative to total intake was assessed. No sex differences were observed within any age group. Differences in diet preference between social and non-social conditions became apparent at p28, where rats in the social condition consumed significantly more cumin compared to those in the non-social condition, indicating salience of social over non-social learning cues. The findings suggest that juvenile rats begin to exhibit selectivity for social learning around p28, coinciding with a critical period of neurodevelopmental refinement in olfactory and social memory circuits. This work contributes to understanding of typical developmental trajectories in early social learning.

Disclosures: S.N. Smith: None. **M.R. Holahan:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.05/LBP077

Topic: A.08. Adolescent Development

Title: The Effects of Early Life Stress on Dopamine Release and Locomotion

Authors: *E. MAKOWICZ[1], A. R. HUROWITZ[2], E. V. MOSHAROV[1], D. L. SULZER[1]; [1]Columbia University, New York, NY; [2]Division of Systems Neuroscience, New York State Psychiatric Institute, New York, NY

Abstract: Early life stress (ELS) markedly elevates lifetime risk for psychiatric disorders, and converging evidence implicates dysregulated dopaminergic signaling in this vulnerability. Here, we combined longitudinal locomotor monitoring, high-performance liquid chromatography (HPLC), and fast-scan cyclic voltammetry (FSCV) to probe how ELS reshapes dopamine system function during early adolescence (P21) and whether these changes persist into adulthood (P75-100). Our data reveal that ELS exposed C57BL/6J mice display disrupted circadian locomotor activity, with significantly elevated activity during both light and dark phases in ELS females. HPLC at P21 but not in adulthood, revealed changes in monoamine concentrations in the midbrain and striatum. FSCV data in adulthood indicate that ELS females exhibit higher evoked dopamine release. By P75-100, HPLC profiles normalize, suggesting that dopaminergic perturbations peak in adolescence. Future directions include investigating release and reuptake properties in early adolescence.

Disclosures: E. Makowicz: None. **A.R. Hurowitz:** None. **E.V. Mosharov:** None. **D.L. Sulzer:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.06/LBP078

Topic: A.08. Adolescent Development

Support: Jacobs Fellowship from the Jacobs Foundation
Pro Futura Scientia Fellowship from the Swedish Colloquium of Advanced study
Hypatia Fellowship from Radboud University Medical Center

Title: The effect of wildfire smoke exposure on adolescent neural and cognitive development.

Authors: *N. JUDD[1], R. A. KIEVIT[2];
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Abstract: A major public health concern is the adverse effects of air pollution. Fundamental research suggests a plausible mechanistic link between greater pollution (e.g., $PM_{2.5}$) and adverse health effects. However, most population-level research has used neighborhood pollution indicators. These are problematic, as they are heavily confounded with a myriad of other socioeconomic and individual-level characteristics. This confounding makes it virtually impossible to determine the causal impact of such pollution measures on health outcomes. Here, we leverage a unique source of air pollution to better estimate the true impact of air pollution: Wildfires. We constructed two wildfire-specific $PM_{2.5}$ measures by pairing a wildfire pollution dataset with 9806 children from the Adolescent Brain Development Consortium; Perinatal exposure (PSE) reflects the first 12 months of life, including gestation, and childhood exposure (CSE) reflects lifetime exposure before the first imaging timepoint (~10 years of age). Using linear mixed effects modeling, we examine how PSE and CSE affect adolescent cognitive and neural development using 4 timepoints (10-16 yrs) as random slopes with imaging site and child as random intercepts. As expected, we find no relationship between SES and CSE (Pearson's R = .004, $p > .05$) and a very small relationship with PSE (Pearson's R = -.02, $p = .03$). We choose to still control for SES in subsequent analyses. We find CSE to negatively influence the rate of cognitive development over adolescence (B = -0.02, $p < .001$), while correcting for SES and neighborhood pollution. For neurodevelopment, we find an effect of CSE on the development of total surface area (B = -5795, $p < .001$) - manifested across 39 regions using the Desikan-Killiany cortical atlas (pFDR < .05). For mean cortical thickness we find no effect from CSE, yet five regions show localized effects which survive multiple comparison correction (pFDR < .05). Lastly, PSE shows no effect on any cognitive or neural developmental measures. We demonstrate that adolescents exposed to higher levels of wildfire pollution show a slower increase in cognitive development and a faster decrease in surface area, independent of SES and neighborhood pollution. These results signify a step towards separating air pollution from socioeconomic factors, yet wildfires only equalize the amount of *potential* exposure. Attained exposure from wildfire smoke will still differ across socioeconomic gradients via protective behaviors and systemic inequities in the built environment. Future work should utilize natural experiments and policy changes to isolate the causal impact of air pollution on neurodevelopment.

Disclosures: N. Judd: None. **R.A. Kievit:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.07/LBP079

Topic: A.08. Adolescent Development

Support: "One Case One Policy" grant awarded to BH from the Ministry of Science and Technology from Shandong Province (China)

Title: Tracking the developing brain: Resting-state aperiodic activity reveals nonlinear cortical maturation in externalizing disorders

Authors: *H. ZHANG, B. HOMMEL, L. S. COLZATO;
Faculty of Psychology, Shandong Normal University, Jinan, China

Abstract: Childhood and adolescence are marked by dynamic reorganization of neural circuits supporting cognitive control, emotion regulation, and adaptive behavior. Resting-state EEG provides a powerful lens into these maturational processes, with recent attention on the aperiodic exponent—a spectral measure indexing population-level excitatory-inhibitory (E/I) balance. This study examines age-related changes in the aperiodic exponent in youth with adjustment disorder (AD) or oppositional defiant disorder (ODD), revealing atypical developmental trajectories relative to age-matched healthy controls. Specifically, the exponent was lower in early childhood and early adulthood, but peaked around 9 to 10 years of age. This U-shaped developmental trajectory suggests a deviation from normative brain maturation in AD and ODD and points to temporally specific alterations in E/I balance. Our findings suggest that deviations in spontaneous neural activity reflect disrupted cortical maturation. By capturing both normative and pathological variation in E/I dynamics, the aperiodic exponent offers a mechanistic, dimensional marker of neurodevelopment, advancing our understanding of how psychiatric vulnerability emerges within the context of typical brain development.

Disclosures: H. Zhang: None. **B. Hommel:** None. **L.S. Colzato:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.08/LBP080

Topic: A.08. Adolescent Development

Support: R01 AG064247

Title: Associations between longitudinal relational memory performance and hippocampal subfield volumes in a periadolescent sample: findings from the PRANK study

Authors: *A. F. WILHELM[1], M. K. RAMIREZ[1], A. HELLER-WIGHT[1], H. V. GHANNAM[1], E. A. ARMBRUSTER[1], V. PHATAK[1], D. MURMAN[2], D. E. WARREN[1];
[1]Neurological Sciences, University of Nebraska Medical Center, Omaha, NE; [2]Neurological Science, University of Nebraska Medical Center, Omaha, NE

Abstract: Adolescence is an important developmental epoch for the brain and cognition. Relational memory (RM), the hippocampal-dependent ability to bind and retain arbitrarily

related information, develops during this period. Maturation of RM abilities may be supported by structural maturation of the hippocampus (Hc), and Hc undergoes significant development during childhood as a whole and within its constituent subfields (cornu ammonis 1 [CA1], CA2/3, dentate gyrus, subiculum). Prior research has shown that subfield volumes may increase until ages 13-15, and concurrent improvements in RM suggest an association with HC subfield development. However, longitudinal investigations to characterize development of RM and HC subfield volumes, and their associations, remain rare. This study uses cross-sectional and longitudinal data from the Polygenic Risk of Alzheimer's disease in Nebraska Kids (PRANK) study to examine associations between RM and Hc subfield volumes. The cross-sectional sample included children ages 8-13 (N=136); a subset of these children ages 10-17 (N=40) also contributed longitudinal data. During each visit (V1 & V2), subjects completed cognitive testing and an MRI scan (Human Connectome Project protocol); only volumetric data from V1 are reported here. Whole brain T1w and high-resolution T2w slab images were collected and segmented into Hc subfields using Automatic Segmentation of Hippocampal Subfields software. RM was measured with objects and places scores from the Child and Adolescent Memory Profile (ChAMP). Regression and linear mixed-effects (LME) models were used to test associations between subfield volumes and memory performance at V1. Exploratory analyses in the longitudinal sample tested whether V1 subfield volume predicted V2 memory. Cross-sectional analyses showed significant associations between CA1 volume and RM: left CA1 with objects ($r=.27$, $p=.002$) and places ($r=.26$, $p=.002$), and right CA1 with objects ($r=.30$, $p<.001$) and places ($r=.34$, $p<.001$). Longitudinally, subjects improved from V1 to V2 by 2.7 points on objects ($t(39)=4.84$, $p<.001$) and 2.9 points on places ($t(39)=4.23$, $p<.001$). Right CA1 volume at V1 predicted object scores at V2 ($r=.37$, $p<.001$), but places scores only after correcting for age ($r=.32$, $p=.045$). Exploratory longitudinal analyses with LME models suggested that larger bilateral CA1 volume was associated with better performance on both tasks in association with age and sex. Our study expands on previous research linking RM and Hc subfield contributions in both cross-sectional and longitudinal samples. Future work will provide insight into these associations in a fully powered longitudinal sample.

Disclosures: A.F. Wilhelm: None. **M.K. Ramirez:** None. **A. Heller-Wight:** None. **H.V. Ghannam:** None. **E.A. Armbruster:** None. **V. Phatak:** None. **D. Murman:** None. **D.E. Warren:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.09/LBP081

Topic: A.08. Adolescent Development

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NIMH Grant R21MH106869
NIMH Grant R61MH132722

Title: Age-dependent associations between experiencing interpersonal violence and frontal gray matter volume in women

Authors: *L. MALLOY, E. HODGE, M. ARNETT, P. BROSKI, J. M. CISLER;
Department of Psychiatry and Behavioral Sciences, Dell Medical School, University of Texas at Austin, Austin, TX

Abstract: Previous research has linked traumatic stress to reduced gray matter volume (GMV) in several brain regions. The present study investigated the impact of interpersonal violence (IPV) diversity - the sum of how many types of sexual and/or physical assaults someone has experienced - on GMV in adolescent girls (n = 117) and adult women (n = 335) ages 11-50 (total n = 452). T1-weighted structural scans were processed by FreeSurfer and harmonized using ComBat-GAM to minimize site effects while maintaining biological variance due to age and IPV diversity. GMV values were extracted in cubic millimeters. The hippocampus and amygdala were selected as regions of interest (ROIs) for their relevance in trauma and PTSD research, and the medial orbitofrontal cortex (mOFC) and frontal pole because their extended development may confer prolonged vulnerability to traumatic stress. It was hypothesized that experiencing more types of IPV would be associated with reduced GMV in all four ROIs, with developmentally contingent effects emerging in the frontal but not limbic ROIs. Linear mixed-effects models tested the interacting effects of age group, IPV diversity, and hemisphere on GMV while controlling for harmonized total intracranial volume and age. Random intercepts accounted for within-subject correlation between hemispheres. The frontal pole was the only ROI to yield no significant IPV-related effects. IPV diversity was negatively associated with gray matter volume in the right amygdala (t(448)=-2.764, p=.006), right hippocampus (t(448)=-2.245, p=.025), and right mOFC (t(448)=-2.527, p=.012), regardless of age group. Interestingly, we found a significant negative association between IPV diversity and bilateral mOFC volume in adolescent girls relative to adult women (t(746)=-2.115, p=.035). These findings suggest a dose-dependent association between IPV and lateralized reductions in limbic GMV across women's development. They also indicate that frontal regulatory regions, particularly the mOFC, may exhibit developmental windows of vulnerability to traumatic stress.

Disclosures: L. Malloy: None. **E. Hodge:** None. **M. Arnett:** None. **P. Broski:** None. **J.M. Cisler:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.10/LBP082

Topic: A.08. Adolescent Development

Support: NIH Grant K01MH117442
NIH Grant R01MH127176
NIH Grant R21MH130817

Title: Delayed Maturation of Functional Brain Connectivity Patterns in Adolescent Depression

Authors: *A. MUMMANENI[1], J. S. NOMI[2], L. Q. UDDIN[2], T. C. HO[2];
[1]UCLA, Santa Monica, CA; [2]UCLA, Los Angeles, CA

Abstract: Adolescent-onset major depressive disorder (MDD) is a recurrent disorder that, in addition to having substantial behavioral symptoms, may adversely impact brain maturation. Typical brain development in adolescence is marked by a refinement of intrinsic functional brain networks. Depressed adolescents, however, appear to have aberrant functional connectivity in the default mode (DMN), attentional, and limbic networks. Intra-network DMN hyperconnectivity and inter-network DMN hypoconnectivity differentiate depressed adolescents from psychiatrically healthy controls (CTL) and anticorrelations between DMN and attentional networks and between the latter and limbic networks scale with depression severity. To better understand whether early-onset depression might alter brain maturation, we analyzed resting-state fMRI data from three cohorts that included adolescents with MDD. One cohort included cross-sectional data from 78 youth (57 MDD; 13.2-18.4 years); another included cross-sectional data from 49 youth (35 MDD; 14.2-22.0); and the Adolescent Brain Cognitive Development (ABCD) Study cohort included longitudinal data (1113 scans) from 100 CTL youth (9.0-14.9) across three bi-annually collected waves. We calculated whole-brain functional connectomes for all participants using the Shen atlas that parcellates cortex into 268 regions-of-interest. We then correlated the average whole-brain functional connectome of the MDD group to that of age-matched CTL and, again, based on age of depression onset (AOO) in the MDD group to age-matched CTL. We found that whole-brain connectivity patterns of MDD adolescents whose AOO matched the chronological age of CTL evinced stronger correlations than observed between age-matched MDD and CTL (12-14 years: $z=9.09$, $p<0.001$; 14-16: $z=11.09$, $p<0.001$; 16-18: $z=1.38$, $p=0.02$). We then replicated this analysis among 8 canonical functional networks and found that the difference between diagnostic groups when matched based on AOO v. chronological age was strongest with the medial frontal network, which includes anterior DMN, temporal, parietal, and limbic regions (12-14 years: $z=8.61$, $p<0.001$; 14-16: $z=12.85$, $p<0.001$; 16-18: $z=0.93$, $p=0.35$) and DMN (12-14: $z=9.14$, $p<0.001$; 14-16: $z=9.96$, $p<0.001$; 16-18: $z=2.80$, $p=0.005$). Our findings suggest that early-onset MDD may lead to delayed maturation of functional brain networks, particularly in the DMN. These results have important implications for understanding the neurobiological sequelae of adolescent MDD and may inform effective intervention strategies for rescuing behaviors compromised by such neural alterations.

Disclosures: A. Mummaneni: None. **J.S. Nomi:** None. **L.Q. Uddin:** None. **T.C. Ho:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.11/LBP083

Topic: A.08. Adolescent Development

Support: NIH K00 MH138293
NIH R01 MH119091

Title: Adolescent Maturation of Cognitive Control-Reward Interactions and Risk Taking in ADHD

Authors: *H. PETERSON-SOCKWELL;
University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: Adolescence is a period during which there is a well-documented rise in rates of risky behavior. Imbalance models of neuronal maturation suggest that reward circuitry matures more rapidly than cognitive control circuitry, resulting in adolescents having relatively mature reward system, but an immature cognitive control system. Additionally, dual-pathway models hypothesize that ADHD may be caused by disrupted development of both cognitive control and reward-related circuitry. In this analysis, dynamic patterns of interaction between cognitive control and reward-related brain networks were assessed to explore potential differences between youth with ADHD and typically developing youth, and to assess how the network dynamics change from pre- to early-adolescence. Youth with ADHD (n = 63) and age, sex, and IQ matched TD youth (n = 16) underwent fMRI scanning at multiple timepoints (TPs) across adolescence (TP1: 10-12 years of age, TP2: 1-3 year later). TP2 data collection is currently ongoing. During fMRI scanning, participants completed a balloon analogue risk task (BART). On each trial, participants chose to inflate a virtual balloon to increase their potential earnings or cash out and secure their earned reward. If the balloon exploded before cashing out, they earned no reward. fMRI data collected during the BART from regions of the executive control (FPN) and reward network (REW) were assessed with a hidden semi-Markov model (HSMM) to determine patterns of dynamic functional connectivity within and between networks. The HSMM identified six distinct network states from fMRI data from TD and ADHD participants. One state was hallmarked by the highest average FC and small-worldness, indicating significant integration and segregation between the FPN and REW in this state. Both groups spent the largest proportion of the scan time in this state, and significantly increased their total occupancy time in this state at TP2 compared to TP1 ($p < 0.05$). TD participants spent more time in this state than ADHD participants and increased their time in this state to a greater degree at TP2 than ADHD participants. We observed an increase in time spent in a highly integrated and segregated network state in mid-adolescence differentially among both TD and ADHD participants. This finding supports the potential mismatch in the maturation of cognitive control and motivational systems, as well as suggests that adolescents with ADHD may experience an altered trajectory of cognitive control and motivation integration (supporting the imbalance and

dual-pathway models). These altered brain dynamics could contribute to their increased vulnerability to risk-taking behaviors.

Disclosures: H. Peterson-Sockwell: None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

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Topic: A.08. Adolescent Development

Support: National Institutes of Health (K01MH117442 to TCH)
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Stanford Center for Cognitive and Neurobiological Imaging Center (Seed Grant to TCH)
Ray and Dagmar Dolby Family Fund (to TCH)

Title: Functional and Structural Connectivity of Frontoparietal Networks Predict Longitudinal Depression Symptom Trajectories in Adolescent Major Depressive Disorder

Authors: *S. LIU[1], T. C. HO[2];
[1]University of California, Los Angeles, Los Angeles, CA; [2]University of California, Los Angeles, Alameda, CA

Abstract: Adolescent-onset major depressive disorder (MDD) is associated with poorer long-term prognosis (Naicker et al., 2013), underscoring the need for reliable biomarkers to predict clinical course. Adolescence is also marked with significant maturational changes in functional and structural brain networks via processes such as myelination and synaptic pruning (Andersen, 2003). Although research has documented alterations in these neurophenotypes in adolescent MDD (Barch et al., 2022; van Velzen et al., 2020; Kaiser et al., 2015), less is known about whether and how they influence longer-term symptom outcomes in depressed adolescents. Here, we investigated whether resting-state functional connectivity and white matter microstructure predict depressive symptoms trajectories over 18 months in adolescents with MDD. 68 adolescents (ages 13-18) completed baseline multimodal MRIs and provided depression scores every other month for up to 18 months. All MRI data were collected at the Stanford Center for Cognitive and Neurobiological Imaging using a 3T GE scanner with a 32-channel head coil (see Walker et al., 2020 for more details). We applied latent class growth modeling to identify clusters based on symptom trajectories and a three-factor solution was the best model, with clusters of symptom maintenance (n=34), moderate amelioration (n=20), and large improvement (n=14). Primary predictors were standardized (z-scored) prior to analysis. Controlling for

baseline depression severity and psychiatric medication status, as well as head motion during scan, ordinal logistic regression models showed that greater baseline intrinsic connectivity within the parietal (OR=2.45, p=0.02) and lateral prefrontal cortex (OR=2.65, p=0.01) networks and higher fractional anisotropy (FA) in the left cingulum tract (OR=2.16, p=0.03) predicted a high odds of membership in clusters characterized by symptom amelioration. Previous work has shown that reduced FA in the dorsal and ventral cingulum bundles during adolescence is linked to greater depression severity over the past 17 years (Barch et al., 2022). Our findings extend this work by showing that greater structural integrity of the cingulum prospectively predicts more favorable symptom trajectories. Additionally, our results show that stronger functional connectivity within the parietal cortex and lateral prefrontal cortex was associated with greater symptom reduction in adolescents. Together, these findings suggest that, across structural and functional analyses, connectivity in the dorsal and lateral frontoparietal networks may be a resilience factor against chronic or recurrent depression.

Disclosures: S. Liu: None. **T.C. Ho:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.13/LBP085

Topic: A.08. Adolescent Development

Support: R01 AG064247

Title: Differences in Hippocampal Subfields Across Pubertal Stages in Periadolescent Children: Preliminary Findings from the PRANK Study

Authors: *E. A. ARMBRUSTER[1], A. M. HELLER-WIGHT[2], M. K. RAMIREZ[2], A. F. WILHELM[2], H. V. GHANNAM[3], V. S. PHATAK[2], D. M. MURMAN[3], D. E. WARREN[4]; [1]Neurological Sciences, University of Nebraska Medical Center, Omaha, NE; [2]Department of Neurological Sciences, University of Nebraska Medical Center, Omaha, NE; [3]Department of Neurological Sciences, Univeristy of Nebraska Medical Center, Omaha, NE; [4]Neurosciences, University of Nebraska Medical Center, Omaha, NE

Abstract: The hippocampus (HC) is necessary for normal memory as well as for the normal development of memory processes during childhood. It is composed of cytoarchitecturally distinct subfields including cornu ammonis 1 (CA1), CA2/3, dentate gyrus (DG), and the subiculum (SUB). Prior work has investigated developmental changes in HC subfields in association with age, sex, and cognitive performance. However, the relationship between HC development at the subfield level stage of pubertal development remains underspecified. The objective of the current study was to characterize associations between HC subfield volumes, pubertal staging, and sex in a sample of typically-developing periadolescents. In the current study, a sample of 144 healthy children ages 8-13 years (74 females, 70 males), was drawn from

the ongoing Polygenic Risk of Alzheimer's Disease in Nebraska Kids study. T1w-weigthed images and a high resolution T2-weighted slab were used to segment the HC into subfields using Automatic Segmentation of Hippocampal Subfield software. Subfield volumes were corrected for intracranial volume (ICV) using linear regression methods. Participant Tanner stage was derived from parental responses on the ABCD Study's Perceived Pubertal Development questionnaire. Tanner stages (TS) were: TS1, prepubertal; TS2, early puberty; TS3, midpubertal; TS4, late puberty; TS5, mature/adult. Relationships between subfield volumes and Tanner stages were assessed with regression models. Differences between stages and sex were evaluated with t-tests. Our analysis found that Tanner stages were significantly associated with volume of the right SUB ($F(4,139) = 3.246$, $p < .05$). A significant effect of sex was observed in right SUB, and a planned t-test revealed that on average females had larger ICV-corrected right SUB volumes than males ($t(137.56) = 2.47$, $p < .05$). Pairwise comparisons revealed significant differences in the right SUB between TS1 and TS4 ($t(22.52) = 3.23$, $p < .005$); TS1 and TS3 ($t(76.21) = -2.05$, $p < .05$); TS2 and TS4 ($t((31.18) = -2.32$, $p < .05$). Following FDR correction for multiple comparisons, only the difference between TS1 and TS4 remained significant (adj $p < .05$). The current study showed significant differences in HC subfield volumes (e.g., SUB) and pubertal development, such that greater volume was associated with later stages of puberty. Future directions will incorporate assessment of hormonal changes across this developmental sample and its association with pubertal and brain development. Longitudinal data collection will also provide further opportunities to assess how puberty changes impact structural and functional brain development.

Disclosures: E.A. Armbruster: None. **A.M. Heller-Wight:** None. **M.K. Ramirez:** None. **A.F. Wilhelm:** None. **H.V. Ghannam:** None. **V.S. Phatak:** None. **D.M. Murman:** None. **D.E. Warren:** None.

Late-Breaking Poster

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Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.14/LBP086

Topic: A.08. Adolescent Development

Support: R01 AG064247

Title: Age-related differences in dorsolateral prefrontal-hippocampal structural associations in periadolescence: preliminary findings from the PRANK study

Authors: *H. GHANNAM, M. K. RAMIREZ, A. HELLER-WIGHT, A. WILHELM, E. A. ARMBRUSTER, V. PHATAK, D. MURMAN, D. E. WARREN;
Neurological Sciences, University of Nebraska Medical Center, Omaha, NE

Abstract: Adolescence is an important developmental epoch marked by substantial structural and functional brain maturation, particularly within the dorsolateral prefrontal cortex (dlPFC)

and medial temporal lobes. These regions support diverse cognitive processes including executive functions and memory, processes that likewise undergo significant adolescent-epoch maturation. Prior work is consistent with a developmental inflection point for these cognitive processes and the brain regions that support them in late middle childhood. This motivates further study of age-related differences in associations between structure of the dlPFC and hippocampus (Hc) before and after this inflection point. In this study, we investigated the relationship between cortical thickness of dlPFC regions and Hc subfield volumes in a sample of typically developing adolescents. Structural brain data was collected from 132 periadolescent children (66 F) aged 8-13 years old as part of the NIA-funded Polygenic Risk for Alzheimer's disease in Nebraska Kids (PRANK) study. Participants underwent MRI brain study that included T1w and T2w images processed with FreeSurfer (v. 6.0.0) and parcellated with the Desikan-Killiany atlas to measure the cortical thickness of dlPFC regions. High-resolution T2-weighted MRI data were then used to measure Hc subfield volumes through automated segmentation with ASHS software using the Princeton atlas including the Cornu Ammonis 1 (CA1), 2 and 3 (CA2/3), dentate gyrus (DG), and subiculum. For the current study, we measured the association between HC volumes and dlPFC thickness utilizing linear regression models that included, as predictors, Hc subfield volume (and predictors for age, sex, and intracranial volume) and as an outcome, dlPFC cortical thickness. We observed a direct association (β = .004, p = .02) between the volume of a left-lateralized subfield (CA1) and cortical thickness of a left dlPFC parcel (caudal middle frontal gyrus). Next, we investigated the data by age group (age <10 years: N=52; age >10 years: N=80) and found that the significant association between left caudal middle frontal thickness remained a significant predictor of left CA1 volume only for the older group (β = .008, p = .004). These cross-sectional findings would be consistent with a developmental trajectory in which the PFC and the Hc exhibit associations of structural characteristics during select developmental phases. Future work will examine the functional connectivity between these regions as another characterization of the developmental trajectory between the PFC and the Hc.

Disclosures: H. Ghannam: None. **M.K. Ramirez:** None. **A. Heller-Wight:** None. **A. Wilhelm:** None. **E.A. Armbruster:** None. **V. Phatak:** None. **D. Murman:** None. **D.E. Warren:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.15/LBP087

Topic: A.08. Adolescent Development

Title: Reorganizing the hierarchy: the contribution of social status shifts to behavior and social resilience

Authors: *L. BRYAN, D. DUMITRIU;
Columbia University, New York, NY

Abstract: Social behavior is increasingly being investigated through the lens of social dominance ranking. These organizational structures are highly evolutionarily conserved and have extensive effects on behavior. However, the effects of social rank, and particularly a shift in rank, on stress resilience are less understood; dominance status may contribute to variability in stress response to social stressors. To explore the effect of an induced rank shift on social stress resilience, a paradigm was designed to correlate an acute shift in social status to an acute model of social defeat stress (ASDS), where resilience is indicated by control-level social approach one hour post-defeat.
The social hierarchy of mouse tetrads is characterized via tube testing and baseline behavioral testing is conducted, followed by a reconfiguration of cages according to status (e.g., all rank-one animals in a new tetrad). Rank characterization of the new tetrads is conducted, along with repeated behavioral testing, and then resilience to ASDS is measured.
Preliminary data in n = 16 male mice indicates a positive trend between a mouse's resilience and its shift in social status such that an increase in status is associated with an increase in resilience (Pearson correlation, $R = 0.41$, $p = 0.12$) and indicated no correlation with their new rank (Pearson correlation, $R = -0.17$, $p = 0.47$). Preliminary data in n = 32 male mice also indicates differential sociability and anxiety-like behaviors according to original rank status, where higher rank trends towards less anxiety (Pearson correlation, $R = 0.34$, $p = 0.054$) and higher sociability (Pearson correlation, $R = 0.36$, $p = 0.042$).
Next steps include the analysis of chronic neuronal activation during the week of reconfiguration as captured with the DeltaFosB protein. It is hypothesized that key brain regions, such as the medial prefrontal cortex, will show increased activation in animals who rise in social rank in comparison to those who fall in rank. By further investigating the behavioral changes and neuronal activation associated with rank shift, these data will hopefully contribute to the stress field and offer a better understanding of the brain's reaction to shifting social status.

Disclosures: L. Bryan: None. **D. Dumitriu:** None.

Late-Breaking Poster

LBP008: A.08. Adolescent Development

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP008.16/LBP088

Topic: A.08. Adolescent Development

Title: Growth And Development, Psycho-Emotional And Social In Early Adolescence

Authors: *R. BALTAZAR TELLEZ[1], E. PEREZ CAMACHO[2], J. ARIAS-RICO[3], J. HERNÁNDEZ-HERNÁNDEZ[4], M. SANCHEZ PADILLA[3], M. MONTER[5], E. RAMÍREZ MORENO[6];
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México, Mexico; [5]Instituto de Ciencias de la Salud, Universidad Autónoma del Estado de Hidalgo, Actopan, Mexico; [6]Instituto de Ciencias de la Salud, Universidad Autónoma del Estado de Hidalgo, Pachuca, Hidalgo, Mexico

Abstract: Adolescence is one of the most special stages in human life, marked by profound changes in the structure, function, and psychological-social development of the brain. It is a period of change that begins in childhood and culminates in adulthood. During this phase, there is an increase in hormones that act as catalysts for neuronal remodeling in processes such as synaptic pruning, myelination, and neuronal reorganization. As a result, the individual begins to develop their definitive identity. Therefore, this psychological and social development is a process full of uncertainties, fears, and emotional instability. This research increases knowledge and identifies problems faced by adolescents in the early stages, paving the way for improvements or sources of support for this age group. The objective is to identify the factors of emotional, social, and psychological growth and development in early adolescence. The design is quantitative, descriptive, and cross-sectional, using a sample based on the formula for a finite population, which yielded a working result of 62 students between the ages of 11 and 12, with a confidence level of 95%, an acceptable error of 0.05, and an acceptance limit of 1.25. The KIDDO KILL instrument, which measures quality of life, was used in a public school in the city of Pachuca, Hidalgo. It is based on six dimensions (physical well-being, emotional well-being, self-esteem, family, and friends), where each response is collected on a Likert scale, where 1 is never and 5 is always, with a reliability level of 0.84. We can conclude that of the 54 participants, 52% were male and the average age was between 11 and 12 years old. In terms of the adolescents' perceptions, only 35% reported feeling proud of themselves. In the family context, 68% responded that they felt comfortable at home, and 54% said they always got along well with their friends. finally the conclusions suggest that the educational environment also has an impact on development standards, as 42% reported always feeling worried. Adolescent development is determined by multiple factors in their environment, from the family and educational environment to friendships, which are a main support network for this study group.There were no conflicts of interest or dissemination restrictions, and the study did not receive external funding.

Disclosures: R. Baltazar Tellez: None. **E. Perez camacho:** None. **J. Arias-Rico:** None. **J. Hernández-Hernández:** None. **M. Sanchez Padilla:** None. **M. Monter:** None. **E. Ramírez Moreno:** None.

Late-Breaking Poster

LBP009: A.09. Development and Evolution

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP009.01/LBP089

Topic: A.09. Development and Evolution

Support: NIH Grant BP-Endure Research Fellow (NeuroID)/ Project Number: 5R25NS080687-15

Title: Characterizing hair cell development in the lateral line of the larval blind Mexican tetra

Authors: *C. A. GONZALEZ-GERENA[1,2,3], R. RODRIGUEZ[2,3];
[1]Biology, University of Puerto Rico Rio Piedras Campus, San Juan, PR; [2]Anatomy & Neurobiology, UPR School of Medicine, San Juan, PR; [3]Molecular Sciences Research Center, San Juan, PR

Abstract: Over 1.5 billion people live with hair cell damage due to natural aging, noise pollution, or underlying genetic conditions across the globe. A central question in neuroscience is whether natural variation affects hair cell formation to counteract environmental disadvantages and influence auditory and mechanosensory functions. Non-mammalian species, like amphibians and fish, provide an opportunity to address this because they contain a superficial structure called the lateral line that contains hair cells homologous to ours. While significant strides have been made towards understanding the genetic basis underlying hair cell development in the lateral line of zebrafish, less is known about natural variation in hair cells across closely related species. To ask this broader question, we looked into the Mexican tetra, *Astyanax mexicanus*, a fish species that exists as two morphotypes: (1) a river-dwelling surface fish and (2) a blind, cave-adapted fish that has an expanded lateral line. By using this model system, we asked if the expansion of the lateral line occurs in early development stages in the blind cavefish and if these supernumerary or "extra" neuromasts have more hair cells compared to their ancestral surface fish counterpart. We performed immunohistochemistry to label and quantify hair cells and neuromasts in both surface fish and cavefish across different early larval development stages. Our data suggests differences in the anterior lateral line and posterior lateral line at 3 days post fertilization (dpf) and 10 dpf in cavefish, while no significant differences in between these stages (6 dpf). This could mean that in one morphotype (cavefish) the lateral line is developing slower and eventually catches up and expands compared to surface fish. By understanding how these developmental expansions occur, new mechanisms can be uncovered to become another avenue to counteract hearing and balance disorders, or to eventually interrogate hair cell regeneration mechanisms in a model with natural variation of the hair cell sensory epithelia.

Disclosures: C.A. Gonzalez-Gerena: None. **R. Rodriguez:** None.

Late-Breaking Poster

LBP009: A.09. Development and Evolution

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP009.02/LBP090

Topic: A.09. Development and Evolution

Support: MBL: Ernest Everett Just Fellowship
MBL: Whitman Fellowship

Title: Stress-induced early hatching alters growth and the experience-dependent transcriptome in red-eye tree frog (Agalychnis callidrayas) tadpoles

Authors: *S. B. SERAPHIN[1,3], K. WARKENTIN[4], R. MÁRQUEZ[5], M. SALAZAR NICHOLLS[4], K. GENDREAU[5], S. DADINA[2];
[1]Neurosci. Program, [2]Trinity Col., Hartford, CT; [3]Whitman Ctr., Marine Biol. Lab., Woods Hole, MA; [4]Boston Univ., Boston, MA; [5]Virginia Polytechnic Inst., Blacksburg, VA

Abstract: Red-eyed tree frog (Agalychnis callidryas) embryos can “escape-hatch”, niche-shifting from an egg on a leaf to a tadpole in the pond, when confronted by a predator. To assess the physiological correlates of early life stress (ELS) in A. callidryas, 9 adults (3 males, 6 females) were bred in a rain chamber, yielding 7 clutches. Eggs in each clutch were evenly divided into sibling-matched “Early-Hatch” (EH, experimental, N=69) and “Normal-Hatch” (NH, control, N=60) groups, which were separately maintained in humidified incubators. NH were left to hatch on their own schedule. Conversely, around embryonic stage 6, or upon the appearance of a keratinized beak (Warkentin, 2017), escape-hatching was induced in EH using mechanical stimulation. NH and EH tadpoles were maintained in separate aquariums according to clutch number and hatching date. Randomly selected pairs of EH and NH were harvested at daily intervals, weighed, and preserved. An analysis of weights collected for 129 tadpoles suggests early compensatory growth during the first week post-hatching in EH, but not NH. In a trend reversal, weights were significantly greater in NH (N=24, Mean = 123.3 mg) compared to EH (n=49, Mean = 72.5 mg) by 12-21 days post-hatching (Two-sample t(df)=71, p=<.0001). RNA sequencing (RNAseq) was conducted on specimens that were collected during the first week post-hatching, from three sibling-pairs of age-matched, differently reared NH (N=3) and EH (N=3) tadpoles. Transcriptome analysis revealed 270 genes that are differently expressed in the first week of life, when EH animals also show accelerated growth compared to NH. Furthermore, six signal-driving genes were identified: GELS, SMAD4, PELPK1, KDM5C, KLC1 and LIPP. Together, these genes coordinate the proliferation, differentiation, and organization of cells into tissues in a variety of organisms ranging from plants to humans. In conclusion, A. callidryas represents a good model system for elucidating the epigenetic mechanisms by which ELS alters life history, with important implications for future prevention, restoration, and conservation.

Disclosures: S.B. Seraphin: None. **K. Warkentin:** None. **R. Márquez:** None. **M. Salazar Nicholls:** None. **K. Gendreau:** None. **S. Dadina:** None.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.01/LBP091

Topic: A.10. Schizophrenia

Support: Academy of Finland Grant 334525 JK
Sigrid Juselius Foundation JK
Finnish Cultural Foundation 70241648 NR

Title: Heparan sulfate as the underlying factor of synaptic pathology in schizophrenia

Authors: *N. RÄSÄNEN, J. KOISTINAHO;
University of Helsinki, Helsinki, Finland

Abstract: Schizophrenia is a complex mental health disorder with a developmental origin. Due to the unknown mechanisms of schizophrenia, a great number of patients remain non-responsive to antipsychotic medication. To illuminate the cellular mechanisms of treatment-resistant schizophrenia (TRS), we conducted RNA sequencing for induced pluripotent stem cell (iPSC) - derived neurons from three pairs of monozygotic twins discordant for TRS. In differential gene expression analysis, we found broad downregulation of heparan sulfate (HS) sulfotransferase genes in the affected twins (AT) and unaffected twins (UT) compared to controls (CTR). Surprisingly, immunocytochemical (ICC) characterization of HS revealed increased 3O-sulfated HS in AT neurons compared to CTR neurons ($p=0.046$, mixed model) and increased co-localization of 3O-HS with synapses ($p=0.0448$, mixed model). AT and UT neurons also displayed increased synaptic vesicle size but not density compared to CTR neurons ($p_{AT}=0.107$, $p_{UT}=0.0521$, mixed model). Treatment with heparinase I was found to reduce the vesicle size but not density in these cells suggesting that HS had an influence on synaptic vesicle formation. Patch clamp measurements comparing AT and CTR neurons revealed reduced excitatory postsynaptic current frequency in AT ($p=0.0097$, t-test) suggesting that the increased vesicle size was not associated with increased neuronal activity but rather reduced synaptic input. Finally, we added iPSC-derived microglia and HS-blocking peptides in the neuronal cultures to study the role of HS in synaptic pruning. As a result, we observed a greater average decrease in postsynaptic protein expression in AT and UT cultures compared to CTR cultures ($MeanDiff_{AT}=-0.148$, $SE_{AT}=0.0244$; $MeanDiff_{UT}=-0.0923$, $SE_{UT}=0.0244$). However, this decrease was not influenced by the blockage of HS binding sites suggesting that direct microglial contact with HS did not underlie the increased synaptic loss. In summary, our results provide novel evidence for the role of HS in the synaptic pathology in schizophrenia.

Disclosures: N. Räsänen: None. **J. Koistinaho:** None.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.02/LBP092

Topic: A.10. Schizophrenia

Support: NIH Grant R01-NS130185
NIH Grant R01-NS112480

Title: TRIO Haploinsufficiency Connects Schizophrenia Genetic Risk to Hippocampal Circuit Dysfunction

Authors: *A. Z. COHEN, B. E. HERRING;
Neurobiology, University of Southern California, Los Angeles, CA

Abstract: Hippocampal dysfunction is one of the most robust findings in schizophrenia (SCZ), yet the molecular and circuit-level mechanisms driving this pathology remain poorly understood. Despite decades of imaging and clinical studies, how genetic risk translates into hippocampal circuit disruption in SCZ is largely unknown. TRIO is one of only 10 genes to achieve genome-wide significance for SCZ risk, underscoring its importance for disease biology. Intriguingly, TRIO mutations also confer risk for autism spectrum disorders (ASD), though with distinct molecular consequences: SCZ-associated variants reduce Trio protein expression (haploinsufficiency), whereas ASD-associated variants selectively impact Rac1 activation without affecting expression levels. To test how SCZ-relevant TRIO mutations perturb hippocampal circuits, we used miniature endoscopic calcium imaging (miniscopes) in freely behaving mice. Preliminary findings reveal that Trio haploinsufficiency disrupts correlated neuronal activity in CA1, providing a direct mechanistic link between TRIO loss-of-function and SCZ-relevant hippocampal circuit dysfunction. These findings address a critical gap in our understanding of hippocampal pathophysiology in SCZ and set the stage for future studies examining how distinct TRIO mutations contribute to divergent psychiatric outcomes.

Disclosures: A.Z. Cohen: None. **B.E. Herring:** None.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.03/LBP093

Topic: A.10. Schizophrenia

Title: Assessing cognition and prefrontal neural circuit in the schizophrenia and bipolar mouse models

Authors: *H. GANGAL[1], A. HALL[1], W.-C. HUANG[1], S. ARYAL[1], M. KWON[1], T. ZHOU[2], G. FENG[3], P. S. KUNWAR[1];
[1]Broad Institute of MIT and Harvard, Cambridge, MA; [2]Brain and Cognitive Sciences, MIT, Cambridge, MA; [3]Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA

Abstract: Cognitive impairment is a well-established feature of both schizophrenia and bipolar disorder, characterized by deficits in domains such as attention, memory, and executive function, with varying severity and persistence across the two conditions. However, underlying circuit dysfunction and treatments addressing these deficits are yet to be developed. Currently approved pharmacological treatments are only effective in treating positive symptoms of schizophrenia, like delusions and hallucinations. Our aim is to elucidate the functional impact of these mutations on cognitive and neural processes, providing insights into the neurobiological

mechanisms underlying schizophrenia and bipolar disorder. In this study, we utilized operant conditioning tasks to investigate cognitive deficits in mouse models harboring genetic mutations identified in the SCHEMA (Schizophrenia Exome Meta-Analysis) and BipEx (Bipolar Exome Sequencing) studies. In parallel, we are undertaking neural recordings from the prefrontal cortex, a key brain region integral to executive functions. Extensive evidence highlights PFC dysfunction as a central feature in both schizophrenia and bipolar disorder, contributing significantly to the cognitive impairments observed in these disorders.

Disclosures: H. Gangal: None. **A. Hall:** None. **W. Huang:** None. **S. Aryal:** None. **M. Kwon:** None. **T. Zhou:** None. **G. Feng:** None. **P.S. Kunwar:** None.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.04/LBP094

Topic: A.10. Schizophrenia

Support: Long Island Network for Clinical and Translational Science D2 Pilot
Simons Foundation SFARI Bridge To Independence Award

Title: Cellular-resolution mapping of brain-wide cortical defects in a mouse model of 22q11.2 Deletion Syndrome

Authors: A. P. REID[1], R. GALLUCCIO[1], Y.-C. WU[1], H. ZHAN[1], F. BOATO[2,3], ***K. S. MATHO**[2,3];
[1]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; [2]Children's Hospital Los Angeles, Los Angeles, CA; [3]University of Southern California, Los Angeles, CA

Abstract: Individuals with 22q11.2 deletion syndrome (22q11.2DS) exhibit high rates of schizophrenia, autism spectrum disorder, and other cognitive and behavioral impairments. Neuroimaging and postmortem studies indicate consistent anatomical and cellular anomalies associated with 22q11.2DS, including reduced cortical gray matter, periventricular heterotopias, and altered laminar and regional distributions of excitatory and inhibitory neurons. These observations suggest that disruptions in cortical organization contribute to neurodevelopmental pathology and cognitive impairment. Mouse models of 22q11.2DS, including the Df(16)A+/- mouse, recapitulate many of these phenotypes, including behavioral impairments relevant to cognitive function and widespread disruption of cortical architecture. Prior neuroanatomical studies of 22q11.2DS mouse models have detected alterations in the frequency and laminar distribution of excitatory projection neurons, as well as reduced densities of particular inhibitory interneuron subtypes in higher-order cortical areas. Here we assess the use of an emerging, high-throughput neuroanatomical tool, BARseq2, to validate its capacity for detecting alterations in cortical organization in the Df(16)A+/- mouse model of 22q11.2DS. BARseq2 is an in situ sequencing-based platform that reports both the molecular identity and spatial location of tens of

thousands of single neurons, simultaneously, in a single fresh frozen brain slice. We apply BARseq2 to sagittal brain slices of Df(16)A+/- and control mice to map organizational changes in cellular architecture across the entire anteroposterior extent of the cortex. We test whether BARseq2 can identify significant differences in the composition and spatial distribution of excitatory and inhibitory neuron populations associated with Df(16)A+/- mice on both global and local scales. We compare our brain-wide, cellular-resolution measurements to prior reports of cortical phenotypes in Df(16)A+/- mice and highlight the unique capacity of BARseq2 to simultaneously capture the cellular architecture of multiple neuronal populations across several cortical regions. These results establish BARseq2 as a high-throughput, high-resolution platform for detecting disease-relevant cortical organization deficits and provide a foundation for future studies integrating projection-specific mapping and connectivity analyses.

Disclosures: A.P. Reid: None. **R. Galluccio:** None. **Y. Wu:** None. **H. Zhan:** None. **F. Boato:** None. **K.S. Matho:** None.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.05/LBP095

Topic: A.10. Schizophrenia

Support: U.S. National Institute of Mental Health R01MH110438 and S10MH133643 (PI: Vasudevan)
Della Martin Endowed Postdoctoral Fellowship for Mental Health at the Huntington Medical Research Institutes (Rahman MO)
Summer Undergraduate Research Fellowship at HMRI (JD)

Title: In vitro modeling of schizophrenia using human pluripotent stem cells

Authors: *M. RAHMAN[1], J. DRUM[2], A. VASUDEVAN[3];
[1]Huntington Medical Research Institute (HMRI), Pasadena, CA; [2]Huntington Medical Research Institute, Pasadena, CA; [3]Angiogenesis & Brain Development Laboratory, Huntington Medical Research Institutes, Pasadena, CA

Abstract: Schizophrenia (SCZ) is a complex neurodevelopmental psychiatric disorder with a lifetime prevalence of approximately 1 in 100 individuals. Clinical onset typically occurs during adolescence or early adulthood, and the disorder profoundly disrupts cognition, emotion, and behavior. SCZ is classically characterized by disturbances in thought processes, perception, affect, behavior, and social functioning. Despite advances in pharmacological and psychosocial interventions, current treatments often provide only partial symptom relief, and no curative therapy exists. Growing evidence implicates abnormalities in both brain endothelial cells and neuronal cells during development in the pathogenesis of psychiatric disorders. In this context, induced pluripotent stem cell (iPSC) technology has emerged as a transformative platform for

modeling disease mechanisms and advancing personalized therapeutic strategies. Our previous work identified a specialized embryonic forebrain endothelial cell population that plays a critical role in guiding the migration of forebrain GABAergic interneurons and is characterized by a unique transcriptional profile. Perturbations in forebrain endothelial cells function during embryonic development have been linked to neuropsychiatric conditions, including schizophrenia, anxiety, and depression. Importantly, we have translated these findings from mouse models to the human system. Building on this discovery, we established a protocol to generate human forebrain-like endothelial cells from both healthy control and SCZ patient-derived iPSCs. Molecular analyses demonstrated that iPSC-derived forebrain endothelial cells generated with our current protocol was enriched in ventral forebrain endothelial identities, though dorsal forebrain identities were also present. Functionally, patient-derived embryonic forebrain endothelial cells displayed striking abnormalities, including impaired tube formation, reduced proliferative capacity, and diminished migratory potential. These findings not only highlight a previously underexplored neurovascular contribution to SCZ pathogenesis but also position patient-specific embryonic forebrain endothelial cells as a promising model for dissecting disease mechanisms. Moreover, this platform holds potential for the development of cell-based therapies and personalized approaches to psychiatric disorders.

Disclosures: M. Rahman: None. **J. Drum:** None. **A. Vasudevan:** None.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.06/LBP096

Topic: A.10. Schizophrenia

Title: Pharmacological evidence for GluN2A receptor mediation of click train induced 40 Hz neural synchrony in rodent prefrontal and temporal cortices

Authors: S. KASSA[1,2], D. GAUTAM[2], C. CHAPMAN[2], M. PHILLIPS[2], H. RUTHERFORD[2], ***S. V. DIGAVALLI**[3,2];
[1]Department of Pharmaceutical Sciences, East Tennessee State University, Johnson City, TN; [2]Pharmaceutical Sciences, East Tennessee State University, Johnson City, TN; [3]East Tennessee State University, Johnson City, TN

Abstract: Gamma oscillations (30-100 Hz), generated by interactions between parvalbumin (PV)-positive interneurons and pyramidal cells, are a signature of sensory processing in the neocortex. A reliable method to engage these networks across species is through rhythmic auditory stimulation at gamma frequency (~ 40 Hz), which robustly entrains local field potentials with high precision and modulates gain. Converging evidence indicates that NMDA receptor activity on PV interneurons is required for 40 Hz synchrony: genetic ablation of NMDA receptors on PV interneurons in mice and acute NMDA blockade in rodents and humans, robustly disrupt this response, while response to lower frequency (~ 20 Hz) stimulus is

unaffected. Moreover, in schizophrenia patients where reduced NMDA function has been implicated, consistent entrainment deficits are noted at 40 Hz but not at 20 Hz. NMDA receptors are heterotetramers composed of two obligatory GluN1 subunits and two GluN2 subunits (A-D), but the specific GluN2 subtype critical for 40 Hz gamma synchrony remains unknown. Recent genetic studies link rare and common variants in the gene encoding GluN2A subunit to substantial schizophrenia risk, highlighting a compelling target for drug development. In this study, we investigated the role of GluN2A in gamma synchrony using male and female Sprague-Dawley rats implanted with epidural EEG electrodes over prefrontal and temporal cortices. EEG was recorded (Signal 8.02; CED1401 Micro 3) during click train presentations (1 ms sq waves at 40 or 20 Hz, ~65 dB SPL) played over house speakers. Each 5 s EEG sweep included a 1-2 s click train, with 75 trials/rat. In a balanced crossover design, rats received either saline (1 ml/kg) or the GluN2A-preferring competitive antagonist PEAQX (60 mg/kg, s.c.). Sixty minutes post-treatment, intertrial phase coherence (ITPC), a marker of trial-to-trial response consistency, was evaluated in temporal segments corresponding to prestimulus, during and post-stimulus periods. In the during stimulus period only, PEAQX significantly reduced ITPC in response to 40 Hz stimulation at both frontal and temporal sites ($p < 0.05$), while ITPC to 20 Hz click trains was unaffected ($p > 0.05$). These findings provide the first direct evidence that GluN2A subunits mediate 40 Hz auditory steady-state responses in vivo. Combined with clinical data showing reduced 40 Hz synchrony in schizophrenia, our results suggest that impaired GluN2A function may underlie circuit-level deficits in the disorder and support the therapeutic potential of targeting GluN2A augmentation as a promising strategy for new drug development.

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Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.07/LBP097

Topic: A.10. Schizophrenia

Support: Underwritten by Reviva Pharmaceutical Inc.

Title: Brilaroxazine treatment effects on BDNF and inflammatory cytokines in schizophrenia: RECOVER trial in acute and stable patients over 1 year

Authors: *L. BHAT, S. BHAT, W. KHAN, A. RAMAKRISHNAN, S. KHAN;
Reviva Pharmaceuticals Inc, Cupertino, CA

Abstract: Introduction
Studies report that neuroinflammation contributes to schizophrenia pathophysiology. Such includes reduced brain-derived neurotropic factor (BDNF) and elevated proinflammatory cytokines and chemokines, linked to symptom burden and function. Brilaroxazine (RP5063), a

multimodal serotonin-dopamine neuromodulator (5-$HT_{1A/2A/2B/7}$; $D_{2/4}$; 5-HT2B>D2) with effects on neuroinflammation, advanced through REFRESH (Phase 2), RECOVER (Phase 3) in acute patients, and a 52-week open-label extension (OLE) in stable patients. Brilaroxazine showed reductions in multiple proinflammatory cytokines and chemokines in preclinical inflammatory models and clinical trials.

Methods

This analysis evaluated BDNF and cytokines/chemokines (IL-6, IL-8, IL-10, IFN-γ, TNF-α, and MIP-1) changes (baseline to end-of-treatment) from the RECOVER trial (28 days; DBPC; 15/50 mg vs placebo/PBO; N=411) in acute patients and the OLE in stable patients (52 weeks; 15/30/50; N=446).

Results

In the RECOVER trial, brilaroxazine 15 and 50 mg groups displayed significant dose-dependent reductions in proinflammatory cytokine IL-8 levels, 9.20 and 1.90 ng/L, respectively, vs. placebo 27.5 ng/L (P<0.0001). These doses also reduced MIP-1 levels to 17.30 and 10.20 ng/L, respectively, vs. placebo at 19.40 ng/L (P<0.001). They also produced directional improvements vs. placebo specific to BDNF, IL-6, IL-10, IFN-γ, TNF-α, and MCP-1 levels. In the OLE study, pooled doses (15/30/50 mg) produced an increase in BDNF by 1.83 ug/L (P=0.0031). They resulted in decreased proinflammatory cytokine levels (ng/L): IL-6 (-0.95, p=0.01), IL-8 (-2.29, p=NS), IL-10 (-1.10, p=0.001), IFN-γ (-1.80, p=0.03), IFN-γ IP (-32.36, p=0.004), TNF-α (-9.5, p=<0.0001), and chemokine MIP-1 (-10.95, p=0.005) vs. baseline at Week-52.

Conclusions

In the RECOVER study, Brilaroxazine lowered IL-8 and MIP-1 significantly vs. placebo, and improved BDNF, IL-6, IL-10, IFN, TNF-γ, and MCP-1 levels. These findings align with preclinical data and the trial's primary and secondary endpoints. They offer a mechanistic link between brilaroxazine's pharmacology and the modulation of neuroinflammatory pathways in schizophrenia. In the OLE study, brilaroxazine significantly increased BDNF and proinflammatory cytokines (IL-6, IL-8, IL-10, IFN-γ, IFN-γ IP, TNF-α, and MIP-1) vs. baseline at Week 52. These improvements likely contributed to brilaroxazine's sustained efficacy over 1 year, particularly for negative symptoms, and safety profile. These effects hold promise for treatment-resistant schizophrenia patients.

Disclosures: L. Bhat: A. Employment/Salary (full or part-time); Reviva Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reviva Pharmaceuticals. **S. Bhat:** A. Employment/Salary (full or part-time); Reviva Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reviva Pharmaceuticals. **W. Khan:** A. Employment/Salary (full or part-time); Reviva Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reviva Pharmaceuticals. **A. Ramakrishnan:** A. Employment/Salary (full or part-time); Reviva Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reviva Pharmaceuticals. **S. Khan:** A. Employment/Salary (full or part-time); Reviva Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Reviva Pharmaceuticals.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.08/LBP098

Topic: A.10. Schizophrenia

Title: LY379268 and cariprazine but not donepezil differentially recover alterations in spontaneous oscillations, gamma-band auditory steady-state response and MMN caused by MK-801 in a rat EEG study: relevance for schizophrenia drug development

Authors: *F. W. ADRAOUI, C. DRIEU LA ROCHELLE, K. CARVALHO;
BIOTRIAL PHARMACOLOGY, RENNES, France

Abstract: Treating schizophrenia (SZ) continues to represent a major challenge for neuropsychiatric drug development companies. While available atypical antipsychotics are mainly effective on positive symptoms of SZ, their effects on cognition, social-cognitive deficits and their underlying neuropathophysiology remain insufficient and poorly characterized. Disinhibition and subsequent hyperexcitability in the cortex and hippocampus of SZ patients is today considered a key player in the genesis of these symptoms, which would primarily result from N-methyl-D-aspartate receptor (NMDAr) hypofunction on inhibiting interneurons. Besides, electroencephalography (EEG)-based biomarkers of these mechanisms such as spontaneous and evoked gamma oscillations as well as mismatch negativity (MMN) have been highlighted. These biomarkers associate well with cognitive and social-cognitive symptoms, strongly depend on NMDAr function and as such represent relevant tools for new SZ drug development. Finding drugs that recover these parameters would therefore constitute a major advancement. In this study, we have tested 3 drugs: LY379268 (mGluR2/3 receptor agonist), cariprazine (D2 receptor agonist and 5-HT2A receptor antagonist), and donepezil (acetylcholinesterase inhibitor), whose mechanisms of action attract drug developers for restoration of cortical and subcortical excitation/inhibition imbalance. We investigated their effects on gamma-band auditory-steady-state responses (ASSR, a measure of evoked gamma oscillations), spontaneous gamma oscillations and MMN by recording EEG by telemetry on the cortex of a rat model of SZ induced by MK-801 (dizocilpine), a selective NMDAr blocker. Our results show that LY379268 and cariprazine but not donepezil could reverse MK-801-induced impairments on spontaneous and evoked gamma oscillations. Their effects on MMN are also described. These results highlight glutamatergic as well as dopaminergic and serotoninergic systems as interesting targets to recover cortical excitation/inhibition balance in SZ.

Disclosures: F.W. Adraoui: A. Employment/Salary (full or part-time); BIOTRIAL PHARMACOLOGY. **C. Drieu La Rochelle:** A. Employment/Salary (full or part-time); BIOTRIAL PHARMACOLOGY. **K. Carvalho:** A. Employment/Salary (full or part-time); BIOTRIAL PHARMACOLOGY.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.09/LBP099

Topic: A.10. Schizophrenia

Support: National Research Foundation of Korea RS-2023-00266120
Basic Research Program of the Korea Brain Research Institute 21-BR-03-01

Title: Therapeutic effect of electroconvulsive therapy on mismatch negativity in psychosis

Authors: *E. CHOE[1], M. HA[2], M. KIM[1];
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Abstract: Electroconvulsive therapy (ECT) remains one of the most effective interventions for treatment-resistant psychosis, yet its underlying neurophysiological mechanisms are not fully understood. Mismatch negativity (MMN), an event-related potential consistently reduced in schizophrenia, has been proposed as a biomarker of cortical dysfunction and illness progression. However, previous studies did not find enough evidence to conclude that antipsychotic medication alters MMN in psychosis patients. Examining the impact of ECT on MMN therefore offers an opportunity to elucidate its therapeutic mechanisms, distinct from those of antipsychotic medication.

Electroencephalography (EEG) data during a passive auditory oddball paradigm were collected before and after ECT for psychosis patients treated with both ECT and medication, and at matched time intervals for those treated with medication only. Data were also collected once from healthy controls. After preprocessing, MMN was estimated by subtracting the standard from the deviant stimulus waveform at the FCz electrode. Group-time interactions in MMN amplitude and latency were assessed using repeated-measures mixed models, with age and sex included as covariates. Repeated measure correlations between MMN amplitude and PANSS positive, negative, and general scores were each measured for those treated with both ECT and medication.

Data from 26 subjects treated with both ECT and medication, 23 subjects treated with medication only, and 58 healthy control subjects were included in the analysis. ANCOVA with age and sex as covariates revealed that patients at baseline showed smaller MMN amplitude compared to healthy control subjects, while the two patient groups did not show difference in MMN amplitude at baseline. In mixed model analyses, a significant group-time interaction was observed in MMN amplitude, driven by an increase in the ECT group after ECT, whereas MMN latency showed no significant interaction. Significant repeated-measure correlation was observed between MMN amplitude and PANSS positive score in the ECT group.

By directly comparing patients treated with ECT and medication to those treated with medication alone, our study demonstrates a normalizing effect of ECT on MMN amplitude, and its relationship with improvement of positive symptoms. These findings imply that ECT engages

neurophysiological mechanisms relevant to MMN generation, such as excitation-inhibition balance. Furthermore, these findings suggest that the normalization of predictive coding, as indexed by MMN, may be linked to improvements in positive symptoms arising from aberrant predictive processing.

Disclosures: E. Choe: None. **M. Ha:** None. **M. Kim:** None.

Late-Breaking Poster

LBP010: A.10. Schizophrenia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP010.10/LBP100

Topic: A.10. Schizophrenia

Support: DHB Fundation (Equity Trustees)
Ronald Philip Griffiths Fellowship from the University of Melbourne.
University of Melbourne's Faculty of Medicine, Dentistry and Health Sciences graduate research scholarships.

Title: Amplified acute behavioural responses and sex-specific long-term improvements in sensorimotor gating in a mouse model of schizophrenia following psilocybin administration.

Authors: *J. J. GATTUSO[1,2], A. KAMAL[1], J. PAYET[3], J. HENDEY[1], Z. PHELAN[3], M. W. HALE[3], A. J. HANNAN[2,1], T. RENOIR[2,1];
[1]The University of Melbourne, Melbourne, Australia; [2]Florey Institute of Neuroscience and Mental Health, Melbourne, Australia; [3]La Trobe University, Bundoora, Australia

Abstract: Psilocybin, a psychedelic 5-HT_{2A} receptor agonist with therapeutic potential, remains poorly understood in the context of glutamatergic dysfunction relevant to schizophrenia. We examined acute and enduring effects of psilocybin (1 mg/kg) in metabotropic glutamate receptor 5 (mGlu5) knockout (KO) and wild-type (WT) mice. Psilocybin robustly increased locomotor activity and head-twitch responses (HTR), both amplified in KO mice, particularly in males, suggesting enhanced 5-HT_{2A} receptor sensitivity. While psilocybin did not alter anxiety-like behaviour, it increased immobility time in the Porsolt swim test in males, potentially reflecting adaptive coping. Strikingly, psilocybin produced sustained improvements in sensorimotor gating (prepulse inhibition) selectively in female KO mice. This effect occurred independently of acute HTR magnitude, suggesting that psilocybin's therapeutic actions may be dissociable from its hallucinogenic effects. To probe underlying mechanisms, a separate c-Fos cohort (n = 60) was examined 90 min post-injection. Preliminary results show no psilocybin-induced c-Fos changes in the mPFC, pointing to other brain regions mediating the altered behavioural response in KO mice. Together, these findings identify mGlu5 as a key modulator of psilocybin's behavioural profile, raise the possibility that individuals with altered mGlu5 function may exhibit differential responses to psychedelic treatment, and highlight sex-specific and long-lasting effects supporting

further investigation of glutamatergic-serotonergic interactions and neuroplasticity in models relevant to schizophrenia.

Disclosures: J.J. Gattuso: None. **A. Kamal:** None. **J. Payet:** None. **J. Hendey:** None. **Z. Phelan:** None. **M.W. Hale:** None. **A.J. Hannan:** None. **T. Renoir:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.01/LBP101

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: An integrated platform for image-based, quantitative profiling of cytotoxic and neurotoxic phenotypes in human iPSC-derived neurons

Authors: *R. MONGEON, J. CLAYTON;
Agilent Technologies, Inc., Winooski, VT

Abstract: In vitro assessment of human neuronal viability and morphology is a foundational approach to evaluate the effects of environmental, occupational, and pharmaceutical chemical exposure on the nervous system. The adoption of automated technologies for sample preparation, image collection and quantitative analysis enables the scale and reproducibility required for high-throughput neuronal phenotyping. Here we present an integrated platform that pairs live-cell fluorescent indicators with automated imaging and quantitative analysis to profile cytotoxic and neurotoxic effects of compounds with diverse MOAs. iPSC-derived glutamatergic neurons were acutely exposed to a small panel of compounds with previously reported cytotoxic and/or neurotoxic activity. Live-cell dyes were applied in a simple media addition step to provide dual readouts of both neuron morphology and cellular viability through automated image-based analysis. Downstream dose-response analysis provided EC/IC_{50} determination for both viability and neurite morphology endpoints, including neurite number, length and branching. Through this approach, we defined treatments as generally cytotoxic when IC_{50} viability < IC_{50} neurite morphology, whereas neurotoxicity was defined as treatments demonstrating IC_{50} neurite morphology < IC_{50} viability. This approach successfully distinguished compound-specific toxicity profiles and confirmed previously reported phenotypes. In many cases, neurotoxic compounds demonstrated effects on morphology at concentrations 10 to 100-fold lower than those that significantly reduced viability. These findings validate this approach as a robust automated solution for toxicity profiling and characterization. Automating this multiparametric evaluation provides valuable support for high-throughput in vitro applications requiring insight into toxicity mechanisms and characterizing neuronal insults.

Disclosures: R. Mongeon: A. Employment/Salary (full or part-time); Agilent Technologies, Inc. **J. Clayton:** A. Employment/Salary (full or part-time); Agilent Technologies, Inc..

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.02/LBP102

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Relationship between e-cigarette use and susceptibility to neurological damage in college students

Authors: *J. ARIAS-RICO[1], J. HERNÁNDEZ-HERNÁNDEZ[2], R. BALTAZAR TELLEZ[3], M. MONTER[1], E. RAMÍREZ MORENO[4], I. CARVALHO GOMES[1], J. AGUILAR GUTIÉRREZ[1];
[1]Universidad Autonoma Del Estado De Hidalgo, Pachuca, Mexico; [2]Universidad Autónoma del Estado de Hidalgo, México, México, Mexico; [3]Universidad Autónoma del Estado de Hidalgo, Pachuca de Soto, Mexico; [4]Universidad Autónoma del Estado de Hidalgo, Pachuca, Hidalgo, Mexico

Abstract: Electronic cigarettes (ECs) are often promoted as a less harmful alternative to conventional tobacco, yet growing evidence indicates potential neurological risks, particularly in young adults. The objective of this study was twofold: first, to identify environmental, social, and emotional factors associated with EC use among university students; and second, to analyze their relationship with susceptibility to neurological damage. A quantitative, cross-sectional, non-experimental, and observational study was conducted with 395 students (from 17 undergraduate programs) aged 18-24 years (mean = 20.1; 55.3% women). The study was approved by the Bioethics Committee of the Autonomous University of the State of Hidalgo (folio: "eH|ZCEEMG_"). Data were collected through the validated SEQ-12 E-Cigarette questionnaire (20 items; Cronbach's alpha = 0.873) and additional sociodemographic questions. Exploratory factor analysis (KMO index > 0.30) and logistic regression were employed to identify variables associated with use. Results showed that 80% of EC users were between 18 and 22 years old. Women presented higher prevalence of use (55.3%). The presence of friends who smoked was strongly associated with use (odds ratio [OR] = 5.19), as was residing with smokers (OR = 2.41). Key factors included inadequate emotional coping (anxiety, depression, stress), misperceptions of safety, social pressure, and the desire to belong. Most participants reported use between three and 12 months, while a smaller subset reported longer use, suggesting increased risk of dependence. These findings suggest that EC use in university students is significantly influenced by social environment and emotional regulation, and that prolonged nicotine exposure may contribute to increased susceptibility to neurological impairment, including cognitive deficits, developmental alterations, and elevated cerebrovascular risk. This exploratory research provides relevant evidence for prevention strategies, emotional support interventions, and educational efforts regarding the neurological risks of EC use. The study was conducted without conflicts of interest or external funding.

Disclosures: J. Arias-Rico: None. **J. Hernández-Hernández:** None. **R. Baltazar Tellez:** None. **M. Monter:** None. **E. Ramírez Moreno:** None. **I. Carvalho Gomes:** None. **J. Aguilar Gutiérrez:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.03/LBP103

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: RS-2025-00561705

Title: Development of a RAGE-SEAP Screening System to Translate RAGE Modulation into Mechanistic Insights for Alzheimer's Disease

Authors: *S. BAEK[1], D.-G. JO[2];
[1]SungKyunKwan university, SUWON-SI, Korea, Republic of; [2]School of Pharmacy, Sungkyunkwan University, Suwon, Korea, Republic of

Abstract: The receptor for advanced glycation end products (RAGE) is a key mediator of amyloid-β (Aβ) pathology and neuroinflammation in Alzheimer's disease (AD). In our recent study, we demonstrated that a novel RAGE modulator induced soluble RAGE (sRAGE) production, resulting in reduced BACE1 expression and amyloid burden in AD mouse models, ultimately ameliorating cognitive deficits. These findings highlight RAGE as a therapeutic target with disease-modifying potential. Building on this work, we have developed a cell-based RAGE-secreted alkaline phosphatase (RAGE-SEAP) screening system to enable real-time monitoring of RAGE modulation and durg repurposing in vitro. This system incorporates SEAP fused to the extracellular domain of RAGE, allowing quantitative readout of sRAGE secretion under pharmacological or genetic perturbations. Using this platform, we validated functional activity of RAGE modulators identified from our in vivo studies and established assay conditions for high-throughput screening of novel compounds. Our integrated approach bridges mechanistic insights from animal models with translational assay development, providing a versatile tool to accelerate the discovery of RAGE-targeted therapeutics for AD.

Disclosures: S. Baek: None. **D. Jo:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.04/LBP104

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NIA Grant No. R01AG078211
NIH/NIA Grant No. 1R01AG053961

Title: Higher Plasma-Derived TARC/CCL17 Levels, a Marker of Inflammation, is Associated with Thalamic Microsctructural Alterations among Cognitively at-risk Older Adults of African Ancestry

Authors: *S. MOALLEMIAN[1], I. MHATRE-WINTERS[2], S. RAMINFARD[3], M. BUDAK[4], B. A. FAUSTO[5], J. R. RICHARDSON[6], M. A. GLUCK[7];
[1]School of Arts and Sciences, Rutgers-Newark, Roselle, NJ; [2]Florida International University, Miami, FL; [3]Pittsburgh, Pittsburgh, PA; [4]CMBN, Rutgers University-Newark, Newark, NJ; [5]Center for Molecular & Behavioral Neuroscience, Rutgers University–Newark, Newark, NJ; [6]University of Georgia, Athens, GA; [7]Center for Neuroscience, Rutgers University Newark, Newark, NY

Abstract: Systemic inflammation has been implicated in age-related cognitive decline and Alzheimer's disease (AD) risk. Thymus and activation-regulated chemokine (TARC/CCL17) is a chemokine involved in immune regulation and can be detected in peripheral blood. However, the relationship between inflammation, specifically, plasma-derived TARC levels and brain microstructure in aging remains poorly understood. In this study, we examined whether plasma-derived TARC levels are associated with mean diffusivity (MD), a diffusion MRI marker of microstructural brain integrity.Forty-one cognitively at-risk older adults (age range: 60–89 years; mean±SD = 68.68±5.65) were recruited from the *Aging & Brain Health Alliance* at Rutgers University–Newark. Participants completed the Montreal Cognitive Assessment (MoCA; mean±SD = 23.1±3.72). Diffusion-weighted imaging (DWI) data were acquired on a 3T Siemens PRISMA scanner. Plasma TARC levels (pg/mL) were quantified using a customized inflammation panel on the ultrasensitive Meso Scale Diagnostics (MSD) platform. Voxel-wise analyses were performed in SPM12 using a general linear model (GLM), controlling for age, sex, and education. Statistical significance was determined using family-wise error (FWE) correction at the cluster level.Higher plasma TARC levels were significantly associated with increased MD in the left thalamus proper ($p< 0.05$, cluster-level; Figure 1A). Additional voxel-level associations were found in the right lingual gyrus and left middle occipital gyrus ($p< 0.05$; Figure 1B–C). Detailed information on the association is brought in Table 2.These findings suggest that plasma TARC, a peripheral marker of inflammation, is associated with microstructural brain changes in regions vulnerable to aging and early AD pathology. This work highlights the potential of plasma-derived inflammatory biomarkers to inform risk detection and early neurodegenerative processes, particularly in the thalamus, a hub implicated in early AD progression.

Figure 1. Statistical parametric maps from the GLM analysis between mean diffusivity and TARC. For illustration purposes, the results are shown at P< 0.001corrected.
Table 1. Data Descriptives
Table 2. Regression results, Showing the correlation between mean diffusivity map (in GM) and TARC. Brain regions were labeled with the AAL3 atlas toolbox in SPM. Coordinates are reported in MNI space. FWER correction was applied for $p < 0.05$

at voxel or cluster level. These peak voxel coordinates for the significant clusters surviving the p<0.05 FWER correction at cluster level. Clusters highlighted by star are also significant at voxel-level.

Disclosures: S. Moallemian: None. **I. Mhatre-Winters:** None. **S. Raminfard:** None. **M. Budak:** None. **B.A. Fausto:** None. **J.R. Richardson:** None. **M.A. Gluck:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.05/LBP105

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant R21NS135088 (IK)

Title: The spatial distribution of metabolic injury in sepsis-associated encephalopathy

Authors: *N. WOLFF[1], M. TRIANTAFYLLOU[2], D. W. CRAWFORD[3], R. LARSON[4], A. RYAN[5], D. GRAHAM[6], R. SUN[5], P. KRATIMENOS[7], V. GALLO[8], I. KOUTROULIS[9]; [1]Children's National Research Institute, Washington, DC; [2]Children's National Research Insitute, Washington, DC; [3]Psychology, Rutgers University Behavioral and Systems Neuroscience, Piscataway, NJ; [4]Biochemistry and Molecular Biology, University of Florida, Gainesville, FL; [5]University of Florida, Gainesville, FL; [6]Johns Hopkins University, Baltimore, MD; [7]Neuroscience and Neonatology, Children's National Hospital, George Washington University School of Medicine and Health Sciences, Washington, DC; [8]Center for Integrative Brain Research, Seattle Children's Hospital, Seattle, WA; [9]Emergency Medicine, Children's National Medical Center, Washington, DC

Abstract: Background: Sepsis-associated encephalopathy (SAE) is a severe complication of sepsis with poor cognitive and psychiatric outcomes, marked by immune and metabolic alterations in the brain. Brain regions are expected to show variable susceptibility to energy failure that can exacerbate neuroinflammation and apoptosis. However, the spatial distribution and mechanisms underlying regional patterns of metabolic injury remain elusive. Methods: In a cecal slurry induced polymicrobial sepsis model (C57BL/6 mice, 8-12 weeks), we tracked neurologic symptom severity with the Murine Sepsis Scale and profiled brain metabolism using (i) matrix assisted laser desorption/ionization imaging mass spectrometry (MALDI IMS) for whole brain spatial metabolomics at 6h and 24h, co-registered to H&E histology, and (ii) LC MS/MS for targeted cerebellar metabolomics at 24h. Results: Sepsis led to acute neurologic status deterioration, most rapid within the first 6h (Fig 1 a). Investigation of the spatial pattern of metabolic brain injury over time with MALDI IMS, revealed metabolic changes presenting as early as 6h and intensifying by 24h (Fig 1 b, c). The cerebellum, hippocampus, and cerebral cortex harbored the greatest number of altered metabolites (Fig 1 d-f). These indicated cerebellar dysregulation of amino acid (aa)-, mitochondrial- and glutamate (glu)- related metabolism;

hippocampal changes linked to nucleotide and glu metabolism; and cortical alterations dominated by shifts in aa and mitochondrial metabolism. Targeted LC MS/MS of the cerebellum at 24h showed disruption of aa and fatty acid metabolism (Fig 1 g). Conclusions: We define an early, brain-wide, spatially organized metabolic injury pattern in SAE, providing a practical atlas of regional vulnerability that links mitochondrial bioenergetics and metabolism of aa, glu and fatty acids to acute dysfunction. These findings highlight a therapeutic window in the first hours of sepsis and nominate region specific metabolic nodes as targets for interventions to rescue brain metabolism and improve neurological outcomes after SAE.

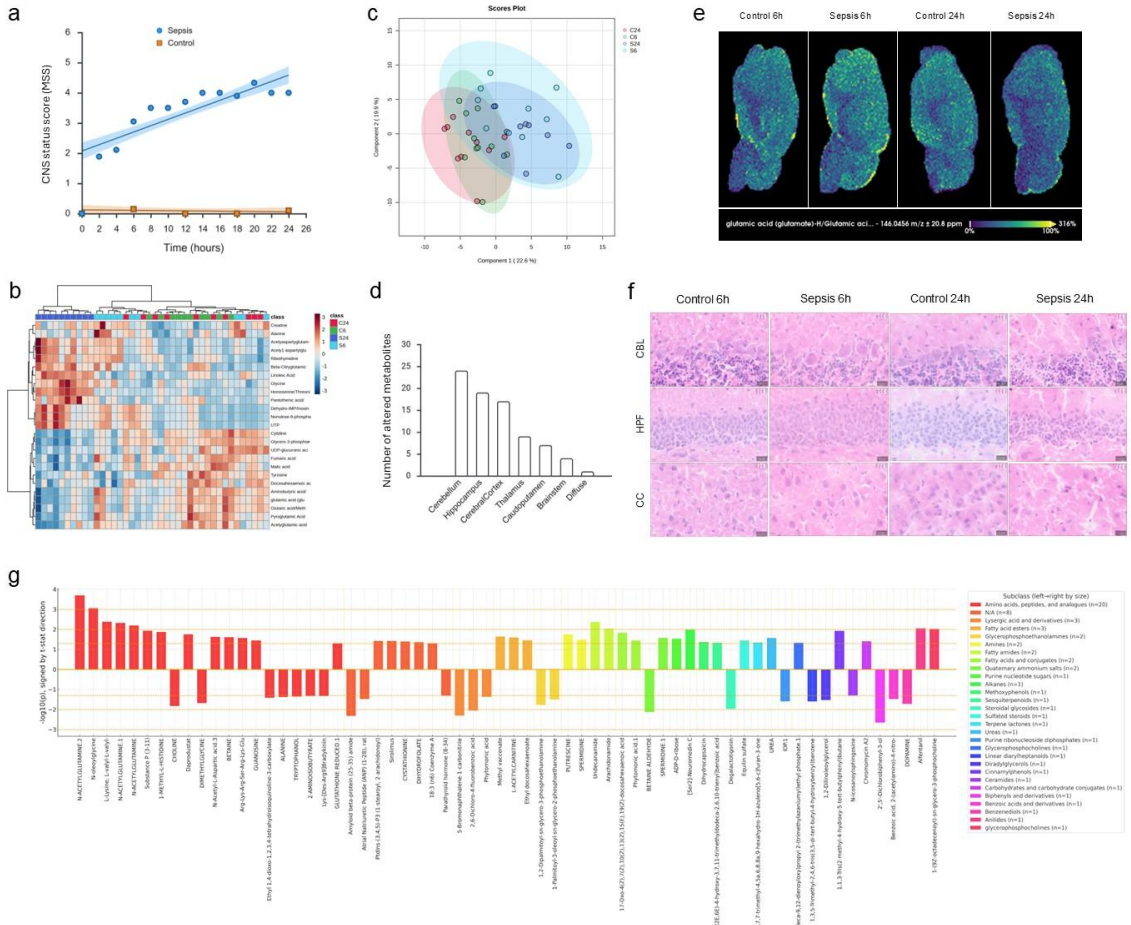

Figure 1. (a) Central nervous system (CNS) score derived from Murine Sepsis Scale (MSS) tracking of mice for up to 24h post-sepsis induction (n=20 per group). **(b, c)** Heatmap of top 25 altered metabolites in the whole brain and Principal Component Analysis plot of 24h-sepsis (blue, S24), 6h-sepsis (light blue, S6), 24h-control (red, C24) and 6h-control (green, C6) animals (n=10 per group). **(d)** Bar plot depicting number of altered metabolites in sepsis per brain region. **(e)** Representative maps of glutamate distribution in the brain of septic and control mice at 6h and 24h, MALDI IMS spatial metabolomics. **(f)** Representative H&E images from the cerebellum (CBL), hippocampus (HPF) and cerebral cortex (CC) of septic and control mice at 6h and 24h at 40X magnification. **(g)** Log_2FC-based metabolite changes in the cerebellum of septic mice (n=15) versus controls (n=16) at 24h post sepsis-induction, LC-MS metabolomics.

Disclosures: N. Wolff: None. **M. Triantafyllou:** None. **D.W. Crawford:** None. **R. larson:** None. **A. Ryan:** None. **D. Graham:** None. **R. Sun:** None. **P. Kratimenos:** None. **V. Gallo:** None. **I. Koutroulis:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.06/LBP106

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Normative EMG data and influencing factors in intraoperative neuromonitoring during thyroid surgery

Authors: *S. SHIN;
Department of Otorhinolaryngology-Head and Neck Surgery, Pusan National University College of Medicine, Busan, Korea, Republic of

Abstract: Normative Electromyography Data and Influencing Factors in Intraoperative Neuromonitoring (IONM) using Adhesive Skin Electrodes during Thyroid Surgery
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Department of Otorhinolaryngology-Head and Neck Surgery, Biomedical Research Institute, Pusan National University School of Medicine, Pusan National University Hospital, Pusan, Republic of Korea
Key words: Neuromuscular monitoring, Thyroid gland, Recurrent laryngeal nerve
AbstractBackground: Skin electrodes have been reported to be an alternative useful recording method of intraoperative neuromonitoring (IONM) and show typical electromyography (EMG) waveform while overcoming the shortcomings of EMG endotracheal tube. However, skin electrodes showed relatively low evoked amplitude compared to that with other recording methods. In this study, we analyzed the normative EMG data using skin electrodes and factors affecting evoked amplitude of thyroid IONM. Methods: A total of 167 patients (242 nerves at risk) who underwent thyroidectomy under IONM with adhesive skin electrodes were analyzed. A pair of skin electrode was attached to the lateral border of thyroid cartilage lamina. Evoked EMG data, including data on mean amplitude and latency, obtained following the stimulation of both recurrent laryngeal nerve (RLN) and vagus nerve (VN) were collected and analyzed.Results: Mean amplitude of both RLN and VN recorded via skin electrodes was 255.48 ± 96.53 μV and 236.15 ± 69.72 μV, respectively. Mean latency of right RLN was 3.22±0.38 mS and left RLN was 3.49±0.83 mS. Mean latency of right VN was 5.37±0.80 mS and left VN was 7.57 ± 0.10 mS. Mean amplitude was significantly lower in obesity, male and total thyroidectomy group. As BMI and age increased, EMG amplitude showed a tendency to decrease significantly.Conclusions: Evoked amplitude recorded with skin electrodes was relatively low. Larger surgical extent, obesity, male and age over 55 group showed significantly lower evoked amplitude.

Disclosures: S. Shin: None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.07/LBP107

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Neurocognitive and Neuroscientific Insights into the Diagnostic Accuracy of Chronic Multi-symptom Illness In Gulf War and Non-Gulf War Era Veterans

Authors: F. S. MOJABI[1], M. M. ADAMSON[2], P. J. BAYLEY[3], ***J. W. ASHFORD, Jr.**[4]; [1]War Related Illness & Injury Study Center, Veterans Affairs Palo Alto HCS, Palo Alto, CA; [2]War Related Illness & Injury Center, Stanford University/VA Palo Alto Healthcare System, Palo Alto, CA; [3]War Related Illness and Injury Study Center, VA Palo Alto / Stanford University, Palo Alto, CA; [4]War Related Illness & Injury Study Center, Stanford University, Redwood City, CA

Abstract: Gulf War Illness (GWI-Kansas Criteria) affects ~250,000 Veterans who served in Operations Desert Shield/Desert Storm (ODS/S) during the 1990-1991 Persian Gulf War. In addition to fatigue, chronic pain, and gastrointestinal dysfunction, many Veterans with GWI report neurocognitive impairments, sensory disturbances, sleep disorders, and autonomic dysfunction, indicating involvement of central and peripheral nervous systems. Understanding the neurological basis of these symptoms is essential for advancing diagnostic precision and therapeutic development. This study aimed to identify patterns of neurocognitive, neurological, and autonomic dysfunction disproportionately affecting ODS/S Veterans. Data were collected from Veterans presenting to the War Related Illness and Injury Study Center (WRIISC, California site). Participants completed intake instruments: Review of Symptoms (ROS), quantifying frequency and severity of self-reported symptoms, and Patient Medical History (PMH), documenting Veteran-reported clinician-diagnosed conditions. Responses were compared across three cohorts: (1) pre-ODS/S deployed, (2) ODS/S-deployed, and (3) post-ODS/S deployed Veterans. ANOVA of ROS data showed ODS/S Veterans were significantly more likely to report neurological and sensory disturbances, including erectile dysfunction, sexual activity difficulties, alterations in taste/smell, and ocular/visual problems ($p < 0.05$). These findings highlight dysfunction across autonomic, sensory, and visual pathways. Chi-squared analysis of PMH data revealed ODS/S Veterans had the highest prevalence of disorders with neurological components—peripheral neuropathy, sleep apnea, fibromyalgia, chronic fatigue syndrome, and thyroid dysfunction,alongside systemic illnesses such as hypertension, diabetes, and musculoskeletal conditions. Post-ODS/S Veterans showed high frequencies of neuropsychiatric and neurological conditions and cardiovascular and infectious disease, which may contribute to long-term cognitive decline. In conclusion, ODS/S Veterans suffer disproportionately from neurological and neurocognitive disorders, underscoring the multisystem nature of GWI. These findings highlight the need to broaden diagnostic frameworks to capture neurological manifestations and support the utility of symptom severity measures in refining the phenotypic definition of GWI. Neuroscience-driven approaches including neuroimaging,

biomarker identification, and neuropsychological profiling are critical for improving diagnostic accuracy and advancing treatment strategies beyond the Kansas criteria.

Disclosures: F.S. Mojabi: None. **M.M. Adamson:** None. **P.J. Bayley:** None. **J.W. Ashford:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.08/LBP108

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Non-hydrocephalic symptomatic pineal cysts: histopathologic and molecular characteristics of cystic tissue

Authors: *E. WILSON, T. PETRUCCI, V. DAYLOR, C. WELSH, S. PATEL, R. NORRIS; Medical University of South Carolina, Charleston, SC

Abstract: Pineal cysts (PC) are a common incidental finding on imaging, but it is a rarer situation in which these pineal cysts become symptomatic. There is debate on how to treat non-hydrocephalic symptomatic PCs (nhSPC) due to the lack of pathophysiological understanding. Our study aims to investigate the molecular landscape of the pineal gland in patients undergoing PC resection using histopathology, biomarker analysis, and proteomic techniques. Eligible participants provided informed consent in person prior to surgery. Biospecimens were collected including blood, saliva, pineal cyst tissue, and cerebrospinal fluid (CSF). Decedent tissue from unaffected individuals were collected on campus at MUSC. Medical records were referenced to report participant's relevant clinical information. PC samples were formalin-fixed, paraffin-embedded and sectioned onto charged slides for analysis. Samples were stained with Masson's trichrome, Hematoxylin and Eosin (H&E), and Picrosirius red. Immunohistochemistry staining for collagen 1 (Col 1), tryptase positive mast cells (tryptase), and alpha-smooth muscle actin (a-SMA) was performed. Primary symptoms pre-op, n=10 (and their reported 1-month post-op improvement, n=10) include headache (100%), visual disturbances (40%), cognitive impairment (70%), and sleep disturbances (30%). Masson's trichrome shows areas of increased cell density, with unique collagen organization compared to the control (n=5). Immunohistochemical evaluation showed higher proportion of mast cells associated with collagen in control and cases ($p=0.821$), and in case tissue there are more mast cells not associated with vascular collagen compared to control ($p=0.005$). The chart review information obtained reflects current literature symptom burden and improvement post-op. Since most of our participants have not yet reached 3-month or longer, the true impact of surgical intervention in our cohort is yet to be seen. Future directions include digital pathology to evaluate the collagen organization, RNA sequencing to evaluate differential expression within the tissue samples.

Disclosures: E. Wilson: None. **T. Petrucci:** None. **V. Daylor:** None. **C. Welsh:** None. **S. Patel:** None. **R. Norris:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.09/LBP109

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: R01NS128018
NSF 2401892

Title: 2-aminoethoxydiphenyl borate (2-APB) protects mouse brain cells from oxidative stress-induced injury

Authors: K. BREWER, J. LENG, T. YANG, Z.-G. XIONG, *T. LENG;
Morehouse Sch. of Med., Atlanta, GA

Abstract: Overproduction of reactive oxygen species (ROS) and a lack of counterbalancing antioxidants create a state of oxidative stress. This condition is linked to many neurological diseases such as Alzheimer's, Parkinson's, multiple sclerosis and stroke. This study explored the effects of 2-aminoethoxydiphenyl borate (2-APB) on ROS-induced injuries in three major types of mouse brain cells: cortical neurons, astrocytes, and cerebral endothelial cells. It aimed to lay the groundwork for the future use of this compound to alleviate ROS-induced brain injury. We tested the effect of 2-APB on H2O2, one of the major ROS, induced injury of these three cell types. Fluorescein diacetate (FDA) and propidium iodide (PI) staining, and lactate dehydrogenase (LDH) assays were used to measure cell injury. Results showed that 2-APB potently reduces the toxicity of H2O2 in all three types of brain cells. These findings suggest that 2-APB has therapeutic potential for oxidative stress-mediated brain injury.

Disclosures: K. Brewer: None. **J. Leng:** None. **T. yang:** None. **Z. Xiong:** None. **T. Leng:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.10/LBP110

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Modeling ceramide deficiency in human iPSCs reveal DEGS1's essential role in sphingolipid metabolism

Authors: *A. GUO[1,2], D. SOOD[1,2], B. ZHANG[1,3], J. C. DODGE[1,4];
[1]Sanofi, Cambridge, MA; [2]Rare and Neurological Disease, Sanofi, Cambridge, MA;
[3]Translational Medicine Unit, Sanofi, Cambridge, MA; [4]Rare and Neurological Diseases, Sanofi, Cambridge, MA

Abstract: Ceramides are bioactive lipids essential for complex lipid synthesis, membrane integrity, and cell signaling. Disruption of ceramide homeostasis is implicated in various inflammatory and cell-death pathways and is observed in several neurological diseases. Ceramide is produced via two main pathways: (1) The salvage pathway from the hydrolysis of complex sphingolipids such as sphingomyelin, glucosylceramide, and galactosylceramide. (2) The de novo synthesis pathway beginning with the rate-limiting enzyme complex serine palmitoyltransferase (SPT), followed by the generation of dihydroceramide through the action of six ceramide synthases (CerS1-6). Dihydroceramide is then desaturated by DEGS1 to form ceramide. Loss-of-function mutations in DEGS1 cause hypomyelinating leukodystrophy type 18 (HLD18), highlighting the critical role of tightly regulated ceramide synthesis in brain development and function. To investigate DEGS1's role in human sphingolipid metabolism, we generated CRISPR/Cas9-mediated DEGS1 knockout human induced pluripotent stem cells (iPSCs). Lipidomic analysis revealed a complete loss of ceramide and downstream sphingolipids, accompanied by a marked accumulation of dihydroceramides. Additionally, lipid labeling with sphinganine (d17:0) demonstrated active de novo sphingolipid synthesis in wild-type cells, which was abolished in DEGS1 knockout iPSCs. These findings confirm the essential role of DEGS1 in ceramide biosynthesis and establish a human cellular model for studying DEGS1-dependent ceramide homeostasis in iPSC-derived neuronal and glial cell types relevant to various neurological diseases.

Disclosures: A. Guo: A. Employment/Salary (full or part-time); Sanofi. **D. Sood:** A. Employment/Salary (full or part-time); Sanofi. **B. Zhang:** A. Employment/Salary (full or part-time); Sanofi. **J.C. Dodge:** A. Employment/Salary (full or part-time); Sanofi.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.11/LBP111

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Lysosome targeted acidic nanoparticles protect against palmitic acid induced neuronal dysfunction

Authors: *K. A. E. BEKHEIT, J. ZENG, C. LO;
Biology, Syracuse University, Syracuse, NY

Abstract: Abstract: Neurodegenerative diseases, including Alzheimer's and Parkinsons's, are increasingly linked to systemic metabolic disorders such as obesity, type 2 diabetes, and metabolic dysfunction-associated steatotic liver disease. A central factor connecting these conditions is disrupted lipid metabolism, which contributes to lysosomal impairment, oxidative stress and chronic inflammation, and central insulin resistance. Since lipids constitute more than half of the brain's dry mass and are vital for energy metabolism, membrane stability, and synaptic function, imbalances in lipid regulation can appreciate severe neuropathological outcomes, including neuroinflammation, blood-brain barrier breakdown, and neuronal dysfunction. Palmitic acid (PA), a saturated fatty acid commonly elevated in high-fat diets, provides a well-established experimental model of lipid-driven neurotoxicity. Exposure to PA interferes with autophagy lysosomal flux, increases reactive oxygen species and activates pro-inflammatory and cell death pathways, with neurons being particularly vulnerable due to their metabolic requirements and their limited regenerative abilities. In this study, the PA treated primary neurons showed significant impaired lysosomal acidification, reduced mitochondrial membrane potential, and elevated necrotic neuron death. Intervention with lysosome-directed nanoparticles (AcNPs) restored lysosomal activity, preserved mitochondrial function, and significantly reduced necrosis *in vitro*. *In vivo*, direct intracranial PA administration in mice elicited significant microglial activation, increased necrotic markers, and heightened neuroinflammatory signaling, consistent with lipid-induced neuropathology. Preliminary data showed that co-treatment with AcNPs attenuated these responses, suggesting that targeting lysosomal repair may offer a therapeutic strategy. These findings highlight lysosomal dysfunction as a key driver of lipid induced neuronal injury and identify lysosome-targeted nanotherapeutics as a promising approach to counteracting metabolic contributions to neurodegeneration.

Disclosures: K.A.E. Bekheit: None. **J. Zeng:** None. **C. Lo:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.12/LBP112

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Application of bilateral temple tDCS with cathode on the injured hemisphere immediately following rat cerebral ischemia maximizes the neuroprotective effect

Authors: H. BU, S. BAO, ***Q. WAN**;
Shenzhen University of Advanced Technology, Shenzhen, China

Abstract: Starting neuroprotection therapy as early as possible is critical for the ischemic stroke patients. Canonical anodal tDCS (transcranial direct-current stimulation) is a safe approach in ischemic stroke therapy but cannot be applied at the early stage after stroke onset, which apparently is the major obstacle that attenuates the therapeutic effectiveness. To develop new

paradigm that allows early application of tDCS in stroke therapy, we established a unique tDCS approach, the bilateral temple tDCS with cathode on the injured hemisphere (BTtDCSc), in which the two electrodes are symmetrically positioned on the bilateral temple regions. We showed for the first time that immediate application of BTtDCSc at 10 min following rat cerebral ischemia reduced the infarct volume and improved the neurobehavior of stroke animals. At the same experimental conditions, however, anodal tDCS aggravated brain injury. We found that immediate application of BTtDCSc or anodal tDCS respectively reduced or increased the levels of glutamate in the ischemic brain. We revealed that BTtDCSc-elicited neuroprotection was mediated through the suppression of both GluN2BRs (GluN2B subunit-containing N-methyl-D-aspartate receptors) and ASICs (acid-sensing ion channels) and subsequently enhanced activation of AMPK (5'-adenosine monophosphate-activated protein kinase). Together, this study provides novel evidence indicating that application of BTtDCSc immediately following cerebral ischemia injury provides neuroprotection through glutamate/GluN2BR+ASIC/AMPK signaling pathways. These results suggest that BTtDCSc, a safe approach of biophysical stimulation, is potentially a novel self-rescue strategy for stroke patients prior to admission.

Disclosures: H. Bu: None. **S. Bao:** None. **Q. Wan:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.13/LBP113

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: The impact of synaptic signaling molecules on intraocular pressure and glaucoma development

Authors: *J. WU[1], G. EDWARDS[2], P. KOULEN[3];
[1]University of Missouri-Kansas City School of Medicine, Kansas City, MO; [2]Ophthalmology, University of Missouri-Kansas City, Kansas City, MO; [3]Biomedical Sciences and Ophthalmology, UMKC, Kansas City, MO

Abstract: Glaucoma is a leading cause of irreversible blindness, characterized by progressive damage to the retina and optic nerve. While elevated intraocular pressure (IOP) is a major risk factor, many patients experience disease progression despite normal IOP levels. Current treatments focus on lowering IOP but fail to address the underlying neurodegeneration responsible for retinal ganglion cell (RGC) death. Growing evidence implicates synaptic dysfunction, particularly involving the Vesl/Homer family of scaffolding proteins, in glaucomatous pathophysiology, with Homer-1a. This protein has been shown to regulate synaptic stability and calcium homeostasis, potentially protecting against oxidative stress-induced RGC loss. To evaluate the contribution of Homer-1a, we examined Homer-1a knockout (KO) DBA/2J mice (n=22, aged 14-21 months) compared with C57Bl/6J KO controls (n=38, aged 8-24 months), assessing visual acuity (VA) and contrast sensitivity (CS) using the

OptoMotry™ system and recording IOP via applanation tonometry. VA was defined as the highest spatial frequency eliciting head tracking, while CS was the lowest contrast at which responses were detected, meaning lower contrast percentages correspond to higher contrast sensitivity. Statistical analyses revealed significantly decreased VA in DBA/2J Homer-1a KO mice compared to C57Bl/6J KO and wild-type (non-KO) mice ($P \leq 0.0001$, $P \leq 0.05$). CS was similarly impaired in DBA/2J KO mice compared to C57Bl/6J KO mice ($P \leq 0.0001$). IOP was variable in DBA/2J KO mice, with younger animals (14-15 months) exhibiting higher values than older animals (20-21 months; $P \leq 0.05$). However, IOP did not correlate with VA or CS ($P > 0.05$). This study represents an important first step in understanding the synaptic mechanisms underlying glaucoma, as KO mice exhibited lower VA and CS than non-KO mice, with CS following VA in KO animals only. The lack of association between IOP and visual function supports the idea that glaucomatous neurodegeneration can occur independently of pressure elevation. Limitations include reliance on historical VA data for non-KO groups and age variability due to delayed collection, but the data highlight a possible correlation between Homer-1a and visual function. As glaucoma continues to impact a significant portion of the global population, advancing our understanding of its pathophysiology and developing novel, non-invasive treatment options are essential to improving patient outcomes and preventing vision loss.

Disclosures: J. Wu: None. **G. Edwards:** None. **P. Koulen:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.14/LBP114

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: RRF-2.3.1-21-2022-00011 (National Laboratory of Translational Neuroscience) NRDI
OTKA K139389 NRDI
OTKA PD138454 NRDI
KKP133871/KKP20 National Research, Development and Innovation Office, Hungary
151490/EXCELLENCE_24 National Research, Development and Innovation Office, Hungary

Title: Psalmotoxin-1 layer specifically alters the neuronal activity during hypercapnia in the newborn pig cortex

Authors: *G. REMZSO, A. BERENYI, F. DOMOKI;
University of Szeged, Albert Szent-Györgyi Medical School, Department of Physiology, Szeged, Hungary

Abstract: Hypercapnia is a potent stimulus of the neurovascular unit resulting in increases in cerebral blood flow. Acid-sensitive ion channel 1A (ASIC1A) has been recently identified to play a critical role in the microvascular response to hypercapnia in adult mice, however, we found that the selective ASIC1A inhibitor psalmotoxin-1 (PcTx1) only partially affected this response in newborn pigs. We hypothesized that the neuronal electrophysiological response to hypercapnia in the piglet may also be affected by the ASIC1A inhibitor PcTx1, altering the cortical layers' activity in a distinct manner.The experiments were performed on anesthetized, mechanically ventilated male piglets (n=7) in accordance with state regulations and ARRIVE guidelines. The animals were equipped with an open cranial window over the parietal cortex for multichannel electrode insertion. Graded hypercapnia was elicited 3 times with 5-10%CO_2 ventilation, first under control conditions, then during topical application of PcTx1 (10nM), and after toxin washout. The obtained local field potential (LFP) and neuronal firing data were analyzed using spike sorting methods and power spectral density (PSD) calculations (Klusta/MATLAB). After euthanasia, the brain was harvested and we performed ASIC1A-HuC/HuD double-labeling for immunohistochemistry.Prominent neuronal ASIC1A immunoreactivity was observed in all cortical layers with homogenous distribution among the cortical areas. Graded hypercapnia caused a typical biphasic PSD response constituting an increase (5%CO_2) then a decrease (10%CO_2) in the δ and the θ range, always originating from the deep cortical layers gradually shifting upwards. PcTx1 application completely abolished the θ PSD elevation, however, the PSD depression was unaffected. Toxin removal resulted in long lasting depression of cortical neuronal activity, especially in the upper cortical layers. Population firing rates were increased to 10%CO_2 (from 943 spike/min to 1438 spike/min) in the presence of PcTx1, especially by elevating the activity of layer II/III and V.Our data highlight that pharmacological inhibition of ASIC1A with PcTx1 also affects the biphasic electrophysiological response of cortical neurons to hypercapnia. PcTx1 limited PSD increases to 5%CO_2 and caused increased spiking to 10%CO_2. Moreover, the toxin appears to induce long-lasting and layer specific neuronal effects that persist after toxin removal. We conclude that the cortical neurons are likely active contributors to the normal neurovascular response to hypercapnia in the newborn pig, and the activation of ASIC1A is clearly involved in the response mechanism.

Disclosures: G. Remzso: None. **A. Berenyi:** None. **F. Domoki:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.15/LBP115

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH/NINDS R01NS136464
NSF CAREER 2047700

Title: Neurobehavioral, Structural and Microglial Alterations in a Mouse Model of Gordon Holmes Syndrome

Authors: *D. PYARAM;
Georgia State University, Atlanta, GA

Abstract: Gordon Holmes Syndrome (GHS) is a neurodegenerative disorder associated with mutations in the E3 ubiquitin ligase RNF216, leading to a range of neuroendocrine, cognitive, and motor impairments. Disruptions in the hypothalamic-pituitary-gonadal axis have been identified in *Rnf216* knockout (KO) mice, suggesting a role for RNF216 in neuroendocrine function. To determine if RNF216 regulates cognitive and motor functions, we performed motor and learning tasks in adult and middle-aged male and female *Rnf216* KO and Wildtype (WT) mice. Although no significant motor phenotypes were observed, female KO mice exhibited abnormal limb clasping. Both sexes displayed age-dependent deficits in strategy and associative learning. We next examined microglia density, area, soma size, and morphology in multiple brain regions of *Rnf216* KO mice at **adolescent, adult, and middle-age time points** to characterize the developmental and age-related changes in microglial populations in these mice. Our results revealed sex- and region-specific changes in microglia, as-well-as neurobehavioral and structural alterations in *Rnf216* KO mice. Future experiments will use conditional knockout strategies to determine if selective deletion of *Rnf216* in microglia causes similar phenotypes to *Rnf216* global KO mice.

Disclosures: D. Pyaram: None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.16/LBP116

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Multimodal dissection of microglia state dynamics via an arrayed perturb-seq: a screening platform for Target ID in microglia

Authors: *L. JU[1], M. LABRANCHE[1], S. HROMADKA[1], J. LI[1], K. WORRINGER[1], C. FREYRE[2], J. HSIAO[1];
[1]Neuroscience, Novartis Biomedical Research, Cambridge, MA; [2]Neuroscience, Novartis Biomedical Research, Basel, Switzerland

Abstract: Microglia (MG), the primary immune cells in the CNS, are highly dynamic and play critical yet "double-edged" roles in many neurological diseases. Therapeutic efforts increasingly focus on modulating MG states to influence disease outcomes by targeting MG-specific pathways. However, large-scale MG-focused Target Identification (Target ID) solutions, especially for CRISPR screenings, remain rare. Additionally, due to the dynamics and heterogeneity of MG, integrating multiple essays into screening platforms is crucial for characterizing robust MG signatures.
Here, we engineered a hPSC-derived transcription factor-induced microglia model (TF-iMG) by

overexpressing SPI1 and CEBPA. TF-iMG displayed human MG-like transcriptomic, morphological and phagocytic phenotypes while overcoming scalability, cryopreservation, and Cas9 silencing issues commonly seen in traditional models. Starting from cell recovery, TF-iMG enables high-fidelity CRISPR-KO assays to be completed in one week.
Next, we established a MG-focused arrayed Perturb-seq platform using lentiviral CRISPR-KO arrays combined with low-cost multiplexed single-cell RNA sequencing (Parse Bioscience) and live imaging. This single-cell, multimodal screening approach permitted information-rich profiling across hundreds of conditions, dissecting target-associated MG state dynamics and disease associations. We further broadened platform utility by integrating diverse inputs (e.g., disease stimuli, co-cultures) and outputs (e.g., cytokine release, behaviors), enabling efficient multimodal assessments in a single experiment.
Applying this arrayed Perturb-seq platform in TF-iMG, we profiled MG responses to diverse disease-relevant stimuli, characterizing 6 transcriptomic states and 20 phenotypic measures to build a comprehensive MG state reference. IL1B and IL4 robustly induced disease-associated pro/anti-inflammatory state shifts. IL1B/IL4 pathway-wide genetic perturbations validated KO efficiency and demonstrated efficient Target ID workflows. Scaling up, we profiled a panel of putative regulators of MG states, revealing strong pro/anti-inflammatory shifts with distinct disease-associated microglia (DAM) signatures.
This study presents the TF-iMG model and an arrayed Perturb-seq platform to enable multimodal dissection in MG, incorporating scRNA-seq, cytokine analysis, and phenotypic profiling. Their low-cost, customizable design may offer broad applications in Target ID and drug discovery beyond MG model.

Disclosures: L. Ju: A. Employment/Salary (full or part-time); Novartis Biomedical Research. 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.; Novartis Biomedical Research. **M. LaBranche:** A. Employment/Salary (full or part-time); Novartis Biomedical Research. 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.; Novartis Biomedical Research. **S. Hromadka:** A. Employment/Salary (full or part-time); Novartis Biomedical Research. 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.; Novartis Biomedical Research. **J. Li:** A. Employment/Salary (full or part-time); Novartis Biomedical Research. 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.; Novartis Biomedical Research. **K. Worringer:** A. Employment/Salary (full or part-time); Novartis Biomedical Research. 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.; Novartis Biomedical Research. **C. Freyre:** A. Employment/Salary (full or part-time); Novartis Biomedical Research. 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.; Novartis Biomedical Research. **J. Hsiao:** A.

Employment/Salary (full or part-time); Novartis Biomedical Research. 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.; Novartis Biomedical Research.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.17/LBP117

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Microglial development in the eye and the potential of eye microglia as a marker for changes in the brain in health and disease

Authors: *R. LI;
UCL, London,UCL IfWH, United Kingdom

Abstract: 'The eye is the window to the soul,' but for the developing newborn, it may also be the window to the brain. Hypoxic-ischemic encephalopathy (HIE) is a leading cause of neonatal mortality and disability, with male newborns showing greater vulnerability for reasons that remain unclear. Current diagnostics rely on delayed MRI, leaving no rapid, sensitive, noninvasive method to identify HI within the therapeutic window. As the retina is an anatomical and developmental extension of the central nervous system (CNS) and microglia are its first immune responders, I hypothesized that eye microglia and tear-derived extracellular vesicles (EVs) could provide as early markers of neonatal HI.In healthy C57BL/6J mice (n=5/sex/age), I mapped microglial morphologies from postnatal day P0-P28 in brain and retina using IBA1 immunohistochemistry/immunofluorescence, morphology-based classification, and ramification index (two-way ANOVA, Tukey). Retinal microglia matured 3 days later than brain microglia ($p=0.0001$; brain P0 ≈ retina P3). At P0-P1 in brain, females had more amoeboid cells (P0: 12.1±0.5% vs males 10.0±0.4%, $p=0.002$), whereas males had more ramified cells (P0: 72.6±1.2% vs females 49.6±1.3%, $p<0.0001$). In retina, the pattern inverted at P0 (males 40.4±2.0% amoeboid vs females 28.2±1.8%, $p<0.0001$), reversing by P3.At P9, unilateral carotid ligation + 10% O_2/90% N_2 for 60 min induced robust amoeboid increases in injured (left) brain ($F(2,36)=94.38$, $p=4.8\times10^{-15}$) and retina ($F(2,26)=14.77$, $p=5.2\times10^{-5}$), with smaller but significant contralateral effects (brain +18%, retina +9%, $p<0.05$). Ramified fractions remained statistically unchanged, indicating amoeboid activation as the principal remodeling.To test EVs as biomarkers, I extracted vesicles from eye lavage (simulating tears) 60 min post-HI using a µL-scale ultracentrifugation protocol. Nanoparticle tracking showed significant group differences (males: left $F(2,36)=118.1$, $p=1.2\times10^{-16}$; females: right $F(2,36)=142.4$, $p=1.2\times10^{-18}$). In males, injured eyes had higher EVs vs sham ($+6.77\times10^{9}$/mL, $p<10^{-11}$) but lower vs naïve; females showed increases vs both controls. Both sexes shifted toward smaller EVs (<100 nm), most pronounced contralaterally, though not statistically significant.Tissue-cleared brain/retina with AI-based 3D mapping revealed spatial microglial paralleling EV changes, supporting a

mechanistic link between eye immune status and CNS injury. These findings establish retinal microglia and tear EVs as sex-sensitive, non-invasive biomarkers capable of detecting neonatal HIE with direct translational potential for bedside screening and personalized neuroprotection.

Disclosures: R. Li: None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.18/LBP118

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: CCCRP (CO240045)

Title: Impact of bupivacaine and bitopertin on neuroinflammatory responses in bv2 microglial cells

Authors: *B. P. CHEPPUDIRA[1], A. FRIESENHAHN[2], A. TREVINO[2], C. BROYLES[2], N. DAVIDSON[2], C. HINOJOSA-LABORDE[3,2];
[1]Institute of Surgical Research, SAN ANTONIO, TX; [2]US Army Institute of Surgical Research, JBSA Fort Sam Houston, TX; [3]US Army Institute of Surgical Research, Fort Sam Houston, TX

Abstract: Bupivacaine HCl is a widely used local anesthetic to prevent pain during various medical procedures. It exerts its analgesic effects by binding to voltage-gated sodium channels. While often combined with other medications to enhance pain relief, repeated or high-dose administration, especially in conjunction with opioids—can lead to adverse effects such as allergic reactions and central nervous system (CNS) depression. Bitopertin is a glycine transporter 1 (GlyT1) inhibitor that increases levels of the neurotransmitter glycine by inhibiting its reuptake from the synaptic cleft. Recent reports indicate that GlyT1 inhibitors can be effective analgesics. Yet, whether bupivacaine can exert synergistic analgesia with bitopertin is still unknown. In the present study, the nature of bupivacaine-bitopertin anti-inflammatory interaction was evaluated in vitro using lipopolysaccharide (LPS)-induced SIM-BV-2 microglia cells.SIM-BV2 microglial cells were exposed to varying concentrations of bupivacaine (1, 0.5, 0.1, and 0.01 mM) and bitopertin (50, 25, 10, and 5 μM), both individually and in combination. After two hours, the cells were stimulated with lipopolysaccharide (LPS, 0.5 μg/mL). Twenty-four hours following LPS exposure, the culture supernatants were collected and analyzed for pro-inflammatory cytokines TNF-α and IL-6 using the ELISA method. Additionally, the impact of bupivacaine and bitopertin on GlyT1 transporter expression in microglial cells was assessed via immunofluorescence.Increased level of TNF-α and IL-6 were observed in LPS-challenged BV-2 cell culture. Bupivacaine and bitopertin treatments showed dose-dependent reduction in pro-inflammatory mediators in the LPS-challenged BV-2 cells. Further combination of bupivacaine and bitopertin at 1:1 fixed ratio of their ED50 doses enhanced inhibition of release of pro-inflammatory mediators. Additionally, there were no marked differences between bupivacaine,

bitopertin, or combination of them on GlyT1 expression levels in the LPS-treated BV2 cells.Our initial results suggest that bupivacaine and bitopertin synergistically inhibits the inflammatory responses in activated microglia. Combination of these drugs holds promise as a potential therapeutic strategy to improve efficacy and reduce neuroinflammation.

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Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.19/LBP119

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Microglial dynamics in response to recurring capillary injury in vivo

Authors: *F. V. ARMAS[1], C. E. BROWN[2];
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Abstract: Cerebral microbleeds (CMBs) are small, chronic hemorrhages resulting from microvascular rupture that are often asymptomatic but have been linked to cognitive impairment, likely mediated by persistent neuroinflammation following injury. This neuroinflammatory response is orchestrated by the brain's diverse array of cells that collectively protect its function and integrity, with microglia playing a role as the central nervous system's resident sentinel. These highly dynamic cells respond to injuries, such as CMBs, by migrating to the area of insult, where they modulate inflammation and facilitate tissue repair. Additionally, microbleeds often recur, highlighting a need to understand microglial response to repeated injuries *in vivo*. In this study, we utilized two-photon microscopy to characterize microglial dynamics following successive microbleeds. To achieve this, we performed chronic cranial window implantation on adult mice that express Cre-dependent fluorescent reporter tdTomato, and tamoxifen-inducible microglia-specific Cre recombinase for real time imaging of microglia. Following recovery, a microbleed is induced by ablating cortical capillaries using a femtosecond laser. The induction of CMBs occurred repeatedly over a four-week period, with each microbleed separated by a week. Preliminary findings indicate a gradual decrease in the percentage of migrating microglia with each additional bleed. Notably, cells that were mobile after the first event displayed reduced mobility and shorter displacements in later bleeds. However, tracking individual cells across multiple bleeds demonstrated that microglia identified as mobile after the first injury are more likely to exhibit continued mobility during later bleeds, whereas those categorized as stable rarely transitioned to a mobile phenotype. Continuing experiments are focused on further evaluating microglial migration, phagocytic activity, and morphological changes with repeated CMBs. Investigating how microglia change their behaviour in response to recurring insults may

yield critical insights into the neuroinflammatory regulation and injury adaptation within the brain.

Disclosures: F.V. Armas: None. **C.E. Brown:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.20/LBP120

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH UL1TR002378
NIH R21NS136877
NIH R01AG065611
NIH RF1AG079256
NIH R01MH139822

Title: SARS-CoV-2 induces variant-specific metabolic remodeling and inflammatory responses in human iPSC-derived microglia

Authors: *C. MICHALSKI[1], J. LECHER[2], S. REZAEI[2], J. MOUA[2], W. NIU[3], L. CHENG[2], S. SHOOTER[2], R. DE[2], R. SCHINAZI[2], Z. WEN[4];
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Abstract: SARS-CoV-2 infection frequently leads to persistent (non-)respiratory symptoms termed Post-Acute Sequelae of COVID-19 (PASC) or “Long COVID”. Symptoms can vary substantially between individuals but often involve the central nervous system, presenting as depression, fatigue, or cognitive dysfunction (“brain fog”). The molecular mechanisms underlying Neuro-PASC remain poorly understood, hindering the development of effective treatment strategies. While neuroinflammation has been proposed as a key driver, the human microglial response to SARS-CoV-2 remains unclear.
Here, we utilized induced pluripotent stem cell (iPSC) technology to investigate the impact of SARS-CoV-2 on human microglia in a physiologically relevant model. We examined the microglial response to three distinct SARS-CoV-2 variants - Washington, Delta, and Omicron - and assessed transcriptomic and functional responses 48 hr post-infection. While each variant produced a distinct transcriptomic response, all variants led to remodeling of inflammatory and metabolic pathways, including lipid and mitochondrial metabolism. Significantly, the transcriptomic signature induced by in vitro infection of human microglia overlapped with that observed in microglia of postmortem COVID-19 studies ($p<0.05$, Fisher’s exact test). Using flow cytometry and multiplex cytokine profiling, we confirmed that SARS-CoV-2 induced variant-specific production of cytokines (e.g., production of CCL2 with Delta and CCL3 with

Omicron; $p<0.001$, 1-way ANOVA followed by Dunnett's multiple comparisons test comparing each strain vs mock) and led to upregulation of microglial activation (CD38 and CD68) and senescence (PD-L1, γH2AX) markers. SARS-CoV-2 infection also led to cholesterol production as well as increased expression of APOE and the cholesterol efflux pumps ABCA1 and ABCG1. Interestingly, inflammatory responses to SARS-CoV-2 were intensified in microglia carrying APOE4 ($p<0.0001$; CCL2 or CCL3 production by SARS-CoV-2 Washington infected APOE4 vs APOE3 carrying microglia), a major genetic risk factor for Alzheimer's Disease, suggesting that individuals with a genetic predisposition to Alzheimer's disease may be at increased risk for severe Neuro-PASC. Lastly, we also provide evidence that the SARS-CoV-2-mediated microglial activation leads to neuronal damage as demonstrated by increased levels of neurofilament light chain in co-culture experiments ($p<0.0001$).
Overall, our data offer valuable insights into how SARS-CoV-2 strains affect human microglia and could help identify new diagnostic and therapeutic options for treating Neuro-PASC.

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Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.21/LBP121

Topic: B.09. Glial Mechanisms

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NRF Grants RS-2024-00349908
KHIDI Grant RS-2024-00405120
KBSI Grant RS-2024-004-4574

Title: Functional specialization of border-associated macrophages is defined by niche-specific transcriptomic and ultrastructural profiles in mouse and human

Authors: *D. KIM[1,2], T.-R. T. RIEW[1,2];
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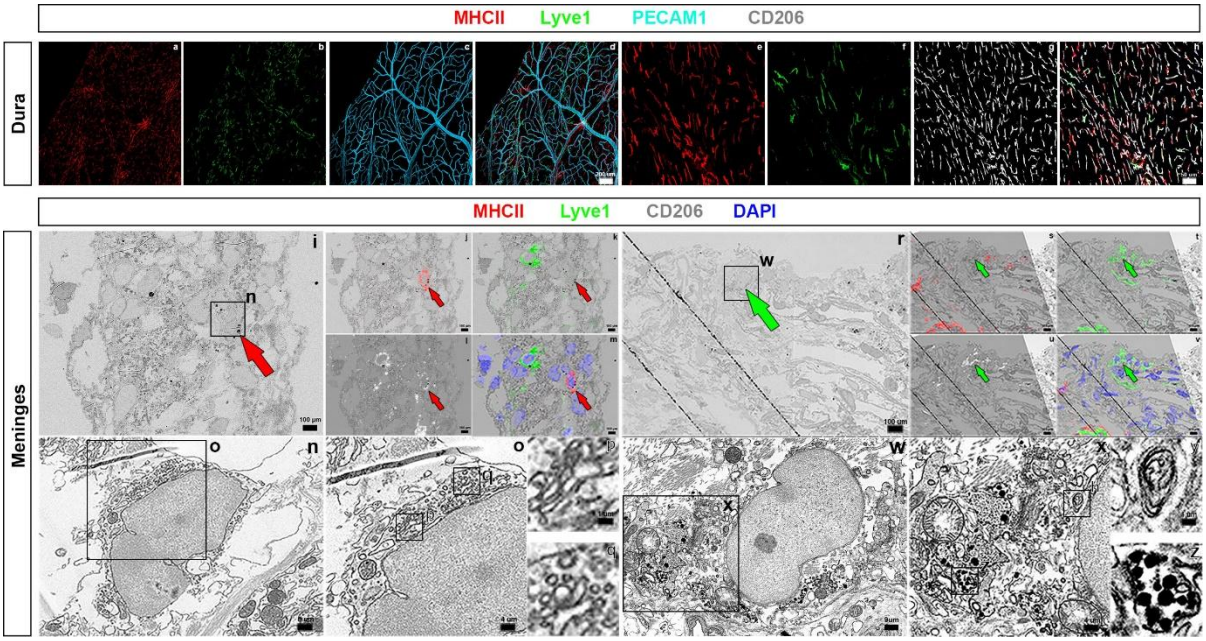
Abstract: Border-associated macrophages (BAMs) are a specialized population of tissue-resident macrophages at interfaces between the central nervous system and the periphery, including the meninges, choroid plexus, and perivascular spaces. Meningeal macrophages are categorized into dural and leptomeningeal types, which differ both anatomically and transcriptomically. Differential expression of MHC Class II (MHCII) and Lyve1 is a hallmark of this heterogeneity. We conducted a multi-modal investigation to 1) validate these transcriptomic distinctions, 2) determine if they translate to protein and ultrastructural features, and 3) assess

their conservation in humans. By integrating single-cell RNA sequencing datasets from mice and humans, we confirmed regional heterogeneity of BAMs. Dural macrophages were predominantly MHCII-high, while leptomeningeal and perivascular macrophages were Lyve1-high. Within MHCII-high dural cells, we identified a subtype with monocyte-like transcriptomic features and low expression of canonical BAM genes, distinct from another subtype resembling differentiated, tissue-resident macrophages. Lyve1^{+} BAMs contained abundant phagocytic inclusions, autophagosomes, and lipid droplets, consistent with roles in phagocytosis and metabolic support. In contrast, MHCII^{+} BAMs exhibited a well-developed endoplasmic reticulum, typical of antigen-presenting cells. We also identified a novel BAM subpopulation with low MHCII and Lyve1 expression, enriched for interferon (IFN)-responsive genes. Human single-cell data showed a conserved specialization pattern, including segregation of MHCII^{+} and Lyve1^{+} BAMs and an IFN-responsive cluster. Histological analysis of postmortem human brain confirmed spatial localization of these subtypes. Our study provides a multi-modal atlas of BAMs, demonstrating that their functional specialization is closely linked to anatomical niches and defined by distinct transcriptomic and ultrastructural features.



Disclosures: D. Kim: None. **T.T. Riew:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

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Program #/Poster #: LBP011.22/LBP122

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NSTC114-2221-E-155-009-MY2
NSTC114-2321-B-418-003

Title: Normative modeling across aging relates peripheral immune subsets to individualized brain structural deviations

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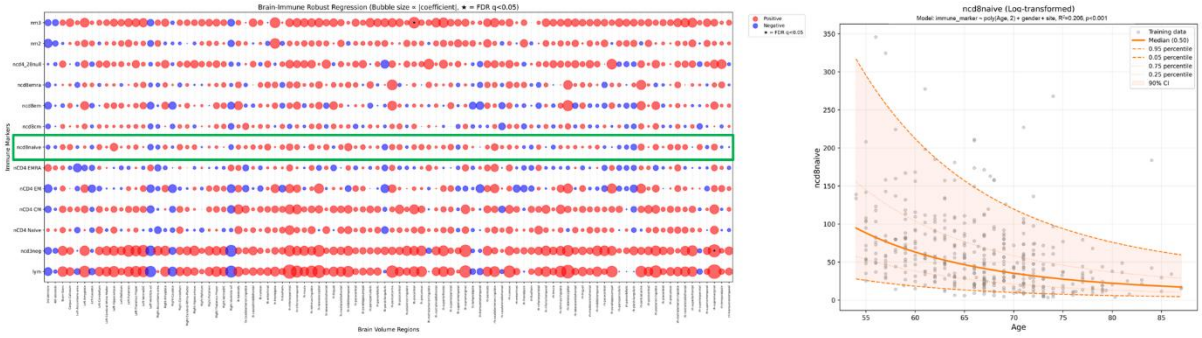
Abstract: Aging is characterized by cortical and subcortical structural changes and by immunosenescence; however, the links between specific circulating immune-cell subsets and regional brain integrity remain unclear. Here we established age-dependent normative models of brain structural MRI morphometry and peripheral lymphocyte/monocyte subsets using Ridge regression adjusted for sex and site for N=416 community-dwelling healthy older adults (54-87 years). Each brain MRI data was parcellated to 94 subregions to calculate their thickness or volume using DL+DiReCT, a deep-learning-based toolkit. Peripheral immune phenotyping used bead-based single-platform flow cytometry on EDTA whole blood to derive absolute counts of lymphocyte (T-cell)/monocyte subsets. Individual deviations from brain normative models were calculated as z-scores. Robust regression assessed the association between immune and brain structural deviations of N=99 testing set (N=99; 55-88 years). Robust regression with FDR correction revealed that higher levels of CD3-negative lymphocytes were strongly linked to greater volume in the right supramaginal gyrus (β=0.69, q=0.016), and higher levels of nm3 (CD14-CD16+) with greater volume in the left precentral gyrus (β=0.53, q=0.037). Specifically, normative trajectories also showed an age-related reduction in CD8+ naïve T-cells (R^2=0.21, p<0.001) that related to lower structural deviation z-scores (thickness or volume) in the left middle temporal gyrus, limbic and precentral regions, and the right frontal pole. Age-adjusted normative modeling shows immune subsets in relation to individualized brain deviations across motor, language/semantic, executive, and mnemonic networks, indicating direct brain-immune links and motivating longitudinal and mechanistic studies.



Disclosures: E. Chiu: None. **Y. Chuang:** None. **Y. Chiu:** None. **Y. Shih:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

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Title: Immune isoform diversity revealed by single-cell long-read sequencing establishes a framework for investigating peripheral immune contributions to neurological disease

Authors: *P. H. DOYLE[1,2], M. PAGE[1,2,3], B. AGUZZOLI HEBERLE[1,2], J. A. BRANDON[1,3,2], A. M. STOWE[4,2], M. EBBERT[1,3,2];
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Abstract: Peripheral blood mononuclear cells (PBMCs) are major mediators of systemic inflammation. Changes in their abundance, as well as their gene and protein expression profiles, are linked to neurodegenerative disease via dysregulated immune signaling. Since clinical neural samples are rarely accessible, biomarkers for neurological diseases are difficult to identify; however, PBMCs offer a peripheral window into immune contributions in neurological disorders and a potential biomarker source. The isoform-level transcriptomic landscape in PBMCs remains largely unexplored due to the limitations of short-read sequencing—the conventional approach. We adapted PIPseq, a benchtop single-cell technique, to be used with long-read sequencing and performed the first single-cell long-read profiling of PBMCs to characterize isoform expression and evaluate its utility in revealing isoform-driven immune mechanisms relevant to neurodegeneration. We prepared two technical replicates of a human PBMC sample and performed deep long-read sequencing using Oxford Nanopore Technologies' PromethION (3 flow cells each), yielding 492M reads. A custom barcode recovery pipeline enhanced read yield before pseudobulk isoform discovery with Bambu. Cell clustering was performed at the gene- and isoform-level and characterized by canonical cell-type markers. AutoZI modeling addressed depth limitations in isoform detection. We discovered 166 novel isoforms, including from unannotated genes. Cell-type-specific isoform signatures resolved major PBMC populations (TCell, BCell, Natural Killer, Monocyte-derived, and Megakaryocytes) and TCell subtypes (memory, effector, cytotoxic, transition). While canonical isoforms localized to the expected cell-type clusters, small protein-coding isoforms of immune marker genes were enriched in

unexpected clusters, suggesting previously unrecognized regulatory roles. This exploratory study demonstrates the feasibility and value of long-read single-cell sequencing for isoform discovery in PBMCs. Isoform-level studies reveal hidden diversity in immune populations, highlighting how transcriptional regulation differs according to cell identity and specialization. This establishes a foundation for using isoform-level studies and PBMCs to investigate systemic immune responses relevant to neurodegeneration.

Disclosures: **P.H. Doyle:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Fluent Biosciences. **M. Page:** None. **B. Aguzzoli Heberle:** None. **J.A. Brandon:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Fluent Biosciences. **A.M. Stowe:** None. **M. Ebbert:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Fluent Biosciences.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.24/LBP124

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Triveni

Title: KLK7 as a key mediator of dry skin itch

Authors: ***A. IIJIMA**, R. SHIBUYA, F. GAO, N. D. ROSSEN, N. P. BISCOLA, K. ANTHONY, H. HU, B. KIM;
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Abstract: Chronic itch is a persistent and debilitating sensation affecting up to 20% of the population and is associated with marked reduction in quality of life. The pathophysiology of chronic itch has been primarily studied in inflammatory skin disorders such as atopic dermatitis (AD). However, other chronic itch conditions are accompanied by minimal inflammation such as chronic pruritus of unknown origin (CPUO). CPUO is characterized by aging-associated skin barrier dysfunction and dry skin. Epidermal barrier function is tightly regulated by balancing epithelial turnover, whereby serine proteases such as kallikreins (KLK) regulate this process. While aberrant activities of KLKs such as KLK5 and KLK7 are already implicated in AD, it remains unknown if they play a role in CPUO. Here, we investigated the contribution of KLKs to dry-skin itch in the acetone/ether-water (AEW)-induced dry skin itch mouse model, which recapitulates many of the features of CPUO in humans. Indeed, AEW-induced itch resulted in upregulation of *Klk5* and *Klk7* in skin. We also found that systemic administration of a KLK-7 neutralizing antibody significantly reduced itch, while anti-KLK5 had no effect. Further, $Klk7^{-/-}$ mice exhibited attenuated scratching after AEW treatment compared with wild-type control mice. Next, we tested if KLK7 alone can induce itch. Intradermal injection of recombinant murine KLK7 into naïve murine skin elicited acute itch, whereas a catalytically inactive KLK7

mutant did not. Our preliminary data suggest that the serine protease KLK7, important for barrier homeostasis, promotes chronic itch through an unknown mechanism. IL-33 is an 'alarmin' released from keratinocytes upon damage or stress. Our preliminary studies show that IL-33 is elevated in the sera of patients with CPUO compared to healthy controls. Further, a recent study showed that IL-33 is required for the development of dry skin itch in the AEW model by directly activating sensory neurons. The activity of IL-33 is dramatically enhanced upon cleavage by proteases. We found that KLK7, but not the catalytically inactive mutant or KLK5, cleaves pro-IL-33 to its active form. Understanding the mechanisms of IL-33 and KLK7-mediated dry skin itch will inform the development of effective and novel therapies for itch in CPUO and other dry skin-related conditions.

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Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.25/LBP125

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Development of a swine model of temporomandibular joint pain using retrodiscal complete freund's adjuvant injection - a preliminary study

Authors: *S. RAMAN[1], C. L. RENN[2], M.-K. CHUNG[3];
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Abstract: Swarnalakshmi Raman[1,3], Martin Guzman[2,3], Cynthia Renn[2,3], Man-Kyo Chung[1,3]1Department of Neural and Pain Sciences, School of Dentistry, [2]Department of Pain & Translational Symptom Science, University of Maryland School of Nursing,[3]UM Center to Advance Chronic Pain Research, University of Maryland Baltimore, Baltimore MD 21201

Temporomandibular disorders (TMD) are a common group of chronic orofacial pain conditions, often involving pain in the temporomandibular joint (TMJ) due to inflammation or trauma. Despite their high prevalence and impact on quality of life, the underlying pain mechanisms remain poorly understood, and no consistently effective treatments are available. A better understanding of TMJ pain etiology is critical for developing targeted therapeutics. The objective of this study was to develop and validate a translational, preclinical swine model of TMJ pain using Sinclair miniature pigs (Nanopigs, 6-12 months old, Male). This model was selected due to the similarities in temporomandibular anatomy and physiology, including comparable disc morphology, cartilage thickness, and innervation patterns. To induce localized inflammation,

varying concentrations of Complete Freund's Adjuvant (CFA; 50-200 µg) were injected into the left TMJ retrodiscal tissue, while saline was injected into the right TMJ as a control. Pain-related behaviors were evaluated using von Frey filaments and pressure algometry, complemented by continuous home-pen video monitoring to capture spontaneous activity, feeding, and sleep. Results showed dose-dependent mechanical hypersensitivity on the CFA-injected side. Pigs receiving 200 µg CFA exhibited clear responses to lower-force von Frey filaments and sustained pressure threshold reductions up to Day 28. In contrast, saline-injected sides maintained stable high thresholds with minimal variations. On Day 28, pigs were euthanized, and tissues from the trigeminal ganglion, brain, and TMJ were collected for further analysis. To assess therapeutic responsiveness, a separate cohort received daily intramuscular carprofen (4 mg/kg) for seven days, beginning on Day 8 post-CFA. Treatment yielded variable and generally limited analgesic effects which reflects a clinically relevant pattern of partial responsiveness to NSAID therapy, commonly observed in patients with temporomandibular disorders. These results demonstrate that retrodiscal CFA injection in the pig TMJ induces sustained, dose-dependent mechanical allodynia. This supports the miniature pig as a viable translational model for chronic TMJ pain, suitable for investigating the underlying mechanisms and testing potential treatments.

Disclosures: S. Raman: None. **C.L. Renn:** None. **M. Chung:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.26/LBP126

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Title: Investigating Sympathetic Nervous System-Mediated Immune Modulation in Pulmonary Fibrosis

Authors: *B. PAN, R. SALAMON, X. SUN;
University of California, San Diego, San Diego, CA

Abstract: Pulmonary fibrosis (PF) is a chronic, progressive lung disease characterized by immune dysregulation and fibrotic remodeling. Despite rising global incidence, no current therapies can halt or reverse PF, highlighting the need to identify novel mechanisms driving disease progression. The sympathetic nervous system (SNS) is increasingly recognized as a regulator of fibrosis, yet its role in shaping immune responses during PF remains unclear. We hypothesized that SNS signaling promotes a pro-inflammatory landscape during early fibrotic injury.
To investigate this, we used a bleomycin (BLM)-induced PF mouse model with or without 6-hydroxydopamine (6-OHDA)-mediated SNS ablation. Immune cell populations from myeloid and lymphoid lineages were analyzed by flow cytometry at 7 days post-BLM, a key window of acute immune influx in PF. We found that SNS ablation reduced total immune recruitment, with striking decreases in neutrophil and monocyte populations compared to saline controls. As

monocytes are well-established drivers of PF progression, these results identify a previously unrecognized role for SNS activity in shaping the early inflammatory landscape that can prime fibrotic remodeling.
Building on this, we recently performed cytokine profiling to assess inflammatory states. Most notably, new data from these analyses demonstrated that SNS ablation led to a significant reduction in monocyte chemoattractant protein-1 (MCP-1), a chemokine strongly linked to monocyte recruitment and fibrosis. This novel finding suggests that SNS-dependent regulation of MCP-1 may act as a key mechanism linking neuroimmune signaling to the initiation of fibrotic processes.
Together, our findings indicate a selective role for SNS signaling in regulating neutrophil and monocyte dynamics through MCP-1 as a potential neuroimmune mechanism driving early PF progression. These novel insights set the stage for future studies aimed at targeting early neuroimmune pathways as a strategy to halt fibrotic remodeling.

Disclosures: B. Pan: None. **R. Salamon:** None. **X. Sun:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.27/LBP127

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NRF (RS-2025-00555372)

Title: Characterizing an in vivo model of aminoglycoside ototoxicity in mice

Authors: *S. CHOI;
Otorhinolaryngology, Pusan National University Hospital, Busan, Korea, Republic of

Abstract: Background: Hair cells are vulnerable to damage caused by excessive noise, aging, and ototoxic agents. Aminoglycoside ototoxicity is a well-established cause of sensorineural hearing loss and degeneration of outer hair cells is the primary cause of hearing loss induced by aminoglycoside. Macrophages, the major resident immune cells in the cochlea that become activated in response to tissue injury, are important drivers of both inflammatory and tissue repair responses. However, the role of macrophages in hair cell regeneration is conflicting and warrants further investigation. Here, we use a aminoglycoside-induced ototoxicity mice model to examine whether macrophages play a role in hearing loss and outer hair cell loss in response to aminoglycoside. Methods: Csf1rΔFIRE/ΔFIRE mice were used as a harbor a specific deletion of the microglial-associated fms intronic regulatory element (FIRE) enhancer of Csf1r locus to produce mice that lack microglia but retain peripheral macrophage populations. C57/BL6 mice were used as WT controls. For FIRE mice, a dose of 850 mg/kg body weight kanamycin sulfate was given twice daily for 15 consecutive days by subcutaneous injection. Control mice were injected twice daily with saline for 15 consecutive days. We assessed hearing immediately after

15 consecutive days of injection and 3 weeks after the last dose of kanamycin. Results: In our aminoglycoside-ototoxicity model in mice, the number of outer hair cells (OHCs) decreased from the apex to the basal turn of cochlea. There was significant OHC loss in the basal turn ($P < 0.01$), however there was no significant loss of IHCs. ABR and DPOAE were measured before and 21 d after the injection. Kanamycin injection led to significant elevation of ABR and DPOAE thresholds in frequencies at 16, 22.6, and 32 kHz ($P < 0.001$). Furthermore, OHCs can uptake Texas Red gentamicin conjugate (GTTR) both in vitro and in vivo throughout the whole cochlea. Conclusions: Kanamycin induces outer hair cell loss after 15 consecutive days of administration, and the degree of hair cell loss accompanied the significant increase in the ABR and DPOAE threshold in the kanamycin treated group. Future directions will use Csf1rΔFIRE/ΔFIRE mice which harbor a specific deletion of the microglial-associated fms intronic regulatory element (FIRE) enhancer of Csf1r locus to produce mice that lack microglia but retain peripheral macrophage populations to examine whether macrophages play a role in hearing loss and outer hair cell loss in response to aminoglycoside.

Disclosures: S. Choi: None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.28/LBP128

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: TTUHSC School of Medicine

Title: Goji Berry Supplementation Reduces Pain Hypersensitivity Through Gut-Brain Axis Regulation of Amygdala and Colon Gene Expression in an LPS Induced Rat Model of Chronic Fatigue

Authors: *X. LIU[1], H. DESHMUKH[1], P.-H. LEE[1], P. PHAM[1], G. JI[2], T. KIRITOSHI[2], V. NEUGEBAUER[2], C.-L. SHEN[1];
[1]Pathology, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX; [2]Pharmacology and Neuroscience, Texas Tech. Univ. Hlth. Sci. Ctr., Lubbock, TX

Abstract: Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a debilitating disorder characterized by persistent fatigue, pain, neuroimmune dysregulation, and limited treatment options. The gut-brain axis is increasingly recognized as a critical pathway linking peripheral inflammation to central nervous system dysfunction. Goji berry (Lycium barbarum), traditionally used in Asian medicine, is rich in polysaccharides, flavonoids, and carotenoids that exhibit anti-inflammatory, antioxidant, and neuroprotective properties. These bioactivities make Goji a promising dietary intervention to target systemic inflammation and central neuroimmune imbalance. This study investigated whether dietary Goji berry supplementation could alleviate pain hypersensitivity and restore gene expression across the gut-brain axis in a

lipopolysaccharide (LPS)-induced rat CFS model. Male Sprague Dawley rats were randomly assigned to three groups: control (PBS, i.p., 2×/week), LPS (O111:B4, 250 μg/kg, i.p., 2×/week), and GOJI (LPS + 1% Goji diet) for six weeks (n=6-7/group). Mechanical pain sensitivity was assessed using the von Frey test. Gene expression in the right amygdala and colon was evaluated by quantitative real-time PCR (qRT-PCR), normalized to β-actin. Statistical analyses were performed using one-way ANOVA followed by Fisher's LSD post hoc test, with significance set at $p < 0.05$. LPS treatment significantly increased mechanical pain sensitivity compared to the control group, while Goji supplementation attenuated LPS-induced hypersensitivity. In the amygdala, LPS treatment downregulated PGC1α (mitochondrial biogenesis), Claudin-3 (tight junction), TLR2 (neuroimmune signaling), BDNF (neuroplasticity), and neurotransmission-related genes (GAT1, NMDAR2B, GABABR1). Goji reversed LPS-induced alterations, restoring gene expression toward control levels. In the colon, LPS upregulated pro-inflammatory cytokines (IL-1β, TNF-α), while downregulating SOD1 (an antioxidant marker), Claudin-3, and PGC-1α in the LPS model. Goji suppressed IL-1β and TNFα and increased SOD1, mitochondrial, and barrier-related gene expression. In summary, goji supplementation alleviates pain hypersensitivity in CFS-like rats by modulating neuroimmune, mitochondrial, synaptic, and barrier gene expression in both the amygdala and colon. These findings highlight Goji as a promising nutritional intervention that acts through gut-brain axis regulation to mitigate pain and systemic dysfunction in CFS.

Disclosures: X. Liu: None. **H. Deshmukh:** None. **P. Lee:** None. **P. Pham:** None. **G. Ji:** None. **T. Kiritoshi:** None. **V. Neugebauer:** None. **C. Shen:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.29/LBP129

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: HHMI Emerging Pathogens Initiative

Title: A lung-to-brain chemokine relay following respiratory infection drives white matter microglial activation and oligodendrocyte loss

Authors: *H. XU, T. PHAM, K. ASHLEY, A. NGUYEN, A. GERAGHTY, M. MONJE; Stanford University, Palo alto, CA

Abstract: Mild respiratory infections can result in microglial reactivity, consequently dysregulated oligodendroglial lineage cells, and persistent cognitive symptoms. However, the mechanisms by which peripheral immune activation results in central nervous system (CNS) immune reactivity remain incompletely understood. We hypothesized that a cytokine/chemokine relay originating in the lung contributes to neuroimmune activation and the downstream consequences in the brain. In a non-neuroinvasive mouse model of mild SARS-CoV-2 and H1N1

influenza infection, we observed selective microglial reactivity and oligodendrocyte loss in subcortical white matter 7 days after infection. We hypothesized that the chemokine CCL2 may initiate a relay from periphery to CNS. Peripheral (intravenous) administration of recombinant CCL2 phenocopies these effects, inducing widespread microglial reactivity and white matter-selective oligodendrocyte loss. This was accompanied by elevated CCL2 and CCL5 in cerebrospinal fluid, supporting the concept of a peripheral-to-central signaling cascade. We focused on CCR3 as a potential downstream effector because it is a known receptor for CCL5. Prior work from our lab showed that CCR3 inhibition mitigated white matter impairment in a distinct context after CAR-T therapy. Although the upstream ligands differ, this highlighted CCR3 as a candidate mediator of pathogenic microglia-oligodendrocyte interactions. In our current model, systemic administration of a BBB-permeable CCR3 antagonist partially rescues oligodendrocyte loss, suggesting that CCL2-CCL5-CCR3 signaling may contribute to the observed pathology. Ongoing work is also testing whether early CCR2 blockade can interrupt this putative chemokine relay at its initiation. Taken together, these findings provide emerging evidence for a peripheral inflammatory cascade that engages CNS chemokine pathways and perturbs white matter glial homeostasis. Continued investigation of this lung-to-brain communication axis may offer insight into the mechanisms underlying post-acute infection syndrome (PAIS)-associated cognitive impairment and identify new opportunities for therapeutic intervention.

Disclosures: H. Xu: None. **T. Pham:** None. **K. Ashley:** None. **A. Nguyen:** None. **A. Geraghty:** None. **M. Monje:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.30/LBP130

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant #R25GM060566-22
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Burroughs Wellcome PDEP

Title: Estrogen receptor activation as a potential modulator for HIV induced neuroinflammation

Authors: *R. COOK[1], K. WILLIAMS[2], J. DE VASTEY[1], M. HICKSON[1];
[1]Spelman College, Atlanta, GA; [2]Environmental and Health Sciences, Spelman College, Atlanta, GA

Abstract: HIV Associated Neurocognitive Disorder (HAND) is seen in 30-50% of people living with Human Immunodeficiency Virus (HIV). HAND is characterized by changes in cognition, memory loss, motor skill loss, and behavioral changes. HAND occurs upon the early entrance of

HIV into the central nervous system through infected monocytes/macrophages, which release unidentified neurotoxins and lead to neuroinflammation. Current HIV therapeutics cannot cross the blood-brain barrier and novel therapeutics are needed. Our lab aims to understand whether the anti-inflammatory properties of estrogen and estrogen receptor modulators could serve as a potential therapeutic avenue for reducing HIV-induced neuroinflammation. We hypothesize that natural and selective estrogen modulators will block HIV-induced proinflammatory phenotypes and neurotoxin production in human macrophages. To test this, we stimulated macrophages with HIV plus or minus natural estrogen and G1, a selective activator to the non-classical estrogen receptor GPER. After stimulation, macrophages were fixed and stained with an F actin dye to assess morphological changes. We also collected protein lysates to measure changes in the anti-inflammatory ERK pathway. Conditioned media from macrophages was collected to measure changes in secretory profiles and neurotoxicity. HIV stimulation resulted in proinflammatory morphologies, increased neurotoxin production and reduced growth factor secretion. Estrogen and G1 induced anti-inflammatory morphologies, reduced neurotoxin secretion and increased growth factor. 10-minute stimulation of macrophage with HIV lead to a slight increase in activation of the ERK. Co-stimulation with Estrogen reversed the phosphorylation of ERK. Given the current results, activation of estrogen receptors such as GPER may reduce HIV induced neuroinflammation and serve as a potential pathway to target in future therapeutic avenues.

Disclosures: R. Cook: None. **K. Williams:** None. **J. de Vastey:** None. **M. Hickson:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.31/LBP131

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: Summer Scholarship and Research Program Funding from Ohio Wesleyan University
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Title: Combined antiretroviral therapy reduces SIV-induced astrocyte morphological alterations in the hippocampus

Authors: S. PANDEY[1], *M. HORN[2,1];
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Abstract: HIV remains a significant global health issue with many individuals now living longer due to combined antiretroviral therapy (cART). However, despite the improvement in lifespan, cognitive decline in people living with HIV continues to occur earlier than in the uninfected population. The effects of long-term cART on the brain, and especially on astrocytes, remains poorly understood. In this study, we aimed to determine how cART affects astrocyte morphology in the hippocampus, since previous work has shown this brain region to be especially sensitive to infection. We hypothesized that the treatment of Simian immunodeficiency virus (SIV)-infected rhesus macaques with cART would reduce astrocyte morphological changes associated with SIV infection. To test this, we used fluorescence microscopy to analyze archival hippocampal tissue from three groups of rhesus macaques aged 4 - 14 years: SIV-naive controls (Naive; n = 3), SIV-positive animals without treatment (SIV; n = 2), and SIV-positive animals receiving cART (SIV-cART; n = 5). Both male and female animals were included, but due to the scarcity of female rhesus macaque tissues, the study was not powered to analyze sex differences. To assess changes in astrocyte morphology across these groups, we remained blinded while tracing astrocytes using Neurolucida® software from MBF Bioscience. Our findings demonstrate that relative to the SIV group, the SIV-cART group had branch points appear more gradually, at larger radii (20 - 40 μm) with a higher number and length of branches further from the cell body. We also found that cART treated animals had a larger cell body area than seen in the SIV-only animals. Together, these data demonstrate that cART treatment alters astrocyte morphology from that seen in SIV infection and may suggest a healing or protective effect.

Disclosures: S. Pandey: None. **M. Horn:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

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Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: This work was performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344. IM Release #: LLNL-ABS-2006598

Title: Functional and Molecular Characterization of Venezuelan Equine Encephalitis Virus Infection in Complex Neuronal Cultures

Authors: *B. AMIRI[1], N. GOSHI[2], C. BOGGURI[3], M. RANGEL[3], A. SEBASTIAN[1], N. O. FISCHER[4], H. A. ENRIGHT[5];
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Abstract: Venezuelan equine encephalitis virus (VEEV) is a mosquito-borne alphavirus that targets the central nervous system (CNS). VEEV infection and the associated neuroinflammatory response can lead to severe symptoms including cerebral edema, long lasting neurological deficits, and death. We investigated the effects of an attenuated VEEV strain (TC-83) on human relevant neuronal cultures, with and without the presence of microglia to gain a better understanding on the importance of neuroinflammation on the observed response. Complex cultures of human iPSC-derived excitatory and inhibitory neurons, astrocytes, and microglia were cultured together at ratios mimicking the human cortex. These cultures were allowed to mature for 25 days to establish robust synaptic connections and network activity, after which they were inoculated with TC-83 at MOI 0.01. Electrophysiology, cytotoxicity, and transcriptomic profiling were assessed over a 96-hour period post-infection. Both co-cultures (containing excitatory/inhibitory neurons and astrocytes) and tri-cultures (containing excitatory/inhibitory neurons, astrocytes, and microglia) inoculated with TC-83 showed significant increases in viral titers at 48h and 96h post infection, indicating robust infection and viral replication within the cultures, which was not attenuated by the presence of microglia. Additionally, both co- and tri-cultures showed significantly reduced neural activity and bursting frequency starting at 48h post inoculation, with no significant differences between the two culture types. Single nuclei RNA sequencing at 96h showed a loss in astrocyte population, which corresponded to a slight (4-5%), but not statistically significant increase in cytotoxicity, in both culture types. Neurons exhibited upregulation of axon regeneration-associated genes and downregulation of synaptic genes, which may account for the sharp decline in neural activity that is not accompanied by neuron death. Microglia in the tri-culture showed an upregulation of many neuroinflammatory pathways, and bulk RNAseq from tri-cultures showed an upregulation of a subset of immune response associate genes specific to microglia not observed in the co-cultures, highlighting the importance of microglia in capturing the neuroinflammatory response to VEEV. Finally, we demonstrated the active form of the antiviral drug Molnupiravir (EIDD-1913), was able to reduce viral titers and rescue neural activity in both the co- and tri-cultures.

Disclosures: B. Amiri: None. **N. Goshi:** None. **C. Bogguri:** None. **M. Rangel:** None. **A. Sebastian:** None. **N.O. Fischer:** None. **H.A. Enright:** None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.33/LBP133

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NMRC Grant MOH-000558-00

Title: Comparison of human cerebral organoids infected with wild-type Zika versus attenuated DN-2 virus strains uncovers differences in host immune responses underlying viral pathogenesis

Authors: *J. CHUA;
Physiology, National University of Singapore, Singapore, Singapore

Abstract: Zika virus (ZIKV), a neurotropic virus, poses significant global health challenges because of its ability to cause severe neurological complications and congenital brain abnormalities. Prenatal ZIKV infection impairs early brain development. However, details of the molecular mechanisms driving their virulence remain incompletely understood. Here, we performed comparatively analyses of infection outcomes caused by 2 different ZIKV strains - wild-type (WT) ZIKV versus an attenuated strain (DN-2) - in human cerebral organoids (hCOs) to dissect host responses that could contribute to pathogenicity. Although both viral strains productively infected hCOs with indiscernible gross pathological changes, differences in host responses and subtypes of cells infected discriminate WT ZIKV from DN-2 infections. Single cell RNA sequencing analyses uncovered differently expressed genes (DEGs) that were common to both virus strains, as well as DEGs that were specific to either WT ZIKV or DN-2. For common DEGs, WT ZIKV infections elicited stronger expression of key genes involved in host immune response pathways, such as *IFIT2*, *DDX60*, *OAS1* and *XAF1*. Moreover, analyses of WT ZIKV-specific upregulated DEGs uncovered mobilisation of additional innate immune response pathways not found in DN-2. Additionally, while WT ZIKV infected a broad range of cell types in hCOs, DN-2 infections were predominantly limited to radial glial, which are neuroprogenitors essential for neurogenesis. These results highlight that differences in host immune responses and tropism distinguish neurotropic WT ZIKV and attenuated DN-2 infections, underscoring the mechanistic differences involved in pathogenicity. Our study provides further insights into mechanisms used by neurotrophic ZIKV to drive neuropathogenesis during infection of the developing brain.

Disclosures: J. Chua: None.

Late-Breaking Poster

LBP011: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP011.34/LBP134

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Wings for Life WFL-US-01/18

Title: C1q drives neural stem cell quiescence by regulating cell cycle and metabolism through BAI1

Authors: *Z. H. ELRACHID[1], K. M. PILTTI[2], A. LAKATOS[3], A. NAVA[4], V. NGUYEN[5], A. ZAHEDI[6], W. SONG[5], X. CHEN[5], A. PORTILLO[5], A. J. ANDERSON[7];
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California, Irvine, Los Angeles, CA; [5]University of California, Irvine, Irvine, CA; [6]Clinical Pharmacy Practices, University of California Irvine, Irvine, CA; [7]PM&R, University of California, Irvine, Irvine, CA

Abstract: C1q levels in the CNS are elevated by inflammation and neurovascular trauma, yet the consequences of C1q on the neural stem cell (NSC) regeneration response remain poorly understood. We report the novel finding that C1q can drive NSC quiescence, a reversible state of cell cycle arrest that is primarily characterized by decreased proliferation and metabolic function, and investigate the mechanisms by which C1q mediates this effect. We have recently identified novel C1q receptor candidates that enable direct receptor-mediated regulation of NSC behavior. One of these is Brain Angiogenesis Inhibitor 1 (BAI1), which has no previously discovered role in NSC. Here, we establish a direct BAI1-dependent role for C1q in NSC quiescence.
To investigate the role of C1q in NSC function, we exposed NSC to purified human C1q at physiological concentrations ranging from 0.1nM to 300nM, then assessed NSC proliferation and metabolism as outputs of quiescence. To measure proliferation, we performed BrdU and Edu incorporation assays on C1q-treated NSC. We then assessed the effects of C1q on metabolic function by measuring the NADH/NAD+ redox ratios and mitochondrial morphologies of C1q-treated NSC. To determine the role of BAI1 in the effect of C1q on NSC, we generated a BAI1 knockout (KO) NSC line using CRISPR/Cas9. We then tested the effects of BAI1 KO on proliferation, metabolism, and C1q binding to intracellular p32/gC1qR, a mitochondrial protein. To further investigate C1q interactions with BAI1 and p32, we utilized a pull-down assay to validate C1q interactions with BAI1 and p32 individually and in complex.
These data show that C1q exposure decreases NSC proliferation and induces a metabolic shift from oxidative phosphorylation to aerobic glycolysis (Warburg effect). BAI1 KO reverses these effects of C1q, identifying BAI1 as a critical mediator of C1q-driven NSC quiescence. With this, we show that BAI1 mediates C1q internalization, promotes an increase in intracellular C1q-p32 interactions, and decreases functionally available p32 as one mechanism of action. Decreased availability of p32 within the cell results in altered proliferation and metabolism, highlighting a novel mechanism by which BAI1 mediates C1q-driven NSC quiescence.

Disclosures: Z.H. Elrachid: None. **K.M. Piltti:** None. **A. Lakatos:** None. **A. Nava:** None. **V. Nguyen:** None. **A. Zahedi:** None. **W. Song:** None. **X. Chen:** None. **A. Portillo:** None. **A.J. Anderson:** None.

Late-Breaking Poster

LBP012: D.02. Ischemia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP012.01/LBP135

Topic: D.02. Ischemia

Title: Protective effects of apocynin on vascular dysfunction and remodeling in a rat model of vascular dementia

Authors: *P. THANGWONG[1], J. SENGKING[2], C. TOCHARUS[2], J. TOCHARUS[2];
[1]Walailak University, Nakhon Si thammarat, Thailand; [2]Chiang Mai University, Chiang Mai, Thailand

Abstract: BACKGROUND: Vascular dementia (VaD) is the second most common type of dementia, primarily caused by chronic cerebral hypoperfusion, leading to oxidative stress, neurovascular dysfunction, and cognitive impairment. Reduced cerebral blood flow results in endothelial dysfunction, impaired nitric oxide (NO) signaling, and vascular remodeling, which further exacerbate secondary pathological damage. Among the key molecular changes, increased inducible nitric oxide synthase (iNOS) and decreased endothelial nitric oxide synthase (eNOS) contribute to oxidative stress and vascular instability. Apocynin, a well-known NADPH oxidase inhibitor, exhibits antioxidant and anti-inflammatory properties, suggesting its potential in mitigating oxidative stress and improving vascular function. However, its protective effects on neurovascular integrity in cerebral hypoperfusion-induced VaD remain unclear. Hence, the aim of this study was to investigate the protective effects of apocynin on vascular dysfunction, and NO-related pathways in a rat model of cerebral hypoperfusion-induced VaD.
METHODS: Cerebral hypoperfusion was induced in male rats by bilateral common carotid artery occlusion (BCCAO) for 7 days. After surgery apocynin (25 mg/kg) was administered orally once daily during the entire period. On day 8, rats were euthanized for molecular and histological analyses. Vascular dysfunction was evaluated by measuring NO levels and the expression of iNOS and eNOS. Vascular remodeling was assessed by using lectin for vascular density and diameter and α-smooth muscle actin (α-SMA) for vascular integrity.
RESULTS: Compared with sham rats, BCCAO rats showed vascular dysfunction as evident by elevated NO levels (~1.6-fold), iNOS expression (~1.8-fold), and decreased eNOS expression (~0.5-fold). Furthermore, vascular remodeling was impaired, demonstrated by narrowed vascular diameter (~0.7-fold) and a partial reduction in α-SMA expression(~0.6-fold). Compared with BCCAO rats, treated with apocynin markedly attenuated vascular dysfunction by reducing NO levels (~0.5-fold) and iNOS expression (~0.5-fold) while enhancing eNOS expression (~1.8-fold). Additionally, it improved vascular remodeling by increasing vascular diameter (~1.4-fold) and enhancing α-SMA expression (~2.4-fold).
CONCLUSION: Apocynin effectively mitigated neurovascular alterations induced by cerebral hypoperfusion. Its protective effects were associated with improved nitric oxide signaling, reduced iNOS expression, increased eNOS expression, and restoration of vascular structure, including vascular diameter and α-SMA integrity.

Disclosures: P. Thangwong: None. **J. Sengking:** None. **C. Tocharus:** None. **J. Tocharus:** None.

Late-Breaking Poster

LBP012: D.02. Ischemia

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP012.02/LBP136

Topic: D.02. Ischemia

Support: SECIHTI Mexico Grant number CBF-2025-I-4046

Title: Hydrogen sulfide protects cardiac mitochondria after global cerebral ischemia-reperfusion

Authors: *K. SOLIS CRUZ[1], J. RAMIREZ C[2], A. SÁNCHEZ-LÓPEZ[1], D. CENTURIÓN[1]; [1]Departament of Pharmacobiology, Ctr. for Res. and Advanced Studies (CINVESTAV), Ciudad de México, Mexico; [2]Dept. of Pharmacol., Fac. of Medicine, Natl. Autonomous Univ. of Mexico UNAM, Ciudad de México, Mexico

Abstract: Global cerebral ischemia/reperfusion (I/R) damages the brain and triggers peripheral organ dysfunction through brain-heart interaction. Mitochondria are central regulators of both oxidative stress and cell survival, making them critical players in this systemic response. Hydrogen sulfide (H_2S), an endogenous gasotransmitter, has emerged as a potential therapeutic molecule due to its antioxidant and cytoprotective effects. Our research focuses on the effects of H_2S treatment on cardiac mitochondria in a rat model of global cerebral ischemia/reperfusion (I/R) induced by transient bilateral carotid artery occlusion. Adult male Wistar rats (250-300 g; n=4-6 per group) were randomly assigned to sham, I/R, or I/R+NaHS (an H_2S donor) groups. Hemodynamic variables (heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure) were monitored. Isolated cardiac mitochondria were used to evaluate electron transport chain activity, antioxidant defences (total glutathione, superoxide dismutase 2), apoptosis markers (Bax, Bcl-2), and H_2S-producing enzymes (cystathionine γ-lyase, cystathionine β-synthase, and 3-mercaptopyruvate sulfurtransferase). Cerebral I/R increased heart rate and arterial pressure, decreased total glutathione, reduced Bcl-2, increased Bax, and downregulated the expression of mitochondrial 3-MST. Mitochondrial dysfunction was evidenced by reduced activity of complexes I and IV. NaHS treatment improved hemodynamic parameters, preserved mitochondrial respiration by maintaining complex I activity, restored glutathione levels, and modulated apoptotic signalling (Bax decreased, Bcl-2 increased). NaHS prevented the I/R-induced reduction of mitochondrial 3-MST expression. These findings suggest that H_2S confers cardioprotection after cerebral ischemia/reperfusion (I/R) by preserving mitochondrial function, mitigating oxidative stress, and modulating apoptotic pathways. This study provides novel insights into the role of H_2S in regulating the brain-heart axis, revealing potential neuroprotective and systemic therapeutic strategies. This project was funded by SECIHTI Mexico (Grant number CBF-2025-I-4046).

Disclosures: K. Solis Cruz: None. **J. Ramirez c:** None. **A. Sánchez-López:** None. **D. Centurión:** None.

Late-Breaking Poster

LBP013: D.03. Stroke

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP013.01/Web Only

Topic: D.03. Stroke

Support: DGAPA-PAPIIT IN216422
DGAPA-PAPIIT IN224425

Title: Soluble Epoxide Hydrolase Inhibition Confers Neuroprotection via PPAR-αActivation during Intracerebral Hemorrhage

Authors: *C. M. NAVARRO-MABARAK[1], A. MARTINEZ[1], J. MORAN[2];
[1]División de Neurociencias, IFC, UNAM, CDMX, Mexico; [2]Neuroscience, National University of Mexico, CDMX, Mexico

Abstract: Epoxyeicosatrienoic acids (EETs), are known to possess potent anti-inflammatory and antioxidant neuroprotective properties. However, the molecular mechanisms responsible for these effects are not well understood. In this work, we aimed to evaluate the neuroprotective role of EETs in a hemorrhagic stroke model and the possible involvement of PPARa activation in this neuroprotection. Hemorrhagic damage was induced in mice through the intracerebral administration of collagenase VII in the striatum. The neuroprotective effect of EETs was tested in mice by pre-treatments of 2 h with TPPU, an inhibitor of the EETs metabolism. TPPU was administered intraperitoneally at a dose of 0.5, 1.0, or 2 mg/kg. Brain damage was evaluated based on measurements of motor activity, hematoma volume, brain water content, and blood-brain barrier (BBB) permeability. Additionally, the levels of enzymes involved in the oxidative stress balance, such as NADPH oxidase 2 (NOX-2) and superoxide dismutase (SOD), were determined by Western blot analysis. Our results showed that EETs exert neuroprotective effects by significantly decreasing all parameters related to brain damage, improving motor function and promoting an antioxidant state, as evidenced by increased levels of SOD and reduced levels of NOX enzymes. Subsequently, PPARa involvement was evaluated through the administration of GW6471, a PPARa antagonist. Pre-treating mice with GW6471 for 30 min, reverted all neuroprotective effects, including the observed changes in SOD and NOX levels. Our results demonstrate that EETs confer neuroprotection in hemorrhagic brain injury, and this effect is dependent on PPARa activation.

Disclosures: C.M. Navarro-Mabarak: None. **A. Martinez:** None. **J. Moran:** None.

Late-Breaking Poster

LBP013: D.03. Stroke

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP013.02/Web Only

Topic: D.03. Stroke

Title: Endovascular thrombectomy in large ischemic stroke: an updated meta-analysis of randomised trials

Authors: *A. AMJAD;
Independent researcher, Faisalabad, Pakistan

Abstract: Background: The role of endovascular thrombectomy (EVT) in patients with large ischemic infarcts remains debated. While EVT benefits smaller strokes, its impact on brain recovery after extensive injury is less established. Clarifying its efficacy is essential to guide treatment in this high-risk population.Methods: We performed a systematic review and meta-analysis of six randomized controlled trials (n =1,665) including patients with large infarct cores (ASPECTS 3-5). Outcomes assessed were functional independence, neurological recovery, mortality, and safety.Results: EVT significantly improved functional independence at 90 days (mRS ≤ 2; RR 2.49, 95% CI 1.89-3.29) and reduced severe disability or death (mRS 4-6; RR 0.81, 95% CI 0.76-0.86), with benefits persisting at one year. EVT also enhanced early neurological recovery (RR 2.22, 95% CI 1.53-3.22).Mortality did not differ significantly, but EVT was associated with a higher risk of symptomatic intracranial hemorrhage (RR 1.73, 95% CI 1.11-2.69), reflecting the vulnerability of patients with large infarcts.Conclusion: EVT substantially improves functional and neurological outcomes even in patients with extensive ischemic injury, a group historically considered unlikely to benefit. These findings highlight the brain's capacity for recovery when reperfusion is achieved and position EVT as a pivotal therapy in severe stroke. Future studies integrating advanced imaging and biomarker-guided selection are needed to optimize treatment strategies and uncover mechanisms of neural resilience.

Disclosures: A. Amjad: None.

Late-Breaking Poster

LBP013: D.03. Stroke

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP013.03/LBP137

Topic: D.03. Stroke

Title: When vision misguides movement: Lesion network mapping of visuomotor deficits in optic ataxia

Authors: *E. J. SOUTHAM[1], J. E. TRAN-KHANH-BICHON[1], M. MARCUCCI[1], O. BENZLEY[1], K. BUNNELL[1], M. FRIEDRICH[2], M. FERGUSON[3], J. A. NIELSEN[1]; [1]Brigham Young University, Provo, UT; [2]Department of Psychiatry, University Hospital Wurzurg, Würzburg, Germany; [3]Harvard University, Cambridge, MA

Abstract: Optic Ataxia is a disorder defined by impaired visually guided reaching, despite visual and motor function being intact (Perenin & Vighetto, 1988). It is one of three symptoms that make up Balint syndrome as defined by R. Balint in 1909, in addition to simultanagnosia and oculomotor apraxia. Typically associated with damage or lesion to the posterior parietal cortex, other studies have reported inconsistent localization of optic ataxia, suggesting the need for a network based approach. To investigate the lesion network of optic ataxia, a systematic literature search was performed with specific inclusion criteria to identify patients experiencing full and partial Balint's syndrome. Further exclusion identified 12 cases from this cohort that reported partial Balint's syndrome with isolated optic ataxia due to ischemic stroke. Lesion network

mapping analysis (Fox et al., 2018) was performed on the 12 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. We found lesion network overlap in 11/12 cases in areas including but not limited to the left fusiform gyrus at the ventral temporal-occipital junction (at MNI coordinates X: -45 Y: -55 Z :-6), the left superior parietal lobule at the dorsal surface of the parietal cortex (X :-32, Y: -51, Z: +58), and the precuneus/ superior parietal lobule in medial parietal cortex (X :-14, Y=- 55, Z:+ 58). These findings demonstrate that optic ataxia reflects a distributed visuomotor network linking occipitotemporal and dorsal parietal cortices, rather than exclusively depending on focal posterior parietal lesions. These results also give insight to areas specifically associated with isolated optic ataxia, independent of simultanagnosia or oculomotor apraxia that often accompany it, and help clinicians to more accurately treat optic ataxia. Further research is necessary to understand the mechanism of how these networks interact to contribute to optic ataxia and interact with other symptoms, especially in Balint syndrome relative to simultanagnosia and oculomotor apraxia.

Disclosures: E.J. Southam: None. **J.E. Tran-Khanh-Bichon:** None. **M. Marcucci:** None. **O. Benzley:** None. **K. Bunnell:** None. **M. Friedrich:** None. **M. Ferguson:** None. **J.A. Nielsen:** None.

Late-Breaking Poster

LBP013: D.03. Stroke

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP013.04/LBP138

Topic: D.03. Stroke

Title: Metabolic activity of visceral adipose tissue and its therapeutic modulation in post stroke dementia

Authors: *Y. MOON;
Seoul national university hospital, Seoul, Korea, Republic of

Abstract: Dysregulated adipose tissue metabolism is a significant risk factor for cognitive decline in stroke patients, but the specifics of the relationship are complex and still being studied. In particular, in midlife obesity is related to increased risk of dementia possibly by elevated inflammation and insulin resistance. This study aimed to investigate the association between metabolic activity of adipose tissue and post-stroke cognitive impairment, and to identify modifiable factors related to this association that may serve as potential therapeutic targets. Between August 2015 and February 2020, patients with acute cerebral infarction admitted to a tertiary hospital in Seoul, Korea, underwent whole body 18F-FDG PET following clinical stabilization (N=110, mean age=72). FDG uptake in visceral fat and other organs was quantified, and patients were prospectively followed for the development of dementia. Kaplan-Meier survival analysis and Cox proportional hazards modeling were performed. Proteomic and

microRNA profiles from venous blood samples were compared between patients with and without dementia. In addition, we utilized an in vitro adipose tissue model to identify modifiable factors that influence adipose tissue activity under disease conditions. The patients with dementia had significantly increased glucose uptake in the visceral fat which was correlated with neutrophil-lymphocyte ratio and initial neurological severity and inversely associated with body mass index and bone mineral density. The elevated metabolic activity of visceral adipose tissue was independently associated with increased risk of post-stroke dementia (hazard ratio=3.14, confidence interval 1.10 - 8.96). The expression level of miR-let7i was significantly lower among the patients with dementia than those without dementia. In the in vitro adipose tissue model under inflammatory conditions, downregulation of miR-let7i was associated with increased adipose tissue proliferation. However, this effect was not reversed by treatment with a miR-let7i mimic. In contrast, treatment with an SGLT2 inhibitor reduced the expression of proteins related to adipose tissue activity that were elevated under disease conditions. Our findings provide evidence that increased metabolic activity of adipose tissue may be a risk factor for post-stroke dementia and suggests potential therapeutic strategies to modulate this activity.

Disclosures: Y. Moon: None.

Late-Breaking Poster

LBP013: D.03. Stroke

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Support: NSF 2401215
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Title: Cathodal HD-tDCS on Contralesional Dorsal Premotor Area for Stroke Rehabilitation

Authors: J. WILLIAMSON, X. CHEN, ***Y. YANG**;
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Abstract: Background: Stroke is the leading cause of serious, long-term movement disability in adults. Specifically, a motor stroke occurs in the upper motor neuron in the brain and causes damage to the motor cortices and to their descending pathways. This leads to compensatory activation of the dorsal premotor cortex (PMd) in the contralesional hemisphere; this supports recovery by engaging alternative motor pathways via the brainstem, but also contributes to chronic motor impairments, including the expression of abnormal limb synergies and spasticity. We hypothesize that inhibiting contralesional PMd activity is expected to diminish its downstream excitatory effects to spinal motor neurons, reducing synergy and spasticity-related motor impairments. Methods: Transcranial magnetic stimulation (TMS) guided high-definition transcranial direct current (HD-tDCS) was used to test our hypothesis in chronic hemiparetic stroke (N = 14). Results: We found that when applying TMS to the contralesional PMd,

ipsilateral motor evoked potentials (iMEP) were detected in the paretic limb of more severely impaired stroke survivors while not in mild survivors. Additionally, after cathodal HD-tDCS stimulation was applied to PMd, the contralesional PMd iMEP either delayed or disappeared. Furthermore, PMd cathodal stimulation resulted in significant improvement of upper extremity Fugl-Meyer assessment scores ($p<0.001$) and resting state brain function as shown by a significant reduction in delta-alpha ratio ($p=0.04$). Conclusion. This early-phase result supports our hypothesis. This work indicates a novel neuro-target - contralesional PMd for future development of neuromodulatory intervention for treating motor impairment in chronic stroke.

Disclosures: J. Williamson: None. **X. Chen:** None. **Y. Yang:** None.

Late-Breaking Poster

LBP013: D.03. Stroke

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP013.06/LBP140

Topic: D.03. Stroke

Support: Brain Pool Program funded by the Ministry of Science and ICT (MSIT) through the National Research Foundation of Korea under Grant RS-2024-00446461
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National Research Foundation of Korea Grant funded by Korean Government (MSIT) under Grant RS-2023-00208052

Title: Enhancing Paretic Propulsion Post-Stroke via Real-Time Visual Biofeedback and Adaptive Dual-Belt Treadmill Control

Authors: A. RIVERA[1], H. PARK[1], C. LEE[2], J. AHN[2], S. PARK[1], *B.-C. LEE[1];
[1]University of Houston, Houston, TX; [2]Seoul National University, Seoul, Korea, Republic of

Abstract: Reduced propulsive force on the paretic side is a primary contributor to impaired gait patterns, decreased walking speed, and compromised mobility in individuals suffering from chronic stroke. While current gait rehabilitation strategies, such as increasing treadmill speed, applying backward resistance, or utilizing inclined walking, aim to enhance latent propulsive capacity, these methods often lead to rapid muscle fatigue and insufficient engagement of the affected limb's propulsive reserves. This study investigated the efficacy of a novel gait training platform that we developed called the Adaptive Propulsion Enhancement eXperience (APEX) system, which utilizes a dual-belt instrumented treadmill capable of measuring ground reaction forces and modulating belt speed in real time. The system delivers dynamic visual biofeedback synchronized with gait phase to facilitate propulsion in a personalized manner. Six chronic-stage stroke survivors completed two gait training trails in which they were equipped with: 1) eight Inertial Measurement Units (IMUs) attached at the sternum, pelvis, left and right upper legs, left

and right lower legs, and left and right feet, ; 2) eight electromyography (EMG) sensors attached on the affected side at the tibialis anterior (TA), medial gastrocnemius (MG), soleus (SOL), vastus medialis (VM), rectus femoris (RF), medial hamstrings (MH), hip adductors (HADD; adductor longus), and hip abductors (HABD; gluteus medius); and a safety harness. Following determination of each participant's preferred walking speed (PWS), two APEX-assisted conditions were tested in a randomized order: the propulsion-facilitating mode (P-FM) and the propulsion-augmenting mode (P-AM). Each condition included three periods: a 30-step unassisted baseline period, a 100-step training period with visual biofeedback and propulsion enhancement, and a 30-step unassisted post-training period. A mandatory 10-minute rest separated the two conditions. Results indicated that both modes significantly increased maximum propulsive force and stride length during the training period, with these gains partially retained during the post-training period. Similarly, EMG activity of MG, SOL, VM, and RF showed significant increases during training and remained increased post-training. However, no significant changes were observed in the TA, MH, HADD, and HABD across the three periods. These findings underscore the potential of real-time, phase-specific interventions to address the limitations of conventional gait rehabilitation and highlight the APEX system as a promising tool for personalized propulsion-focused therapy in stroke recovery.

Disclosures: A. Rivera: None. **H. Park:** None. **C. Lee:** None. **J. Ahn:** None. **S. Park:** None. **B. Lee:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.01/LBP141

Topic: D.04. Brain Injury and Trauma

Support: Independent Research and Development Program, Research and Exploratory Development Department

Title: In vitro system for studying traumatic brain injury from low-level repetitive blast overpressure

Authors: *E. BAR-KOCHBA[1], A. C. TIMM[1], S. BHUSHAN[1], W. E. SUERO[1], A. SRIKANTH[1], A. N. ELAYADI[1], P. L. PERANICH[1], N. STEINER[1], C. L. RODRIGUEZ[1], I. E. MORALES PANTOJA[2], L. SMIRNOVA[2], T. HARTUNG[2];
[1]Johns Hopkins Applied Physics Laboratory, Laurel, MD; [2]Department of Environmental Health and Engineering, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD

Abstract: Service members and law enforcement personnel are frequently exposed to blast overpressure during training and combat with heavy weaponry such as large-caliber rifles, explosives, and ordnance. The cumulative effects of these repeated low-level pressure exposures remain poorly understood, particularly on the cellular scale. To address this gap, we developed a

high-throughput piezoelectric transducer-based platform capable of delivering repetitive low-level pressure waveforms (<10 kPa) to human induced pluripotent stem cell-derived brain organoids (BOs). The pressure waveforms were informed by intracranial pressure profiles predicted by finite element modeling of the human head exposed to training-relevant blast conditions. BOs were subjected to pressure pulses at varying intervals from 1 to 100 s for 6 hours, after which they were assessed for alterations in glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), and neurofilament light chain (NfL), as well as apoptosis and necrosis. Results indicate elevated astrogliosis, structural disruption, and increased cell death following prolonged exposure. Together, these findings demonstrate that BOs are highly sensitive to long-duration, low-level repetitive pressure exposures, highlighting the potential of this system as a physiologically relevant *in vitro* model for investigating occupationally induced traumatic brain injury.

Disclosures: E. Bar-Kochba: None. **A.C. Timm:** None. **S. Bhushan:** None. **W.E. Suero:** None. **A. Srikanth:** None. **A.N. Elayadi:** None. **P.L. Peranich:** None. **N. Steiner:** None. **C.L. Rodriguez:** None. **I.E. Morales Pantoja:** None. **L. Smirnova:** None. **T. Hartung:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.02/LBP142

Topic: D.04. Brain Injury and Trauma

Support: NIH/NINDS 1R01NS140268-01A1
Internal Research Competition (IRC) Grant, VMCVM

Title: MERTK regulates efferocytosis and undergoes cleavage after traumatic brain injury

Authors: *E. SOLIMAN[1], J. BAKIR[2], A. WILLISON[2], M. ELHASSANNY[3], M. THEUS[2]; [1]East Carolina Univ., Greenville, NC; [2]Translational Biology, Medicine, and Hlth. Grad. Program, Blacksburg, VA; [3]Virginia Tech., Blacksburg, VA

Abstract: Efficient clearance of apoptotic cells (efferocytosis) is essential for limiting inflammation and supporting repair after traumatic brain injury (TBI). The TAM receptor tyrosine kinase MERTK has been linked to phagocytic function, but its temporal regulation and susceptibility to cleavage in the injured brain remain poorly defined. Controlled cortical impact (CCI) was used to induce TBI in adult CD1 mice (P60-90). MERTK and GAS6 expression were evaluated by western blotting. To track infiltrating myeloid cells, GFP bone marrow (BM) chimeric mice were used. To study the role of MERTK in efferocytosis, we used *mertk*$^{f/f}$ *Cx3cr1* $^{CreEREYFP/+}$ mice, in which tamoxifen administration conditionally deletes m*ertk* in Cx3cr1-expressing cells, with *mertk*$^{+/+}$ *Cx3cr1* $^{CreEREYFP/+}$ littermates as WT controls. Efferocytosis was quantified using Imaris-based 3D analysis, and receptor cleavage was assessed by ELISA and immunofluorescence. Animals were randomized, analyses blinded, and group sizes ranged from

n=3-7 per condition, with sham-operated control mice included. Western blotting showed increased GAS6 and MERTK expression in the injured cortex from 1-7 days post-injury (dpi). MERTK is upregulated in CX3CR1-expressing cells at 3 dpi. GFP BM chimeric mice revealed that most $GFP^+Cx3cr1^+$ infiltrating cells were $CD11b^+CCR2^+$ monocytes, whereas $Ly6G^+$ neutrophils were rare. Consistently, quantitative analysis showed that ~98% of $MERTK^+$ cells were $Cx3cr1^+$ microglia and blood-derived monocytes, with <1% derived from neutrophils. Conditional deletion of m*ertk* in $Cx3cr1^+$ cells significantly reduced efferocytosis, increased IgG extravasation, and worsened tissue damage, accompanied by delayed cerebral blood flow recovery. Concurrently, MERTK cleavage was observed, with loss of extracellular domains in $Cx3cr1^+$ cells and increased soluble MERTK in plasma at 3 and 7 dpi, suggesting reduced receptor availability. These findings demonstrate that MERTK regulates efferocytosis by Cx3cr1-expressing phagocytes after TBI and undergoes post-injury cleavage, which may limit receptor function. Loss of MERTK impairs clearance of apoptotic cells and exacerbates pathological and functional outcomes after TBI.

Disclosures: E. Soliman: None. **J. Bakir:** None. **A. Willison:** None. **M. Elhassanny:** None. **M. Theus:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.03/LBP143

Topic: D.04. Brain Injury and Trauma

Support: ONR Grant N00014-22-1-2828

Title: Network-Wide Excitotoxic Disruption Following In Vitro Traumatic Brain Injury Model to Assess Critical Injury Thresholds

Authors: *J. SERGAY[1], A. HAI[1], C. FRANCK[2];
[1]Biomedical Engineering, University of Wisconsin - Madison, Madison, WI; [2]Mechanical Engineering, University of Wisconsin-Madison, Madison, WI

Abstract: Mechanical stretch drives TBI, but network activity responses over 24 h are unclear. We cultured rat cortical neuron-astrocyte co-cultures on PDL/laminin-coated PDMS dogbones expressing AAV1-hSyn-GCaMP6s, imaging 2-minute timelapses before (0-), immediately after (0+), and 24 h later. Radial strain (0.1/0.3/0.5 at 1 s^{-1} or 50 s^{-1}) was applied; shams were device-mounted. Outcomes: (i) % neurons with immediate Ca^{2+} loading, (ii) spike rate among active cells, and (iii) active cell count per field. Statistics: mixed-effects models; strain-dependent variability at 0+ via GLS. At 0+, samples stretched at 50 s^{-1} increased % neurons with elevated baseline fluorescence strain-dependently: 1.6%, 1.9%, 50.1% at 0.1/0.3/0.5 (strain and strain×rate $p<1\times10^{-15}$). 1 s^{-1} showed minimal increase vs sham. Spike rate among active cells declined with strain: -16.7%, -37.1%, -75.0% at 0.1/0.3/0.5 ($p=0.47$, 0.10, 0.005). Active-cell

count was lower at 0+ (-10.8%, -18.4%, -29.4% at 0.1/0.3/0.5; all $p \geq 0.13$). At 50 s^{-1}, between-sample spike-rate variability decreased with strain (GLS $\chi^2=7.08$, $p=0.0078$), indicating a more convergent early response at higher strains. At 24 h, the spike rate among active cells increased vs 0+ at moderate/high strains: -21.6%, +42.3%, +163% at 0.1/0.3/0.5 ($p=0.07$, 0.05, 0.02). Compared to baseline (0-), rates showed non-significant decreases: -34.7%, -10.5%, -34.1% at 0.1/0.3/0.5 (all $p \geq 0.074$). Active-cell count further declined from 0+ to 24 h: -35.4%, -46.4%, -73.2% at 0.1/0.3/0.5 ($p=0.09$, 0.036, 0.009). The count remained depressed vs baseline: -42.3%, -56.2%, -81.1% at 0.1/0.3/0.5 ($p=0.023$, 0.002, 0.0001), indicating a smaller active network despite near-baseline firing in remaining cells. At 50 s^{-1}, cell death increased only at 0.5 vs sham ($p=0.02$), implying functional silencing at strains ≤0.3, and combined silencing and cell loss at 0.5. As an excitotoxicity control, 10 μM glutamate (continuous exposure) mirrored stretch Ca^{2+} loading with a smaller active network. Elevated baseline fluorescence increased at 0+ vs sham (+31.2%, $p<1\times10^{-15}$). Spike rate among active cells showed no significant change (0+ vs 0- -50.7%, $p=0.98$; 24 h vs 0- -36.5%, $p=0.98$; 24 h vs 0+ +28.9%, $p=0.99$). Active-cell count decreased (0+ vs 0- -24.7%, $p=0.035$; 24 h vs 0- -28.1%, $p=0.017$; 24 h vs 0+ -4.5%, $p=0.77$). These findings support excitotoxic Ca^{2+} loading as a mechanistic driver. Conclusions: High-rate stretch elicits rapid, strain-graded Ca^{2+} loading and hypoactivity, followed by near-baseline firing but a reduced active network at 24 h. These results help define strain/rate thresholds and identify early imaging biomarkers of injurious signaling.

Disclosures: J. Sergay: None. **A. Hai:** None. **C. Franck:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.04/LBP144

Topic: D.04. Brain Injury and Trauma

Title: Noggin bonks and neurogenesis: Mapping neurogenesis following a rodent model of traumatic brain injury

Authors: *T. KAHL[1], E. MOSS[2], C. BUTLER[3];
[1]Anesthesia and Perioperative Medicine, Oregon Health Sciences University, Portland, OR; [2]Anesthesiology and Perioperative Medicine, OHSU, Portland, OR; [3]Portland Department of Veteran Affairs, Portland, OR

Abstract: Traumatic Brain Injuries (TBIs) produce a variety of symptoms and complications in humans and often result in extensive cell death in the brain. Neurogenesis, or the proliferation of new neurons following a TBI, is well-documented but whether neurogenesis is a net positive or negative remains an open question. While brain damage and subsequent neurogenesis can vary based on the impact location or severity of a TBI, understanding the nature and extent of adult-born neuron migration post-TBI is lacking in current research. This study establishes an observational foundation for understanding the extent of migrating cells post-TBI and to explore

lesser-understood destinations for these adult-born cells. We used a CCI impact model followed by cell proliferation tracking using BrdU pulse labeling at 7-10 days post-injury. We found surprising increases in adult-born cells on the ipsilateral side of the brain, particularly near the injury site, in the peri-infarct cortex, dentate gyrus and ipsilateral thalamus. At the same time, we found a decrease in adult-born neurons in the olfactory bulb, suggesting that neurons born in the subventricular zone (SVZ) may be diverted from their usual migratory path to the olfactory bulb. Our findings offer insights into destinations for SVZ adult-borncells and potential unconventional migration patterns that divert them to brain tissue and structures ipsilateral to the injury. Confirmation of these atypical migratory paths is ongoing via retroviral labeling studies to confirm cell origins, phenotypes, and circuit integration.

Disclosures: T. Kahl: None. **E. Moss:** None. **C. Butler:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.05/LBP145

Topic: D.04. Brain Injury and Trauma

Title: Contribution of astrocytes to thalamic damage following cortical traumatic brain injury

Authors: A. DELGADO, S. YASMINE, ***F. GU**;
University of North Texas, Denton, TX

Abstract: Beyond the initial cortical damage from traumatic brain injury (TBI), progressive neuroinflammation and neuronal degeneration arise in the thalamus, driving long-term deficits. This secondary thalamic pathology contributes to epilepsy, cognitive decline, and emotional/behavioral changes, severely reducing quality of life. Understanding mechanisms underlying this delayed damage is essential for developing interventions to prevent chronic neurological impairments after cortical TBI. Prior work indicates that activated microglia exacerbate injury by releasing cytokines that induce formation of neurotoxic astrocytes, which promote neuronal death. We hypothesized that microglial activation in the thalamus after cortical TBI triggers neurotoxic astrocyte generation, leading to secondary neuronal injury. To test this, we utilized a controlled cortical impact (CCI) mouse model. Brain tissue collected seven days post-CCI was analyzed immunohistochemically for neuronal integrity, microglial activation, astrogliosis, and reactive astrocyte phenotypes, focusing on thalamic nuclei most vulnerable to secondary damage: ventral posterolateral (VPL), ventral posteromedial (VPM), and reticular (nRT). We also assessed the expression levels of key inflammatory mediators, including complement component 1q (C1q), interleukin-1 alpha (IL-1α), and tumor necrosis factor alpha (TNFα), known to be associated with neurotoxic astrocyte formation. Our results revealed marked neuronal loss in the VPL, VPM, and nRT seven days post-CCI. This degeneration was accompanied by widespread microgliosis and robust astrogliosis. Importantly, C3-positive neurotoxic astrocytes were detected within these thalamic nuclei. We also observed strong

upregulation of C1q, IL-1α, and TNFα in the injured hemisphere, consistent with activation of the signaling cascade driving neurotoxic astrocyte formation. Together, these findings support the hypothesis that microglial activation following cortical TBI initiates neurotoxic astrocyte formation, contributing to secondary thalamic neuronal injury. The co-localization of neuronal degeneration with microgliosis, astrogliosis, neurotoxic astrocytes, and elevated inflammatory mediators highlights a pathogenic cascade underlying thalamic damage. These results identify neurotoxic astrocytes as critical players in post-TBI progression and suggest therapeutic strategies aimed at modulating microglial and astrocytic responses to preserve thalamic integrity and mitigate long-term functional decline.

Disclosures: A. Delgado: None. **S. Yasmine:** None. **F. Gu:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

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Program #/Poster #: LBP014.06/LBP146

Topic: D.04. Brain Injury and Trauma

Support: NS061817
NS076511
5R01HL174611
NYFIRST135896

Title: Nutritional Intervention with Bis-Allylically-Deuterated Arachidonic Acid Inhibits Ferroptosis and Enhances Cognitive Recovery After Traumatic Brain Injury

Authors: *T. KELESTEMUR[1,2], E. SARITAS[2], S. SAMOVICH[2], H. DAR[3], L. J. SPARVERO[3], M. AKDOGAN[3], K. SHANKAR[2], Y. TYURINA[3], M. SHCHEPINOV[3], V. E. KAGAN[3], H. BAYIR[2];
[1]Columbia University Medical Center, New York, NY; [2]Department of Pediatrics, Division of Critical Care and Hospital Medicine, Redox Health Center, Columbia University Medical Center, New York, NY; [3]University of Pittsburgh, Pittsburgh, PA

Abstract: Ferroptosis, a non-apoptotic cell death mechanism driven by robust oxidation of polyunsaturated fatty acid-containing phospholipids, is implicated in neuronal death and functional deficits after traumatic brain injury (TBI). A required step in TBI-induced ferroptosis is peroxidation of arachidonic acid (AA) containing phosphatidyl-ethanolamines (PE) catalyzed by 15-lipoxygenase (15LOX) that is robustly induced in pericontusional neurons. A key step in AA-PE oxidation is hydrogen abstraction at C7, C10, and C13 bis-allylic positions between double bonds in AA. We hypothesized that dietary supplementation with 7,7,10,10,13,13-D_6-arachidonic acid (D6-AA), in which hydrogens at C7, C10, and C13 bis-allylic positions are replaced with deuterium, would attenuate injury by taking advantage of the kinetic isotope effect, whereby C-D bonds are more resistant to hydrogen abstraction than C-H bonds hence slowing

the rate of lipid peroxidation. We randomized 8-12-week-old male mice to D6-AA containing or regular diet for five weeks starting two weeks before controlled cortical impact (CCI, 3-mm tip, 5 m/s velocity, 100 ms dwell time, 2.2 mm depth). Neurocognitive evaluation using novel arm maze and fear conditioning tests at 17 and 21 days after CCI, respectively, showed D6-AA diet enhanced both amygdala- and hippocampal-dependent learning and memory vs control diet. Supplementation attenuated CCI-induced increases in plasma GFAP levels and activated Akt-mTOR pathway in pericontusional cortex. In parallel experiments we evaluated concentration dependence of D6-AA for antiferroptotic activity after treatment with RSL3 (a GPX4 inhibitor) and Ferrostatin-1 (ferroptosis inhibitor as a control). Cell death was assessed using LDH-release. To test the success and specificity of our approach we also tested the effect of non-bis-allylically-deuterated arachidonic-acid (D11-AA). Cells were incubated with D6-AA or D11-AA to also examine the effectiveness of integration of deuterated-AA into major phospholipids by LC-MS based redox lipidomics. We showed successful incorporation D6-AA and D11-AA into various phospholipid classes, including PE, cardiolipin, phosphatidylinositol and phosphatidylcholine. Importantly, cells loaded with D6-AA (but not with D11-AA) exhibited full protection against phospholipid peroxidation and ferroptotic death. Taken together, these results suggest that D6-AA may provide neuroprotection after TBI by attenuating 15LOX-driven lipid peroxidation through the kinetic isotope effect, thereby reducing secondary injury and enhancing functional recovery.

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Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.07/LBP147

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01EB027769
NIH Grant R01EB028661

Title: Flexible, metamaterial-loaded Vivaldi antenna for handheld thermoacoustic imaging of neonatal intracranial brain hemorrhage

Authors: M. ISLAM[1], D. RAMIREZ ARAUJO[2], L. REED-LAUGHBAUM[3], F. CHARBEL[3], D. ERRICOLO[4], ***D.-A. M. PILLERS**[5], K. AVANAKI[6];
[1]Graduate College, University of Illinois Chicago, Chicago, IL; [2]Pediatrics/Neonatology, University of Illinois Chicago, Chicago, IL; [3]Neurosurgery, University of Illinois Chicago, Chicago, IL; [4]Department of Electrical and Computer Engineering, University of Illinois Chicago, Chicago, IL; [5]Pediatrics, University of Illinois Chicago, Chicago, IL; [6]Biomedical Engineering, University of Illinois Chicago, Chicago, IL

Abstract: Ultrasound remains the clinical standard for neonatal brain screening due to its safety, portability, and accessibility. However, its limited sensitivity hinders accurate assessment of intraventricular hemorrhage (IVH), particularly in the lower grades. In this work, we present a compact, handheld thermoacoustic imaging (TAI) system integrated with a custom-designed, flexible metamaterial-loaded Vivaldi antenna. The antenna is housed in a 3D-printed holder that encases the ultrasound probe, enabling a single, portable device optimized for neonatal cranial applications. The TAI platform exploits intrinsic tissue contrast arising from water content and electrical conductivity, thereby enhancing sensitivity for detecting hemorrhagic lesions. The metamaterial-loaded Vivaldi antenna facilitates efficient electromagnetic energy delivery through the neonatal fontanelle while preserving a compact and ergonomic design. System performance was validated in a live sheep brain model with an optical cranial window analogous to the human fontanelle, and with *ex-vivo* sheep brains. Initial evaluation on *ex-vivo* sheep brains with controlled hemorrhage volumes confirmed sensitivity, and were followed by *in-vivo* imaging after induction of Grade III-IV IVH. Results demonstrate that TAI can detect subtle variations in intracranial hemorrhage, allowing finer differentiation of IVH severity compared to conventional ultrasound. These findings establish handheld TAI, incorporating a metamaterial-loaded Vivaldi antenna and custom 3D-printed integration, as a promising approach for early, noninvasive detection and monitoring of neonatal brain hemorrhage.

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Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.08/LBP148

Topic: D.04. Brain Injury and Trauma

Support: NIH NICHD R01 HD099397

Title: Which is worse for the immature brain: early traumatic seizures or seizures with GABA agonists?

Authors: *B. A. COSTINE-BARTELL;
Massachusetts General Hospital, Charlestown, MA

Abstract: The standard of care in the pediatric intensive care (ICU) is to stop acute symptomatic seizures or neonatal seizures for any reason with anti-seizure medications (ASMs). These guidelines are not evidence-based in children but are based upon a paper by Meldrum in 1973, where seizures induced by bicuculline caused neuronal death in adolescent baboons that were not ventilated nor ICU managed. Moderate to severe TBI in children is often a multi-pathoanatomic lesion and multi-insult (MULMI). It is not known if seizures contribute to the pathophysiology or are just a symptom of the pathology. Hypoxic-ischemic injury is the most common

pathoanatomic lesion in young children. Seizures are difficult to stop in infants, where GABA might still be depolarizing. In infants, the GABA agonist, phenobarbital, is known for stopping the behavioral expression of seizures while electrographic seizures continue. In our severe TBI MULMI model (lesions: cortical impact, mass effect, subarachnoid hemorrhage; insults: seizure, brief apnea, and hypoventilation), we create seizures with kainic acid while the piglets are on a non-GABA acting sedation regimen, while managed in an ICU. Piglets similar to human infants (PND7) have less hypoxic-ischemic injury than piglets of similar age to toddlers (PND30). The injury follows the location of the subarachnoid hemorrhage (SAH), while the contralateral hemisphere is spared. Here, we tested whether seizure alone, SAH alone, or in combination causes the same extent of hypoxic-ischemic tissue/neuronal damage as the full MULMI model and if standard PICU ASMs (phenobarbital and midazolam) reduce tissue damage. Several hours of seizure alone did not cause hypoxic-ischemic damage in either age. Hemispheres were not different, as both seizure and SAH spread to both hemispheres. Widespread cortical hypoxic-ischemic injury occurred when a seizure occurred with a subarachnoid hemorrhage (SAH) present. ASMs did not reduce damage in the full MULMI model in either age but increased neuronal death in PND7 piglets ($P = 0.06$) when ASMs failed to stop the seizure (age x ASM interaction, $P = 0.07$). ASMs did not reduce tissue damage in PND30 piglets, and failure to stop the seizure in this age group also had no effect. In the full MULMI model in PND30 piglets, SAH but not seizure duration was correlated to tissue damage. We will continue to investigate the effect of ASMs in our full MULMI model until powered per age. Future work will investigate the context of when we should treat seizures in children and how.

Disclosures: B.A. Costine-Bartell: None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.09/LBP149

Topic: D.04. Brain Injury and Trauma

Support: VA BLR&D Merit I01BX006494-01A1 (WBH)
DOD CDMRP HT9425-23-ERP-IDA (WBH)

Title: A Preclinical Model for Investigating Post-Traumatic Epilepsy and Acute Seizure Susceptibility Following Repeated Blast Exposure

Authors: *N. EAPEN[1], S. PRAJAPATI[1], H. MENTZEL[1], G. WILBUR[1], B. HUBBARD[1,2];
[1]Spinal Cord and Brain Injury Research Center, University of Kentucky, Lexington, KY;
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Abstract: Introduction Blast-induced traumatic brain injury (bTBI) is a major risk factor for chronic neurological morbidity in military and veteran populations, including post-traumatic epilepsy (PTE). While epidemiological and experimental evidence supports an association

between blast exposure and epilepsy, the underlying mechanisms and biomarkers remain understudied. We combined two complementary preclinical approaches: (1) long-term monitoring of sleep and spontaneous seizures after repeated bTBI to evaluate epileptogenesis, and (2) a scalable chemoconvulsant pentylenetetrazol (PTZ) assay to probe acute seizure susceptibility one week post-injury. Together, these models assess both early seizure threshold changes and chronic progression.**Materials and Methods***Chronic PTE Study:* Adult Sprague-Dawley rats were exposed to sham (n=12) or two repeated blasts (n=30) at 19.69 ± 1.15 psi, spaced 24 h apart. Animals were socially isolated after injury and, at four months, underwent one month of continuous video and piezoelectric monitoring to assess sleep-wake dynamics and seizure activity. Seizures were detected with Signal Solutions SeizureStats software and video-verified by blinded reviewers.*Acute Susceptibility Assay:* Adult males (n=16) received single (n=5), repeated (n=5) blasts at ~20 psi, or naïve procedures (n=6). On day 7, animals underwent a PTZ challenge (three 25 mg/kg i.p. injections, 15 min apart). Seizure latency and severity were scored on a modified Racine scale. Mann-Whitney U tests compared latencies.**Results***Chronic PTE:* At four months, gross sleep metrics did not differ between groups. However, males slept more than females ($p<0.0001$). Importantly, 80% (24/30) of blast animals developed recurrent seizures (mean 15.5/animal), primarily myoclonic. Seizures occurred in 93% of males (mean 17.3) and 67% of females (mean 12.9). In shams, 50% (6/12) developed seizures.*Acute Susceptibility:* After the second PTZ injection, all blast animals seized. Following the third injection, 100% of single-blast animals seized vs. 60% of repeated-blast animals. Median latency was longer in the repeated-blast group but not significant ($U=8.0$, $p=0.381$).**Conclusion**Repeated blast exposure produced PTE in the context of isolation despite preserved sleep structure, while the PTZ assay revealed possible early alterations in seizure threshold. Together, these approaches underscore the complexity of blast-related epileptogenesis and support scalable assays for early risk detection. Ongoing histological analyses will clarify mechanistic underpinnings and enhance translational relevance for at-risk military populations.

Disclosures: N. Eapen: None. **S. prajapati:** None. **H. Mentzel:** None. **G. Wilbur:** None. **B. Hubbard:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.10/LBP150

Topic: D.04. Brain Injury and Trauma

Support: MRDC MW.4.R24.2

Title: Analysis of memory and blood-brain barrier integrity in a rat model of radiation polytrauma

Authors: W. GREENE[1], M. MCCLOSKEY[1], J. JOHNSON[1], C. ATKINS ANDERSON[1], T. WEAVER[1], R. WASHINGTON[2], J. HANKINS[3], L. CORNELL[4], T. SHUKLA[4], A. LAMMY[4],

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Abstract: Background: Combined blast + radiation exposures present a significant threat to neurological health. Blast and radiation injuries are both well-studied, but synergistic effects remain largely unexplored. Current research often neglects the complex interplay of polytrauma. This study investigates the effect of combined blast and radiation exposure on cognitive function and blood-brain barrier (BBB) integrity.
Methods: A rat polytrauma model was used to assess the neurologic consequences of combined exposure to whole body irradiation (WBI) and blast overpressure (BOP). Adult male Sprague-Dawley rats were randomized into four groups (n=4/group): sham control, WBI only, BOP only, and BOP + WBI. All animals were maintained under isoflurane anesthesia during BOP and WBI exposures. Blast exposure was induced using an advanced blast simulator (175 kPa). 5.5 Gy radiation was administered using a controlled radiation source. At 1-, 2-, 3- and 7-days post-exposure, cognitive performance was assessed using behavioral tests, including Y maze (spatial and working memory), novel object recognition (NOR, short-term memory) and passive avoidance (PA, associative learning). Anesthetized animals were humanely euthanized on Day 7 post-exposure. BBB integrity was evaluated via *in vivo* DyLight 594 lectin perfusion followed by immunohistochemical analysis of brain sections. Data analysis employed ANOVA and non-parametric statistical tests ($p < 0.05$).
Results: Y-maze and NOR data revealed no difference between groups tested post-exposure. PA data revealed significant differences in associative memory detected within 1 day of exposures, with the greatest deficit detected on Day 7 in animals exposed to BOP (46% of baseline), WBI (4.1% of baseline) and BOP + WBI (26.1% of baseline). Exposures to WBI, BOP and BOP + WBI induced increased BBB permeability, indicated by enhanced lectin extravasation.
Conclusions: While the Y-maze and NOR tests did not reveal significant memory deficits after BOP and WBI exposure, the PA test revealed significant loss of associative memory within 24 hours of exposure to BOP and WBI. The polytrauma model of combined BOP and WBI exposures can be used to study mechanisms underlying neurologic sequelae of combined blast and radiation exposure. By characterizing cognitive deficits and BBB disruption, we hope to identify therapeutic targets for mitigating detrimental effects of polytrauma on brain health. These findings will inform future studies investigating neuroprotective strategies and contribute to a more comprehensive understanding of the neuropathology of combined injuries relevant to both military and civilian populations.

Disclosures: W. Greene: None. **M. McCloskey:** None. **J. Johnson:** None. **C. Atkins Anderson:** None. **T. Weaver:** None. **R. Washington:** None. **J. Hankins:** None. **L. Cornell:** None. **T. Shukla:** None. **A. Lammy:** None. **M. Urban:** None. **N. Davidson:** None.

Late-Breaking Poster

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Program #/Poster #: LBP014.11/LBP151

Topic: D.04. Brain Injury and Trauma

Support: NIH R03AG063264
NIH R21NS109918
NIH R01DA048815

Title: A novel FlpO recombinase mouse line to target a subset of reactive astrocytes

Authors: *T. UBINA[1], W. AGNEW-SVOBODA[1], Z. FIGUEROA[1], J. A. MARTIN[2], M. KARGINOVA[1], E. WILSON[3], T. A. FIACCO[4], M. RICCOMAGNO[5];
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Abstract: Astrocytes display strikingly diverse responses to CNS insults, ranging from protective to maladaptive states. These reactive astrocyte (RA) phenotypes differ across brain regions, injury types, and disease contexts, underscoring the need for tools that can dissect their heterogeneity. To address this, we generated a tamoxifen-inducible *Complement 3-FlpOERT2* knock-in mouse line that exploits Complement 3 (C3), a complement cascade component upregulated in specific RA populations. Our objective was to characterize this model across multiple models of neuroinflammation. *C3-FlpOERT2* mice were crossed with the dual recombinase reporter line, *Ai224*, and exposed to direct neuroinflammatory insults (intrastriatal LPS, traumatic brain injury [TBI], *Toxoplasma gondii* infection) or systemic inflammation (Intraperitoneal low-dose LPS). The *Ai224* reporter expresses nuclear EGFP upon recombination by Cre and nuclear TdTomato upon recombination by Flp. Tamoxifen was administered in blinded, vehicle-controlled experiments with both sexes. N≥3 animals per sex per condition were analyzed with replication across experiments. RNAscope and immunohistochemistry quantified C3 expression and cell identity, with Aldh1l1, GFAP, Vimentin, NeuN, Iba1, Olig2, and lectin. Direct CNS insults robustly increased astrocytic C3 expression (intrastriatal LPS: 1293±202 tdTomato$^+$ cells/30um hemisphere section vs. saline 4.6±1.2, P<0.0001; TBI: significant induction in high damage brains, P=0.0339). In contrast, systemic LPS did elevate the number of labeled cells over controls, however did not reach significance (LPS: 24.33±6.984 tdTomato$^+$ cells/30um hemisphere section, P=0.0789). Chronic *T. gondii* infection produced strong RA labeling (0.6±0.4 tdTomato$^+$ cells/30um hemisphere section Sham vs. Acute Toxo 248.8±34.18, P=0.0019), with TdTomato$^+$ cells clustering near immune infiltrates. Labeling was almost exclusively astrocytic (>75% colocalization with Aldh1l1/GFAP/vimentin). Finally, utilizing *Aldh1l1-CreERT2; C3-FlpOERT2; Ai224* crosses demonstrated combinatorial utility, with most

labeled cells coexpressing EGFP and TdTomato, enabling refined targeting of astrocyte subsets. In conclusion, the C3-FlpOERT2 line selectively labels astrocytes responding to direct brain insults and chronic parasitic infection, but not systemic inflammation. This model expands the toolkit for dissecting RA diversity, offering combinatorial potential to manipulate specific astrocyte subsets. Future studies with this tool with sequencing approaches will clarify the molecular programs and functional roles of $C3^+$ astrocytes during neuroinflammation.

Disclosures: T. Ubina: None. **W. Agnew-Svoboda:** None. **Z. Figueroa:** None. **J.A. Martin:** None. **M. Karginova:** None. **E. Wilson:** None. **T.A. Fiacco:** None. **M. Riccomagno:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.12/Web Only

Topic: D.04. Brain Injury and Trauma

Title: Morphological cell changes at early times of focal cerebral ischemia and reperfusion

Authors: *A. ORTIZ-PLATA[1], A. GUERRERO BACA[2], A. SÁNCHEZ GARCÍA[3], P. AGUILERA[4];
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Abstract: Brain ischemia is a leading cause of disability and mortality worldwide. Although its effects on neurons have been studied, less is known about its impact on glial cells. To evaluate the progression of morphological changes in neurons and glial cells in early stages of focal cerebral ischemia (FCI), several staining techniques were applied. FCI in male Wistar rats was induced by middle cerebral artery occlusion: 1 hour of FCI, 1 h-FCI followed by 24-h of reperfusion (R), 1 h-FCI/48-R; sham group as a control. After each time, the rats were perfused in 4% paraformaldehyde-PBS; brain tissue was dehydrated, paraffin embedded and 4 µm sections were made. Cellular injury was assessed by histochemical techniques (H&E, Kluver-Barrera, Nissl, and Hematoxylin-phosphotungstic acid [PTAH]) and immunohistochemistry (GFAP and MBP) as cellular markers. With the staining, cytotoxic-vasogenic edema and decreased apparent cell density were observed, starting from 1h-FCI. Klüver-Barrera revealed evident alterations in myelin fibers at 1 h/ICF-24h-R. Neuropil damage was evidenced by discontinuity and changes in the arrangement of myelin fibers, as well as apparent dendritic thickening; in the lower layers of the cortex, this caused a decrease in fiber density. Intense pallor was found due to significant loss of myelin associated with damage to oligodendrocytes. With Nissl staining in the hippocampus after 1 h/FCI, some neurons showed signs of chromatolysis, evidenced by the displacement of nuclei toward the cell periphery due to the dispersion of Nissl bodies; clear signs of chromatolysis were observed from 1 h to 24 h. In the

cortex, damage begins in the lower cell layers, and cells with chromatolysis predominate from 1 h to 24 h. PTAH staining was useful for detecting damaged glial fibers and neurofilaments. In hippocampus, 1h-FCI revealed glial cells with short, irregular processes. In the cortex, there were scattered glial cells and oligodendrocytes with structural disorganization. Particularly with this stain, cells with early signs of pyknosis were found, acquiring a violet hue. These cells, when stained with H&E, appear to have an apparently preserved morphology. All findings were complementary and revealed crucial information about the severity and timing of early-stage damage, showing that significant cellular alterations occur shortly after ischemia. Given that glial cells are the most abundant cell type in the central nervous system, it is essential to understand how damage processes impact them individually and compare these changes with those observed in neurons as possible therapeutic targets.

Disclosures: A. Ortiz-Plata: None. **A. Guerrero Baca:** None. **A. Sánchez García:** None. **P. Aguilera:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

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Program #/Poster #: LBP014.13/LBP152

Topic: D.04. Brain Injury and Trauma

Support: National Institute of Neurological Disorders and Stroke (5R01NS126449)

Title: Clinical Changes Associated with Head Impact Exposure in Contact Sport Athletes

Authors: C. LO[1], A. SHAH[2], J. HAREZLAK[3], ***B. D. STEMPER**[4];
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Abstract: Traditional head injury risk models emphasize a single, high magnitude head acceleration as the primary concussion mechanism. Over the last decade sub-concussive head acceleration events (HAEs) have become increasingly recognized as significant contributors to long-term neurological dysfunction, especially in contact sport athletes. This study investigated the relationship between repetitive sub-concussive HAEs and functional neurological changes across a single football season. Data were collected from high school and Division III collegiate American football athletes. Head impact exposure was recorded using helmet-mounted accelerometers while clinical assessments—including ImPACT, SAC, SCAT, and BESS—were administered pre-season, mid-season, and post-season. In total, 35 athletes exhibited clinically significant declines on cognitive assessments without formal concussion diagnoses, with some showing changes from baseline at both mid- and post-season timepoints. Surprisingly, no statistically significant differences were observed in cumulative risk weighted exposure (RWE)

or total impacts for the time period of assessment between those with and without declines on cognitive assessments. Pairwise comparisons between these groups suggest that timing between maximum impact and clinical assessment testing, as well as total rotational acceleration per session, were most predictive of clinical changes. In summary, this study provides evidence that meaningful cognitive changes can occur in the absence of diagnosed concussion, supporting the hypothesis that sub-concussive impact exposure contributes to neurological decline. These findings underscore the limitations of current concussion surveillance methods and call for longitudinal, intra-seasonal studies with larger cohorts and improved control groups to better define biomechanical exposure thresholds and guide return-to-play protocols.

Disclosures: C. Lo: None. **A. Shah:** None. **J. Harezlak:** None. **B.D. Stemper:** None.

Late-Breaking Poster

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Program #/Poster #: LBP014.14/LBP153

Topic: D.04. Brain Injury and Trauma

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NINDS K00 NS113419 (HA)
Mind Brain Behavior Harvard Young Investigator Award (HA
NIHMD LRP (HA)
Rainwater Charitable Foundation Tau Leadership Fellowship Research (HA)
NYU - GSoM Start - up funds (HA)

Title: Shorter superior longitudinal fasciculus in former American football players

Authors: *A. WICKHAM[1], B. SZEKELY[2], J. STEARNS[3], A. MIRMAJLESI[4], D. MERCADO[5], M. ESTRADA[5], O. PRUDEN[5], S. CANGE[4], C. ADLER[6], C. BERNICK[7], L. BALCER[5], J. CUMMINGS[8], E. M. REIMAN[9], R. A. STERN[10], M. E. SHENTON[11], R. J. RUSHMORE III[12], S. BOUIX[13], H. ARCINIEGA[14];
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Abstract: Repetitive head impacts (RHI) are linked to alterations in white-matter organization in contact-sport athletes. The superior longitudinal fasciculus (SLF I-III), a long parieto-frontal association pathway, traverses regions subject to linear acceleration-related pressure gradients and tensile-compressive strain, making it a plausible target for axonal stretching. Prior work has focused on diffusion metrics (e.g., fractional anisotropy), but the effect of RHI on SLF tract length, a macroscopic proxy of axonal loss or pruning, remains untested. We compared SLF I-III length in former American football players with unexposed asymptomatic controls and examined associations with head-impact exposure estimates of frequency, linear acceleration, and rotational forces.

We analyzed diffusion MRI from 165 former American football players and 52 unexposed controls in the DIAGNOSE CTE Research Project. Whole-brain tractography was reconstructed with a two-tensor unscented Kalman filter to model crossing fibers, and bundles were segmented with the White Matter Analysis (WMA) pipeline using the ORG atlas to delineate SLF I-III. The primary outcome was tract length for each SLF subdivision (I-III) in each hemisphere (left, right). Group differences (football vs controls) were tested with a generalized least squares model, adjusting
for age, education, body mass index, race, and total intracranial volume.

Within the football group, we examined associations between SLF length and head-impact exposure estimates of frequency (impacts), linear acceleration (g-force), and rotational forces (radians/s^2). Former football players showed shorter right SLF I than controls (95% CI [-8.3, -1.5], p = 0.01). Among football players, greater linear-acceleration exposure was associated with shorter right SLF III (95% CI [-0.00002, -0.000002], p = 0.04). We controlled the false discovery rate (FDR) using the Benjamini & Hochberg method. No other SLF subdivisions or hemispheres exhibited significant group differences or interactions.

SLF tract length showed lateralized, exposure-dependent white-matter alteration after RHI. Former football players showed shorter right SLF I than controls, and greater linear-acceleration exposure related to shorter right SLF III, highlighting the susceptibility of right parieto-frontal pathways to linear forces. These findings position SLF length as a simple, biologically grounded marker of RHI.

Disclosures: A. Wickham: None. **B. Szekely:** None. **J. Stearns:** None. **A. Mirmajlesi:** None. **D. Mercado:** None. **M. Estrada:** None. **O. Pruden:** None. **S. Cange:** None. **C. Adler:** None. **C. Bernick:** None. **L. Balcer:** None. **J. Cummings:** None. **E.M. Reiman:** None. **R.A. Stern:** None. **M.E. Shenton:** None. **R.J. Rushmore:** None. **S. Bouix:** None. **H. Arciniega:** None.

Late-Breaking Poster

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NINDS #R01 NS124854
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NSTC 114-2321-B-A49-015
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NSTC 114-2926-I-A49A-501-G
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Center for Healthy Longevity and Aging Sciences and the Brain Research Center, National Yang Ming Chiao Tung University
Higher Education Sprout Project by the Ministry of Education (MOE)

Title: Fronto-cerebellar Circuit underlying Impulsive and Compulsive Behaviors: A Lesion Network Mapping Study

Authors: *Y.-H. LIU[1,2], C.-Y. LIN[3], C.-P. LIN[2], L.-H. CHANG[2], M. ROSSI[4], S.-H. KUO[1]; [1]Department of Neurology, Columbia University Irving Medical Center and the New York Presbyterian Hospital, NEW YORK, NY; [2]Institute of Neuroscience, National Yang Ming Chiao Tung University, Taipei City, Taiwan; [3]Department of Neurology, Baylor College of Medicine, Houston, TX; [4]Fleni, Buenos Aires, Pilar, Argentina

Abstract: Individuals with cerebellar degeneration have recently been found to exhibit prominent impulsivity and compulsivity. However, it remains unclear whether discrete lesions in the cerebellum can also produce these traits and whether specific lesion locations within the cerebellum or cerebello-cerebral connectivity patterns explain the occurrence of impulsive and compulsive symptoms. We conducted a cross-sectional, observational lesion-symptom network mapping study that included 36 patients with tumors or strokes restricted to the cerebellum and 18 matched 2:1 healthy controls by age, sex, and education. Participants underwent standardized assessments including the Scale for the Assessment and Rating of Ataxia, the Cerebellar Cognitive Affective Syndrome Scale, the Cerebellar Impulsivity-Compulsivity Assessment (CIA), and the Patient Health Questionnaire-9. We studied the cerebellar lesion location and size associated with the symptoms of impulsivity and compulsivity. In addition, we performed lesion network mapping using human connectome data (n=1000). Connectivity patterns were compared between individuals with cerebellar lesions who exhibit high vs. low impulsivity and compulsivity symptoms. We found that patients with cerebellar lesions have impulsive and compulsive symptoms, as reflected by higher CIA scores. Cerebellar lesions associated with higher CIA scores were located predominantly in the right cerebellar hemisphere, particularly in lobule VI, Crus I, and Crus II. Using the lesion network mapping technique, we identified that patients with higher CIA scores were associated with stronger connectivity of the right cerebellar hemisphere with the left frontal cortex, including the medial frontal gyrus, inferior frontal gyrus, caudate nucleus, and angular gyrus. On the other hand, these patients also had a weaker connectivity between the right and left cerebellar hemispheres, including lobules III-V, Crus I-II,

and lobules VII-IX. Finally, these connectivity patterns were not associated with either ataxia severity or other cognitive or emotional symptoms, demonstrating the specificity to impulsivity and compulsivity. Our findings identify the brain circuits related to impulsivity and compulsivity in the context of discrete cerebellar damage. Targeting the fronto-cerebellar connectivity may offer an avenue for neuromodulation to treat impulsivity and compulsivity.

Disclosures: Y. Liu: None. **C. Lin:** None. **C. Lin:** None. **L. Chang:** None. **M. Rossi:** None. **S. Kuo:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

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Program #/Poster #: LBP014.16/LBP155

Topic: D.04. Brain Injury and Trauma

Support: Zatkoff Fellowship

Title: Presentation of promising outcome assessments for the neurological investigation of repeated low-level blast exposure: A needed synthesis for effective research

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Abstract: *Introduction:* Repeated low-level blast exposure (rLLBE) is a nonconcussive exposure from military weapons training. Studying rLLBE is challenging, as its neuropathophysiology differs from impact exposure and it is subclinical (no diagnosable injury). In the past decade, research has advanced understanding of the neurological outcomes of rLLBE, with metrics evaluated for cognitive, symptom, and sensory domains. However, synthesized guidance for appropriate rLLBE outcome metrics is lacking, resulting in studies repeating mistakes and the use of inadequate metrics for research. This issue is significant, as clinicians and researchers across fields often assess rLLBE using conventional tools from their own sectors, perhaps unaware of more appropriate outcome metrics tested by rLLBE experts. Meanwhile, metrics for the exposure itself continue to advance in synthesis such as self-report and objective measures to include the Blast Exposure Monitoring Tool—an assessment of rLLBE via blast overpressure—which reached a milestone in the range of weapon types it covers in August 2025, emphasizing the urgent need to also better synthesize rLLBE outcome metrics. To improve efficiency in rLLBE research, this work reviews current and promising neurological outcome metrics post-rLLBE. *Methods:* We identified cognitive, symptom, and sensory (vestibular, ocular, auditory, balance, visual) outcome metrics used post-rLLBE from peer-reviewed literature through August 2025. We collected information on results, field applicability, implementation lessons, and participant and administrative burden. We then assessed each metric's utility for future research. *Results:* We cohesively present 8 cognitive tests with multiple batteries, 15 self-reports, 12 ocular assessments with several testing sets, 4 auditory evaluation pathways with many

components, and 7 balance assessments. Notably, promising rLLBE outcome metrics include the Defense Automated Neurobehavioral Assessment procedural reaction time for cognition, Neurological Symptom Inventory for symptoms, self-reported hearing outcomes, and thigh movement testing for balance. Further evaluation of ocular outcome metrics is warranted. These outcome metrics are feasibly implemented in military operational training. Last, we present positive and challenging attributes of each outcome metric. *Conclusions:* Ultimately, informed rLLBE outcome metrics enable better integration of findings, support scientific consensus across disciplines, and increase research efficiency. Consistent outcome metrics can reduce variability, promote progress, and improve productivity in the field.

Disclosures: E. Metzger: None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

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Topic: D.04. Brain Injury and Trauma

Support: CSCR16ERG019
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R21 NS132556-01
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HR16C0002
NRF-RS-2025-00515818

Title: Advanced Biomaterial Delivery of Hypoxia-Conditioned Extracellular Vesicles (EVs) as a Therapeutic Platform for Traumatic Brain Injury

Authors: *J. STEIN[1], Z. SONGZI[2], I. HAN[3], K. LEE[4];
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Abstract: Traumatic brain injury (TBI) is a leading cause of long-term neurological disability, yet current therapeutic strategies remain inadequate for promoting recovery. Here, we present a novel approach that delivers extracellular vesicles (EVs) derived from human-induced pluripotent stem cell-derived neural progenitor cells (hiPSC-NPCs) encapsulated within a gelatin-based injectable hydrogel (BIOGEL). Parent cells were conditioned with deferoxamine

(DFO) to simulate hypoxia, enriching EVs with neurotrophic and angiogenic factors. BIOGEL provided sustained EV release while mimicking the biomechanical properties of brain tissue. In a controlled cortical impact rat model (10-week-old female Sprague-Dawley rats, randomized groups, blinded assessments, n = 6-10 per group), BIOGEL loaded with hypoxia-conditioned EVs significantly reduced cortical lesion volume (2.62% ± 0.57 vs. 4.35% ± 1.2 in untreated controls, $p < 0.05$) and improved functional outcomes. Animals exhibited lower modified Neurological Severity Scores (4.53 ± 0.36 vs. 8.77 ± 0.35, $p < 0.001$) and enhanced motor recovery on rotarod testing (152.1 ± 105 s vs. 67.9 ± 42 s, $p < 0.05$). Histological analyses showed increased hippocampal neurogenesis (SOX2, Ki67), neuronal maturation (MAP2, Synapsin1), oligodendrocyte-mediated remyelination (SOX10, MBP), and angiogenesis (CD31), alongside reduced neuroinflammation (Iba1, CD86 down; CD163 up) and glial scarring (GFAP reduction). BDNF levels were markedly elevated (235.6 ± 128.7 pg/mL vs. 52.3 ± 31.8 pg/mL, $p < 0.01$), indicating an enhanced neurotrophic environment.
These findings provide proof-of-concept for a synergistic, multifaceted platform that modulates neuroinflammation while promoting neurogenesis, remyelination, and vascular repair. Our results demonstrate the translational potential of hypoxia-conditioned EV-loaded BIOGEL as a therapeutic strategy for neural repair after TBI.

Disclosures: J. Stein: None. **Z. Songzi:** None. **I. Han:** None. **K. Lee:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

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Program #/Poster #: LBP014.18/LBP157

Topic: D.04. Brain Injury and Trauma

Support: Healx

Title: Testing regenerative potential of therapeutics in human neurons using small footprint compartmentized testing beds

Authors: T. NAGENDRAN[1], W. CHADWICK[2], P. BROWNJOHN[2], ***A. M. TAYLOR**[1]; [1]Xona Microfluidics, Inc., Research Triangle Park, NC; [2]Healx Limited, Cambridge, United Kingdom

Abstract: The identification of therapeutics to promote regeneration and circuit repair following brain injury relies, for the most part, on animal models. Because human neurons may respond differently to injury, there remains an unmet need to develop more rapid and reliable models using human neurons. Further, recent guidance from the FDA articulates a desire to phase out animal testing by replacing testing “with more effective, human-relevant models.” Compartmentalized microfluidic models provide a rapid and reliable in vitro method to injure human iPSC-derived neurons and investigate regenerative responses in the presence of different treatment conditions. A novel compartmentalized microfluidic chip containing 4 small-footprint

testing beds minimizes the number of neurons used per unit (50,000) and speeds up imaging. The objective of this project was to perform an axon regeneration phenotypic assay using this chip with eGFP expressing human iPSC-derived glutamatergic neurons. In this feasibility study we quantified the extent of regrowth in response to treatments with known regenerative properties based on previously published results. These treatments included: (1) a mixture neurotrophins, BDNF and NT-3, (2) the non-muscle myosin II inhibitor, blebbistatin, and (3) a MAP4K4 inhibitor, PF-06260933. Axotomy was performed at 13 days after plating neurons in chips followed by treatment with vehicle, BDNF/NT-3, Blebbistatin, or PF-06260933 until day 15. Conditions were tested in triplicate. The results show that neurite length was significantly enhanced with BDNF/NT-3 (average >8-fold) and blebbistatin (~8-fold) compared with vehicle control ($p<0.05$, one-way ANOVA, Dunnett's multiple comparisons test). Additionally, we found that PF-06260933 significantly enhanced neuritic length by >16-fold compared with vehicle following axotomy ($p<0.05$). In summary, we demonstrated the effectiveness of smaller footprint compartmentalized testing beds to speed up testing for regenerative potential in human neurons.

Disclosures: T. Nagendran: A. Employment/Salary (full or part-time); Xona Microfluidics, Inc. **W. Chadwick:** A. Employment/Salary (full or part-time); Healx. **P. Brownjohn:** A. Employment/Salary (full or part-time); Healx. **A.M. Taylor:** A. Employment/Salary (full or part-time); Xona Microfluidics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor, Patent No. US2024/0034993A1, Xona Microfluidics, Inc..

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.19/Web Only

Topic: D.04. Brain Injury and Trauma

Title: Endoscopic management of complex multiloculated hydrocephalus: case-based review

Authors: *H. PATEL[1], A. MITTAL[2], K. SAHA[3], R. MISHRA[4], A. SHRIVASTAVA[4]; [1]Medical student, All India Institute of Medical Sciences Bhopal, Bhopal, India; [2]Neurosurgery, Queen Hospital, Barking Havering & Redbridge University Hospital NHS Trust, Romford, United Kingdom; [3]Neurosurgery, PD Hinduja Hospital, Mumbai, India; [4]Neurosurgery, All India Institute of Medical Sciences, Bhopal, India

Abstract: The prevalence of multiloculated hydrocephalus remains disproportionately high in low-socioeconomic regions, largely due to elevated infection rates. Consequently, neuroendoscopy has become the preferred minimally invasive strategy, as it allows effective shunt retrieval and reduces the need for repeated revision surgeries. In this context, our study outlines the endoscopic management approaches implemented in two complex cases of multiloculated hydrocephalus complicated by shunt malfunction. Case 1 involves a 12-year-old

male with altered sensorium; whose imaging revealed ventriculomegaly, multiple intraventricular septations, and eight malfunctioning retained ventricular catheters. Consequently, the patient underwent endoscopic fenestration, adhesiolysis, removal of the retained catheter, and placement of three antibiotic-impregnated catheters. In contrast, Case 2 concerns a 1-year-old female with congenital hydrocephalus managed previously with a ventriculoperitoneal shunt, who presented with progressive macrocephaly and a bulging anterior fontanelle. Imaging confirmed multiloculated hydrocephalus with an indwelling shunt. Therefore, she underwent septostomy and endoscopic ventriculocystostomy. Notably, both patients exhibited significant postoperative neurological improvement, with no evidence of shunt failure or infection over the follow-up period. Given that up to two-thirds of shunt malfunctions arise from ventricular-end dysfunction, neuroendoscopy yields critical insight into key pathophysiological processes such as hyperemia, ependymal thickening, septation formation, neovascularization, and catheter encasement. Moreover, this modality enables targeted interventions, including fenestration, septostomy, or third ventriculostomy and helps to restore cerebrospinal fluid dynamics while allowing safe removal of malfunctioning catheters under direct visualization. However, when catheters are adherent or densely encased, they may be left in situ pragmatically to mitigate the risk of iatrogenic intraventricular hemorrhage.

Disclosures: H. Patel: None. **A. Mittal:** None. **K. Saha:** None. **R. Mishra:** None. **A. Shrivastava:** None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.20/LBP158

Topic: D.04. Brain Injury and Trauma

Title: Fecal microbiota transplant alters metabolic expression of disease-associated microglia post-traumatic brain injury

Authors: *A. DE FINA;
Northwestern University, Chicago, IL

Abstract: Background Traumatic brain injury (TBI) affects ~3 million Americans annually, with the elderly (65+) representing a large percentage of cases. Elderly patients exhibit chronic activation of disease-associated microglia (DAM)post-TBI, leading to neuroinflammation and neurodegeneration. Gut dysbiosis occurs with age, influencing response to injury and increasingmorbidityinelderly TBI patients. Previous studies showed that fecal microbiota transplant (FMT) can restore gut microbial community structure and reduce neuroinflammation after TBI in young patients. However, the benefits of FMT in aged TBI subjects remain understudied.
HypothesisRestoring a youthful gut microbiome via youthful FMT in aged TBI mice will attenuate activation of DAM.

MethodsAged C57BL/6 mice (84 weeks old, n=2 per group) underwent severe TBI via open-head controlled cortical impact. Two hours post-injury, the mice received FMT via oral gavage with stool from uninjured young (10-14weeks old) or aged donors. 60 days post-injury, brains were harvested and processed for single-cell RNA sequencing.DAM were subsetted and re-integrated for differential expression analysis among treatment groups. Gene ontology and pathway analyses were performed using *EnrichR*.
ResultsBetween 4,000 and 18,000 cells per group were recovered after quality filtering. Gene ontology and pathway analyses corroborated the effective restoration of a youthful microbial community, as cellular respiration and mitochondrial activity were elevated in the young FMT samples. Enrichment of energy derivation by oxidation of organic compounds and mitochondrial electron transport was representative of increased ATP production and metabolic support of neurons. Gene ontologies and pathway analyses of the TBI ygFMT vs. TBI agFMT showed enrichment of protein degradation & ribosome biogenesis pathways, suggesting cellular stress responses and compensatory repair mechanisms. Thus, TBI imposes a metabolic and inflammatory burden that blunts the full benefits of FMT. Despite this, young FMT still partially restores mitochondrial function, which may underlie its neuroprotective effects.
ConclusionOur hypothesis that youthful FMT would attenuate the activation of DAM in aged TBI subjects was not supported. Given that aging alone results in an increased DAM signature, the current results suggest that a youthful gut microbiota may restore microglia to a homeostatic state in aged mice. These findings highlight the role of FMT as a novel therapeutic not only in injury, but also in other aging-related conditions. Further research is necessary to translate these findings into clinical practice.

Disclosures: A. De Fina: None.

Late-Breaking Poster

LBP014: D.04. Brain Injury and Trauma

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP014.21/LBP159

Topic: D.04. Brain Injury and Trauma

Title: Astrocyte-Specific Deletion or Pharmacologic Inhibition of Sur1 Reduces Neuroinflammation and Improves Cognitive Outcomes After Moderate Traumatic Brain Injury

Authors: *C. TOSUN, K. KELEDJIAN, O. TSYMBALTUK, V. GERZANICH, J. SIMARD; University of Maryland Baltimore, Baltimore, MD

Abstract: Traumatic brain injury (TBI) induces widespread neuroinflammation, which contributes to secondary injury and long-term cognitive deficits. The sulfonylurea receptor 1 (Sur1), a regulatory subunit of the Sur1-Trpm4 channel, has been implicated in post-injury edema and inflammation. Here, we tested the hypothesis that Sur1 in astrocytes contributes to neuroinflammatory responses and behavioral impairments following moderate TBI. A moderate injury was induced in mice using a 3.5-mm impactor tip at 6 m/s velocity with 2 mm

deformation depth. Sham animals underwent the same surgical procedure without impact. Two strategies were employed to target Sur1: (1) pharmacological inhibition using low-dose glibenclamide infused for 7 days post-injury, and (2) genetic deletion via astrocyte-specific Sur1 knockout using a Cre-Lox system. Tissues were collected at 7 days post-injury to assess histopathology, and behavioral testing was conducted using the novel object recognition (NOR) task. Glibenclamide treatment significantly reduced reactive astrogliosis in the ipsilateral thalamus and contralateral hippocampus, as marked by GFAP immunoreactivity, compared to vehicle controls. These astrocytes also showed robust co-localization with CCL2, a chemokine involved in immune recruitment. Similarly, astrocyte-specific Sur1 knockout mice showed significantly reduced GFAP expression in both regions relative to floxed littermate controls. Furthermore, Iba1-positive microglial activation was notably reduced in the contralateral hippocampus, corpus callosum, and ipsilateral thalamus in knockout animals. Behaviorally, both glibenclamide-treated and Sur1 knockout mice exhibited improved performance in the NOR task, indicating preserved recognition memory. Together, these findings suggest that astrocytic Sur1 contributes to post-TBI neuroinflammation and cognitive impairment. Targeting Sur1 in astrocytes, either pharmacologically or genetically, may offer a promising therapeutic approach to mitigate secondary injury mechanisms following TBI.

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Late-Breaking Poster

LBP015: D.05. Spinal Cord Injury and Plasticity

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP015.01/LBP160

Topic: D.05. Spinal Cord Injury and Plasticity

Support: core research grant (CRG/2020/002621/BHS)
ICMR-ECD grant (P-16/ECD/Adhoc/49/2022-23)
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Title: From Injury to Relief: Focal Adhesion Kinase as a Novel Therapeutic Target for Burn Injury-Induced Pain

Authors: *D. SHEKHAWAT[1], D. CHOUHAN[2], A. KOTIYAL[3], V. TIWARI[4];
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Abstract: Abstract: Burn injury-induced pain (BIP) is a significant global health concern, affecting diverse populations, including children, military veterans, and accident victims. Current pharmacological treatments for BIP are associated with severe side effects, including drug addiction, respiratory depression, sedation, and constipation, limiting their clinical utility. Therefore, identifying novel therapeutic targets is crucial. In this study, we investigated the role of focal adhesion kinase (p-FAK) in BIP for the first time and explored its underlying mechanisms. Defactinib (DFT), a potent p-FAK inhibitor, was administered intraperitoneally at doses of 5, 10, and 20 mg/kg, demonstrating significant analgesic efficacy in reducing both evoked and spontaneous pain without inducing addiction or central nervous system toxicity. Burn injury activated p-FAK-mediated phosphorylation of Erk1/2 and NR2B in the dorsal root ganglia (DRG), contributing to hypersensitivity via microglial activation, neuropeptide release, and elevated proinflammatory cytokines. DFT mitigated these effects by downregulating NR2B, reducing substance P levels, inhibiting microglial activation, and restoring IL-10 levels while leaving CGRP levels unchanged. These findings provide novel insights into the pivotal role of p-FAK in BIP pathophysiology and highlight its potential as a promising therapeutic target. Targeting p-FAK with inhibitors like DFT may offer an effective strategy for managing BIP while avoiding the severe side effects of conventional analgesics. This study paves the way for further research into p-FAK-targeted therapeutics for burn injury-induced pain.
Keywords: Burn pain, Defactinib, Focal adhesion kinase, NR2B, Microglia, Neuro-inflammation.

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Late-Breaking Poster

LBP015: D.05. Spinal Cord Injury and Plasticity

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP015.02/LBP161

Topic: D.05. Spinal Cord Injury and Plasticity

Title: Cortical and Subcortical Activation During Phases of Involuntary Bladder Contractions in Complete Spinal Cord Injury

Authors: *R. K. AFSAHI, N. HA, M. MOLINA, E. KREYDIN;
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Abstract: Spinal cord injury (SCI) affects over 15 million people worldwide, frequently resulting in neurogenic detrusor overactivity (DO) and impaired bladder storage. Although neuroimaging studies have characterized brain activity during filling and voiding, the temporal evolution of supraspinal recruitment across the inter-contraction interval remains poorly defined. In this study, 10 adult male patients with a history of complete SCI at levels varying between T6 and L1 underwent 4 filling cycles of urodynamics (UDS) and simultaneous blood oxygen level dependent (BOLD) fMRI. After each fill, they were instructed to hold for 60 seconds and then signaled to void. Voids that occurred outside of 10 seconds of the void command were

considered DO contractions. The period between contractions was then divided into 5 periods of equal length "P1 - P5." Detrusor overactivity events were further subdivided into four contraction phases based on the urodynamic pressure trace: rise (initial upslope), early (first maintained segment following onset), plateau (sustained peak contraction at maximum detrusor pressure), and fall (downslope). BOLD effect during each P-period and contraction phase was then compared to rest using one sample t-tests. Significance was set at $p < 0.005$ with minimum cluster size of 25 voxels. Results showed that supraspinal recruitment during storage was temporally graded. Compared to baseline (P3), P1 and P2 demonstrated widespread clusters in parietal and temporal lobes, while P4 and P5 demonstrated focal recruitment within cerebellum, middle temporal gyrus, and premotor cortex. This shift reflects a transition from diffuse early engagement to targeted cerebellar, temporal, and motor preparatory involvement as the bladder approaches contraction. During contractions, rise DO showed no significant clusters. In contrast, early, plateau, and fall DO each demonstrated distributed activations within frontal and parietal cortices as well as midbrain. Notably, there was no activation of insula or anterior cingulate gyrus, regions commonly associated with lower urinary tract control, at any point during contraction. This study reveals that supraspinal engagement is strongest early in storage and narrows to focal cerebellar and premotor activity late, while contractions involve frontal, parietal, and midbrain recruitment but lack classic limbic and insular activation. These findings suggest DO in SCI is driven primarily by spinal reflex mechanisms with limited supraspinal modulation, highlighting a temporal gradient that may define optimal windows for neuromodulatory intervention.

Disclosures: R.K. Afsahi: None. **N. Ha:** None. **M. Molina:** None. **E. Kreydin:** None.

Late-Breaking Poster

LBP015: D.05. Spinal Cord Injury and Plasticity

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP015.03/LBP162

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Paula and Joseph C. "Rusty" Walter III
Walter Oil & Gas Corporation
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NIH Grant 5R01NS119587

Title: Epidural vs. transcutaneous spinal stimulation: neurophysiological and functional outcomes in motor-complete cervical spinal cord injury

Authors: *J. OH[1], A. G. STEELE[1], M. SCHEFFLER[1], C. MARTIN[1], A. VALDIVIA PADILLA[1], J. SHEYNIN[2], A. STAMPAS[3], P. J. HORNER[1], D. G. SAYENKO[1];
[1]Houston Methodist Research Institute, Houston, TX; [2]Department of Psychiatry and Behavioral Science, Texas A&M University, Houston, TX; [3]TIRR Memorial Hermann Hospital, Houston, TX

Abstract: Cervical spinal cord injury (SCI) causes profound upper-limb (UL) impairments, severely limiting independence and quality of life. Spinal neuromodulation, including non-invasive transcutaneous spinal stimulation (TSS) and invasive epidural spinal stimulation (ESS), has emerged as a promising strategy for motor recovery, yet direct comparisons remain limited. This study investigated the immediate effects of TSS and ESS on UL motor output in two individuals with chronic, motor- and sensory-complete tetraplegia (P01: C5 injury; P02: C4 injury). We hypothesized that ESS would provide greater spatial selectivity and functional gains than TSS, particularly for fine motor tasks critical for independence. A 32-contact epidural array (Boston Scientific, USA) was implanted over the C6-T1 vertebrae in P01 and the C7-T2 vertebrae in P02, targeting cervical circuits projecting to distal UL muscles. For comparison, TSS was delivered using a 5 cm round electrode spanning C6-T1. Neurophysiological and functional assessments were performed under both conditions. Isometric grip and tripod pinch forces were measured with a handheld dynamometer, and electromyography (EMG) recorded UL motor unit activity. Functional outcomes were evaluated through standardized dexterity tasks and object manipulation requiring precision grasp. ESS enabled precise rostrocaudal and mediolateral activation of cervical motor pools compared with the diffuse, less specific recruitment observed during TSS. Tripod pinch strength improved with ESS in both participants, whereas grip strength improved only in P01. TSS did not improve either grip or pinch. EMG confirmed greater motor unit recruitment during ESS. Functionally, ESS enhanced dexterity, object manipulation, and improved trunk stability to support upright posture, extended reach, and more accurate movements. In contrast, TSS elicited widespread activation with limited segmental specificity, often requiring higher intensities that increased discomfort. While grip improvements have been reported in some individuals with incomplete injuries or when suprathreshold stimulation is tolerated, in these motor-complete cases TSS did not improve grip or pinch, indicating limited effectiveness for restoring fine, task-specific motor control. This study highlights the neurophysiological and functional advantages of ESS over TSS. The superior selectivity and improvements in grip and pinch strength, dexterity, and movement precision observed with ESS suggest its potential as a more effective modality for UL rehabilitation in cervical SCI and support the development of patient-specific neuromodulation strategies.

Disclosures: J. Oh: None. **A.G. Steele:** None. **M. Scheffler:** None. **C. Martin:** None. **A. Valdivia Padilla:** None. **J. Sheynin:** None. **A. Stampas:** None. **P.J. Horner:** None. **D.G. Sayenko:** None.

Late-Breaking Poster

LBP015: D.05. Spinal Cord Injury and Plasticity

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP015.04/LBP163

Topic: D.05. Spinal Cord Injury and Plasticity

Support: Philanthropic funding from the Walter Oil & Gas Corporation
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Title: From Circuits to Function: Individualized Epidural Stimulation Approaches for Upper Limb Recovery after Cervical SCI

Authors: J. OH[1], A. G. STEELE[1], C. MARTIN[1], M. SCHEFFLER[1], J. SHEYNIN[2], A. STAMPAS[3], C. KARMONIK[1], T. G. HODICS[1], P. J. HORNER[1], ***D. SAYENKO**[1]; [1]Houston Methodist Research Institute, Houston, TX; [2]Department of Psychiatry and Behavioral Science, Texas A&M University, Houston, TX; [3]University of Texas Health Science Center, Houston, TX

Abstract: Individuals with tetraplegia due to spinal cord injury (SCI) consistently rank restoration of upper limb function as their highest treatment priority, as even modest gains can markedly improve independence and quality of life. Despite advances in rehabilitation and assistive technologies, functional recovery remains limited. Epidural spinal stimulation (ESS) has restored standing and stepping after paraplegia via lumbar cord stimulation, but mechanisms involving weight-bearing input and rhythm-generating networks may not translate to the cervical cord. Upper limb control requires non-rhythmic, task-specific coordination, greater corticospinal integration, and selective motor pool activation, highlighting the need for spatially and temporally precise stimulation. Non-invasive cervical stimulation has shown encouraging results in incomplete injuries but lacks spatial resolution, standardized parameters, and applicability to motor- and sensory-complete injuries. Cervical ESS may overcome these limitations by enabling targeted activation of segment-specific motor circuits. In our study, we implemented a location-specific neuromodulation strategy using a surgically implanted 32-contact epidural paddle array over the cervical spinal cord in two individuals with chronic, motor- and sensory-complete tetraplegia (AIS A, NLI C4 and C5, 10 years post-SCI). Individualized motor pool maps guided electrode configurations and stimulation parameters for upper limb engagement. Targeted ESS produced immediate, reproducible improvements in force generation, multi-joint coordination, and functional tasks such as object manipulation and writing, effects absent under off-target (sham) or no-stimulation conditions. Neurophysiological recordings confirmed activation of spinal and corticospinal pathways, supporting the role of segmental targeting in restoring volitional control. These results demonstrate that cervical ESS can enable rapid, task-specific improvements in upper limb function even in chronic, motor- and sensory-complete SCI. This work supports a shift from generalized spinal stimulation toward function- and segment-specific paradigms and provides a translational framework for individualized neuromodulation protocols aimed at restoring arm and hand function in severe cervical SCI.

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Late-Breaking Poster

LBP015: D.05. Spinal Cord Injury and Plasticity

Location: SDCC Hall B

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Program #/Poster #: LBP015.05/LBP164

Topic: D.05. Spinal Cord Injury and Plasticity

Support: NIH Grant R01 NS116404

Title: Combining neural progenitor cell transplantation with rehabilitation to improve motor function after spinal cord injury

Authors: *V. JAGRIT[1], A. SMITH[2], R. SHETH[3], A. CHIU[3], S. VALLABHAJOSYULA[3], H. THOMAS[3], T. KIM[3], L. FRIEDRICH[4], M. G. BLACKMORE[5], J. N. DULIN[6];
[1]Biology, Texas A&M University, College Station, TX; [2]MD Anderson Cancer Center, Houston, TX; [3]Texas A&M University, College Station, TX; [4]biomedical sciences, Marquette University Department of Biological Sciences, Milwaukee, WI; [5]Biomedical Sciences, Marquette University, Milwaukee, WI; [6]Department of Biology, Texas A&M University, College Station, TX

Abstract: Spinal cord injury (SCI) is a traumatic injury that often leads to lifelong disabilities. The central nervous system lacks the ability to regenerate cells after injury, causing permanent paralysis after injury. Neural progenitor cells (NPCs) are a promising potential treatment due to their ability to replace lost neurons and integrate into injured host spinal cord circuitry. Previous research has shown positive results of neural progenitor cell transplantation and rehabilitation, as individual treatments, on motor functional outcomes. The cellular and molecular mechanism by which engrafted neurons contribute to functional gains remains unclear. Thus, it is important to understand the mechanism of modest gain shown by various treatments to identify effective therapeutic strategies to regain functional neuronal connectivity after SCI. We utilized a combinatorial approach of NPC transplantation with task-specific rehabilitation to determine whether combinatorial treatment could further enhance synaptic integration of graft neurons into forelimb motor neuronal circuits and functional recovery. We administered a dorsal wire knife lesion to the C5 spinal cord and provided rehabilitative training using a skilled specific pellet-reaching task over a twelve-week period. Beginning at week 8 post-injury, we used a chemogenetic approach to acutely silence graft activity for two weeks. In addition, we used pseudorabies virus (PRV) to trace the synaptic integration of grafted cells with host neuronal circuits. We found that combined NPC transplantation and rehabilitation resulted in significant improvement of forelimb motor functional recovery, compared to other treatment groups. Ongoing work is evaluating whether combined treatment can promote plasticity in graft-host synaptic connectivity to a greater extent than either treatment alone. Currently we are quantifying the density and molecular phenotypes of PRV+ neurons within grafts and host tissue to assess their contribution in functional recovery and their integration in host neuronal circuits. These results highlight the therapeutic potential of combining NPC transplantation with activity-based rehabilitation for forelimb motor functional recovery.

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Late-Breaking Poster

LBP015: D.05. Spinal Cord Injury and Plasticity

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP015.06/LBP165

Topic: D.05. Spinal Cord Injury and Plasticity

Support: National Science and Technology Major Project of the Ministry of Science and Technology of China No. 2022ZD0210100
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Tsinghua University-IDG/McGovern "Brain+X" seed Grant Doctoral and Postdoctoral Program

Title: Lesion-targeted epidural electrical stimulation achieves coordinated locomotor recovery after acute complete spinal cord injury

Authors: *Z. LI[1], Z. SHANG[1], Z. WANG[1], Z. LV[1], Y. YANG[1], Y. WANG[1], H. GENG[1], Z. LI[1], Q. YAO[2], S. NI[1];
[1]Shandong University, Jinan, China; [2]Tsinghua University, Beijing, China

Abstract: Epidural electrical stimulation (EES) of the lumbosacral spinal cord has shown promise in restoring locomotor function after spinal cord injury (SCI). This approach enhances plasticity between residual descending projections and lumbosacral spinal networks. However, in complete or severe SCI, insufficient residual axonal connections limit the ability of individuals to regain voluntary and natural movements. In this study, we hypothesized that EES targeting the injury gap, rather than the lumbosacral spinal cord, could promote axonal regeneration across the lesion. Using two complete thoracic SCI rat models, the crush model and transection model, we evaluated the therapeutic efficacy of lesion-targeted EES alone or combined with treadmill training (EES^{TRAIN}) from 2 days post-injury. To ensure stimulation efficiency, finite element simulations were first utilized to optimize electrode configurations above and below the lesion systematically. In the complete crush model, both EES and EES^{TRAIN} significantly improved locomotor recovery, particularly step coordination and body stability, even under the stimulation-off conditions at 6 weeks post-injury. The BBB score of ~16 achieved by the EES^{TRAIN} group is higher than all our previously reported recoveries to date in complete SCI rats. Similar results were observed in the transection model. Histological results revealed that robust regeneration of $5\text{-}HT^{+}$ raphe-spinal projections and TH^{+} dopaminergic projections beyond the lesion gap ~5 mm away, extending into the caudal lumbar locomotor centers, with intense interactions re-established. Additionally, EES^{TRAIN} created a more permissive microenvironment, characterized by a three-fold reduction in GFAP-immunoreactive astrocytes and a four-fold decrease in cavity size. Interestingly, single-cell RNA sequencing demonstrated that although the primary objective of supra- and sub-lesional EES is to promote neural growth at the lesion site, it also remotely regulates the molecular signatures and metabolic activity of lumbosacral segments.

Remarkably, cadherin3 (CDH3)-expressing interneurons, as the signaling hubs for information integration, played a critical role in the neural repair program. The supportive microenvironment constructed by EES influences not only neuronal growth but also glial and non-glial cell responses, thereby facilitating reorganization of the whole neural network. Overall, this novel lesion-targeted neurostimulation strategy highlights the importance of optimizing stimulation location and expands the therapeutic potential beyond classical lumbosacral stimulation.

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Late-Breaking Poster

LBP015: D.05. Spinal Cord Injury and Plasticity

Location: SDCC Hall B

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Program #/Poster #: LBP015.07/LBP166

Topic: D.05. Spinal Cord Injury and Plasticity

Title: A Novel Stimulation Paradigm: Combining Transcutaneous Spinal Cord Stimulation with Peripheral Nerve Stimulation

Authors: *T. N. LE, A. CIMOLATO, N. SECEROVIC, S. RASPOPOVIC;
Medical Physics and Biomedical Engineering, Medical University Vienna, Vienna, Austria

Abstract: Cervical spinal cord injury often disrupts corticospinal pathways, leaving many survivors with chronic upper limb paralysis that limits independence and quality of life. Transcutaneous spinal cord stimulation (tSCS) has shown promise for improving strength and dexterity, but outcomes remain inconsistent due to broad stimulation spread, limited sensory integration, and limited functional transfer. Transcutaneous electrical nerve stimulation (TENS) has the potential to increase functional outcomes by providing patients with sensory feedback. Combining both stimulation paradigms can reap the benefits from both, but is non-trivial due to the possibility of interference. As a result, no study has systematically combined tSCS with TENS for upper limb rehabilitation.
We developed a novel protocol integrating tSCS with sensory feedback through TENS. The system delivers: (1) tSCS at the cervical level, (2) TENS to the ulnar nerve at the elbow, and (3) TENS to the ulnar and median nerves at the wrist. The spinal cord is stimulated during arm and hand movements, with proportional sensory feedback triggered by wearable sensors. This design aligns sensory feedback with motor action, as well as increasing the number of stimulation parameters, allowing for greater control over the perceived sensation.
We tested this protocol with 12 subjects during exploratory tests. Each session included two stimulation paradigms: (1) spinal cord stimulation alone, and (2) spinal cord stimulation combined with TENS delivered to both ulnar and median nerves. We systematically explored different stimulation parameters to minimize interference between the stimulating modalities. Results showed that participants could distinguish the sensory stimulation from the paresthesia induced by tSCS. Sensory parameters were efficiently selected by stimulating below the sub-

motor threshold in order to preferentially recruit afferent fibers. Furthermore, we successfully demonstrated the feasibility of integrating both stimulation types and modulating their output according to motion intention and environmental interaction.
Our findings suggest that combining spinal cord stimulation and peripheral nerve stimulation is technically feasible and may offer complementary benefits for individuals with upper limb paralysis. This approach could support the development of a modular system tailored to individual patient needs, thereby maximizing the potential for recovery.

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Late-Breaking Poster

LBP016: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP016.01/LBP167

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: Belfer Neurodegeneration Consortium
HHMI
Cure Alzheimer's Fund
Ludwig Family Foundation

Title: Interferon-gamma Stimulates Reactive Astrocytes to Functionally Present Antigen to CD4+ T Cells

Authors: *T. M. FISHER[1], F. LIMONE[2], C. WRIGHT[3], S. A. LIDDELOW[4];
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Abstract: In response to pro-inflammatory immune cell-derived cytokines and type II interferon, astrocytes produce components of the machinery required to attract and functionally present antigens to CD4+ T Cells via MHC-II molecules. Re-analysis of astrocyte-enriched single-cell sequencing of bacterial mimetic-injected mice shows that this population of antigen presenting astrocytes is transcriptionally distinct and expanded 24 hours after peripheral immune challenge. We show that these antigen presenting astrocytes are localized to the glia limitans superficilias on the surface of the brain in multiple mouse models of central nervous system inflammation. Importantly, we demonstrate that CD4+ T cells expand rapidly in vitro when cultured with astrocytes treated with these cytokine factors. These findings suggest a novel active role of astrocytes in modulating immune responses in the central nervous system under inflammatory conditions by presenting antigens to CD4+ T cells.

Disclosures: T.M. Fisher: None. **F. Limone:** None. **C. Wright:** None. **S.A. Liddelow:** None.

Late-Breaking Poster

LBP016: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP016.02/LBP168

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: Intracellular Calcium Signaling and Mitochondrial Dysregulation Mediate Vacor-Induced SARM1-Dependent Axonal Degeneration in Ngn2 Neurons

Authors: *Y. KWAK, A. WESTERHAUS, K. WORRINGER, R. IHRY;
Novartis Biomedical Research, Cambridge, MA

Abstract: Axonal degeneration is a defining feature of various neurodegenerative disorders, yet the molecular events remain poorly characterized. In this study, we delineate the mechanisms by which vacor induces SARM1-dependent axonal degeneration in Ngn2 neurons, with a focus on intracellular calcium signaling and mitochondrial dysfunction. Vacor treatment elicited axonal degeneration in a dose- and time-dependent manner, accompanied by elevated intracellular Ca^{2+} levels and mitochondrial dysregulation. Mechanistically, vacor-induced accumulation of cADPR activated intracellular calcium channels such as a ryanodine receptor 3 (RYR3), leading to proteolytic cleavage of axonal architectural proteins including α-spectrin, microtubule-associated protein 2 (MAP2) and neurofilament light chain (NfL). Concurrently, vacor disrupted mitochondrial integrity by cleaving membrane proteins (VDAC, COX IV, and TOMM20) and upregulating cytochrome C expression. Mitophagy was markedly impaired, as evidenced by reduced levels of Ub-Parkin and key mitophagy regulators (Pink1, LC3 I/II, SQSTM1/p62, ULK1). Treatment of vacor immediately increased Ub-Parkin up to 8 hrs. Then, Ub-Parkin was markedly decreased suggesting abnormal mitophagy. Notably, active SARM1 localized to the mitochondrial membrane and SARM1/TRAF6 complex that may hinder mitophagic clearance. JNK plays a selective role in modulating PINK1 stabilization and initiating stress-induced mitophagy in neuronal cells. Following vacor treatment, phosphorylated JNK (T183/Y185) levels markedly increased at the 4-hour time point, indicating early activation of the mitophagy pathway. However, by 16 hours, P-JNK levels were fully downregulated, suggesting a disruption in sustained mitophagic signaling. This transient activation of JNK may compromise the stabilization of PINK1 on damaged mitochondria, a critical step for mitophagy initiation and progression. These findings are consistent with previous reports highlighting the importance of sustained JNK signaling in maintaining effective mitophagic responses. Therefore, these findings underscore the synergistic roles of calcium dysregulation and mitochondrial dysfunction in SARM1-mediated axonal degeneration and highlight potential therapeutic targets for neurodegenerative diseases.

Disclosures: Y. Kwak: None. **A. Westerhaus:** None. **K. Worringer:** None. **R. Ihry:** None.

Late-Breaking Poster

LBP016: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP016.03/LBP169

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Title: ADAM17 Inhibitors Rescue CSF1R Hypofunction in In Vitro Models of CSF1R-ALSP

Authors: A. RENOUX, A. MARTINS, F. GERGITS, B. PANDYA, C. MIRESCU, *K. C. LARSON;
Vigil Neuroscience, Watertown, MA

Abstract: Microglial dysfunction contributes to numerous neurodegenerative disorders, including CSF1R-related adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (CSF1R-ALSP), a rare microgliopathy caused by heterozygous loss-of-function mutations in the *colony stimulating factor 1 receptor* (*CSF1R*) gene. *CSF1R*encodes a membrane receptor essential for myeloid cell differentiation, as well as microglial survival, proliferation, and neuroimmune function. While recent natural history studies of ALSP have established biomarker and neuroimaging frameworks that support interventional approaches, there are no approved therapies to modify disease progression in CSF1R-ALSP, underscoring the urgent unmet medical need for therapies despite advances in clinical understanding. Here, we explored the therapeutic hypothesis that impaired CSF1R signaling in CSF1R-ALSP can be rescued by modulating metalloproteases or sheddases that mediate receptor cleavage. To this end, a focused library of small-molecule protease inhibitors was screened for their ability to block CSF1R shedding, as measured by reduced levels of soluble CSF1R in cell-based assays. Compounds were also screened for their ability to enhance receptor activity and restore downstream signaling as assessed by CSF1R phosphorylation. Notably, inhibitors of ADAM metallopeptidase domain 17 (ADAM17) were identified as modulators of CSF1R surface levels across multiple human cell-based models and were confirmed to restore receptor activity in human microglia harboring the heterozygous I794T mutation associated with CSF1R-ALSP. Collectively, these findings highlight ADAM17 inhibition as a potential strategy to ameliorate CSF1R signaling dysfunction and support the molecular discovery of brain-penetrant inhibitors as a novel therapeutic approach for CSF1R-ALSP.

Disclosures: A. Renoux: None. **A. Martins:** None. **F. Gergits:** None. **B. Pandya:** None. **C. Mirescu:** None. **K.C. Larson:** None.

Late-Breaking Poster

LBP016: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP016.04/LBP170

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH Grant R01 NS110949
NIH Grant R35 NS132326

Title: Neutrophil-microglia interaction drives motor dysfunction in neuromyelitis optica model induced by subarachnoid AQP4-IgG

Authors: *F. QI[1], V. A. LENNON[2], S. ZHAO[2], C. LUCCHINETTI[3], L.-J. WU[4];
[1]Department of Laboratory Medicine/Pathology, Mayo Clinic, Rochester, MN; [2]Mayo Clinic, Rochester, MN; [3]Department of Neurology, College of Medicine, Rochester, MN; [4]Neurology, University of Texas Health Science Center at Houston, Houston, TX

Abstract: Neutrophils and neutrophil extracellular traps (NETs) contribute to early neuromyelitis optica (NMO) histopathology initiated by IgG targeting astrocytic aquaporin-4 water (AQP4) channels. Yet, the mechanisms recruiting neutrophils and their pathogenic roles in disease progression remain unclear. To investigate molecular-cellular events preceding classical complement cascade activation in a mouse NMO model, we continuously infused, via spinal subarachnoid route, a non-complement-activating monoclonal AQP4-IgG. Parenchymal infiltration of netting neutrophils containing C5a ensued with microglial activation and motor impairment, but no blood-brain barrier leakage. Motor impairment and neuronal dysfunction both reversed when AQP4-IgG infusion stopped. Two-photon microscopy and electron-microscopy-based reconstructions revealed physical interaction of infiltrating neutrophils with microglia. Ablation of either peripheral neutrophils or microglia attenuated the motor deficit, highlighting their synergistic pathogenic roles. Of note, mice lacking complement receptor C5aR1 exhibited reduction in neutrophil infiltration, microglial lysosomal activation, neuronal lipid-droplet burden and motor impairment. Pharmacological inhibition of C5aR1 recapitulated this protection. Immunohistochemical analysis of an NMO patient's early spinal cord lesions revealed analogous pathological findings. Our study identifies neutrophil-derived C5a signaling through microglial C5aR1 as a key early driver of reversible motor neuron dysfunction in the precytolytic phase of NMO.

Disclosures: F. Qi: None. **V.A. Lennon:** None. **S. Zhao:** None. **C. Lucchinetti:** None. **L. Wu:** None.

Late-Breaking Poster

LBP016: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Location: SDCC Hall B

Time: Saturday, November 15, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP016.05/LBP171

Topic: D.06. Multiple Sclerosis and Other Demyelinating Diseases

Support: NIH R01 DC020528
DOD MS220167

Title: Knockout of vitronectin increased EAE pathology without affecting demyelination or motor deficits

Authors: *J. H. BULLEN, C. JIA;
Dept. of Biomed. Sci., East Tennessee State Univ., Johnson City, TN

Abstract: Multiple sclerosis (MS) is an autoimmune demyelinating disease of the central nervous system affecting more women than men and lacking both effective treatment after the disease enters the chronic phase and a final cure. Rodent experimental autoimmune encephalomyelitis (EAE) mimics MS pathology in T-cell infiltration, inflammation, and motor deficits measured by clinical symptom scores. Vitronectin (VTN) has been shown to leak and accumulate in EAE lesions, activating microglia and astrocytes. Here, we investigated whether knockout of VTN affected EAE progression and lesion pathology. EAE was induced in both female and male VTN+/+ and VTN-/- mice using MOG_{35-55}. Clinical scores were measured daily with peak scores found between days 15- 20 in both sexes, consistent with previous work in C57BL/6 mice. Scores reached a steady state, i.e., chronic disease phase, after 21-23 days. No clinical differences in peak and chronic phases were noted between sexes or genotypes. At 35 days, demyelination measured by eriochrome cyanine R (EC) staining was comparable between VTN+/+ and VTN-/- in both sexes. However, activation of microglia and astrocytes measured by CD68 and GFAP was increased and leukocyte infiltration measured by CD45 was reduced in the lumbar spinal cord of VTN-/- female mice. Cuprizone-mediated demyelination (CPZ) is a toxin-induced MS model to study demyelination and remyelination that is not significantly attributed to the peripheral immune system. To test the effect of VTN on the CPZ model, we administered 0.2% cuprizone in powdered chow to female VTN+/+ and VTN-/- mice for 5 weeks. EC staining showed no differences in demyelination between genotypes accompanied by no apparent difference in motor coordination deficits. The status of microglia and astrocytes in the CPZ model is under investigation. Together, these data suggest that VTN does not affect demyelination or motor deficits in MS models but does activate microglia and astrocytes in EAE lesions.

Disclosures: J.H. Bullen: None. **C. Jia:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.01/LBP001

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant DA51100
NIH Grant EB022015

Title: Real-Time, Seconds-Resolved Electrochemical Aptamer-Based Biosensors Reveal Weight-Dependent Cocaine Exposure and Age-Related Clearance in Rats but Minimal Sex Differences

Authors: *K. (. WANG[1], N. A. EMMONS[2], T. E. KIPPIN[3];
[1]Psychological & Brain Sciences, University of California Santa Barbara, Santa Barbara, CA; [2]University of California, Santa Barbara, Santa Barbara, CA; [3]Dept Psycholol gical and Brain Sciences, Univ California, Santa Barbara, Santa Barbara, CA

Abstract: Knowledge of the in-brain pharmacokinetics of psychoactive drugs remains incomplete on a number of dimensions, particularly due to a reliance on techniques limited by poor temporal resolution as well as body-mass-adjusted dosing. To address these issues, we have developed electrochemical aptamer-based biosensors (EABs) that are capable of supporting seconds-resolved, real-time measurements of the drugs in vivo. Specifically, using such sensors, we achieve low or sub-micromolar limits of detection with seconds-resolved temporal resolution which are capable of reliably determining the pharmacokinetics (PK) of individual subjects. While the strategy of adjusting dosing based on body mass aims to standardize plasma exposure, interindividual variability in PK parameters still persists. This project examines how body weight, age and sex contribute to such variation, focusing on key PK metrics and total drug exposure. A cohort of Sprague-Dawley rats received identical body-mass-adjusted intravenous cocaine doses. We quantified PK parameters including peak plasma concentration (C_{max}), time to peak (T_{max}), half-life ($t_{1/2}$), and area under the concentration-time curve (AUC). Correlations with body weight, age, and sex were evaluated. Weight showed no significant correlation with C_{max}, T_{max}, or $t_{1/2}$, indicating similar peak levels and timing regardless of size. Weight was significantly correlated with AUC, suggesting that larger individuals experience greater overall drug exposure, likely due to differences in absorption, distribution, or clearance. Age correlated significantly with $t_{1/2}$, indicating that older rats experienced a prolonged cocaine presence in the system. Importantly, no sex differences were detected in any PK measures which aligns with prior ex vivo and blood-sampling studies. These results suggest that behavioral sex differences in response to cocaine are unlikely to arise from differences in plasma PK; rather, they may stem from in-brain PK or pharmacodynamic mechanisms. Here, we also collected preliminary data from three compartments—ventricular CSF, plasma, and subcutaneous interstitial fluid—addressing the question of differences in pharmacokinetics in different compartments. By enabling high-resolution, real-time data collection across multiple compartments, our approach

provides a chance to explore the assumptions almost universally employed in prior compartmental models of drug transport, allowing us to quantitatively address (rather than simply assume), for example, our understanding of sex-specific drug distribution dynamics.

Disclosures: K.(. Wang: None. **N.A. Emmons:** None. **T.E. Kippin:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.02/LBP002

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Mitochondrial Dysfunction and Excitatory/Inhibitory Imbalance in 16p12.1 Deletion: Unraveling Neurodevelopmental Risk Through Integrated Molecular, Genomic, and Genetic Analysis

Authors: *H. BHAVANA;
Pennsylvania State University, State College, PA

Abstract: Genomic copy number variants (CNVs) are significant risk factors for neurodevelopmental disorders (NDDs) such as intellectual disability, autism spectrum disorder, epilepsy, and developmental delay. The recurrent 16p12.1 microdeletion, spanning about 520 kilobases and affecting several protein-coding genes, is associated with diverse neurodevelopmental phenotypes. The mechanisms behind this risk remain poorly understood, especially given the variable expressivity and incomplete penetrance of the 16p12.1 deletion. This complexity points to the combined influence of gene content, genetic background, and environment. Previous analyses have highlighted functional diversity and limited co-expression among 16p12.1 genes, making it difficult to define a single pathogenic pathway. To address this, we used patient-derived induced pluripotent stem cells (iPSCs) and differentiated them into neural progenitor cells (NPCs) and neurons, creating a human in vitro model of neural development. Transcriptomic profiling revealed downregulation of genes involved in energy metabolism and mitochondrial function, especially oxidative phosphorylation (OXPHOS) pathways. These deficits intensified as cells matured, indicating progressive metabolic impairment. Genes linked to the mitochondrial respiratory chain and the glycolysis-to-OXPHOS metabolic switch were notably affected, suggesting a block in metabolic reprogramming. Functional assays showed reduced NPC proliferation and increased apoptosis in 16p12.1 deletion lines, particularly in neurons. Immunocytochemistry revealed a shift toward inhibitory neuron fate, with increased markers for interneuron identity and stable excitatory neuron markers. Upregulation of TUBB3 also suggested accelerated differentiation. To probe gene-specific effects, we used CRISPR activation to upregulate *MOSMO*, *POLR3E*, and *UQCRC2*, which rescued several cellular phenotypes. In summary, 16p12.1 deletion disrupts energy metabolism, increases inhibitory neuron development, and impairs neural maturation. These findings provide

a mechanistic link between 16p12.1 gene dosage and NDD risk and highlight potential targets for personalized intervention.

Disclosures: H. Bhavana: None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.03/LBP003

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH R44 MH119870
NIH R01 DA060925

Title: Real-time, Voltammetric Co-Detection of Serotonin and Glucose at Carbon-Fiber Microbiosensors

Authors: *K. LINDER[1], K. TURNER[1], J. BERGER[2], L. SOMBERS[1];
[1]Cellular and Systems Pharmacology, University of Florida, Gainesville, FL; [2]North Carolina State University, Raleigh, NC

Abstract: Glucose is the major fuel source for the brain. As such, glucose availability and metabolism are inextricably linked to neurotransmission and, thus, to circuit function. Serotonin (5-HT) plays an important role in the human gut-brain axis and is a neurochemical of interest because it has been implicated in diverse neuropsychiatric disorders including mood disorders (anxiety and depression), schizophrenia, substance abuse, and Parkinson's disease. Historically, 5-HT dynamics have been monitored in brain tissue using electrochemical techniques since it is inherently electroactive, and glucose has been studied using microdialysis sampling techniques, since it is not inherently electroactive. However, these methods have very different spatial and temporal resolutions, making direct correlation of these signals difficult. Due to the challenges in the co-detection of these analytes, it remains unknown how local glucose availability directly modulates 5-HT transmission at discrete release sites. Since glucose is not inherently electroactive, electrochemical detection of glucose can be achieved using enzyme modified electrodes that generate electroactive hydrogen peroxide selectively in the presence of glucose. In this work, carbon-fiber microelectrodes were modified with a chitosan matrix containing glucose oxidase to allow for the simultaneous detection of 5-HT and glucose in rat brain tissue using fast-scan cyclic voltammetry (FSCV). FSCV is a differential, electroanalytical technique that affords the high temporal resolution necessary to monitor rapid 5-HT and glucose fluctuations. The voltammetric biosensors have been characterized for stability, selectivity, and sensitivity to glucose and 5-HT, and have been assessed on their ability to exclude a range of potential interferents including dopamine, norepinephrine, and 5-hydroxyindole acetic acid. The goal of this work is to utilize the biosensors for the quantitative co-detection of evoked 5-HT and glucose transients at the same space and time in both male and female rat brain tissue. The ability

to simultaneously record rapid fluctuations of glucose and 5-HT at a single location promises to inform improved therapeutic strategies for a wide range of disorders in which both 5-HT transmission and glucose metabolism is altered, providing a new perspective that links neurotransmission with metabolic activity.

Disclosures: K. Linder: None. **K. Turner:** None. **J. Berger:** None. **L. Sombers:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

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Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.04/LBP004

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant RO1AG085279

Title: Environmental exposome as a driver of Alzheimer's disease

Authors: D. C. GERMAN[1], J. RICHARDSON[2], R. F. PALMER[3], I. CHAKRABORTY[1], D. SMITH[1], J. MCDONALD[1];
[1]University of Texas Southwestern Medical Center, Dallas, TX; [2]University of Georgia, Athens, GA; [3]University of Texas Health Science Center at San Antonio, San Antonio, TX

Abstract: Alzheimer's Disease (AD) is the most common cause of dementia, and it disproportionately affects African Americans and Mexican-Americans. Emerging data suggest that the "causal" pathological markers of AD, as defined by the AT(N) framework (**A**myloid, **T**au, **N**eurodegeneration) vary by race/ethnicity. Further, there are clear racial/ethnic differences in exposures to environmental toxicants, which are increasingly recognized as potential contributors to AD. The current study will examine the role of the chemical *exposome,* the totality of environmental exposures individuals experience throughout their lifetime, and its link to the ATN framework, in the risk of developing AD among the three ethnic groups - Mexican-Americans, African Americans and Non-Hispanic whites. Here we are using samples from the Health and Aging Brian Study - Health Disparities (HABS-HD study) (U19AG078109) that has already made AT(N) and numerous omics measurements in all of the subjects. We have recently developed a novel extraction and mass spectrometry (Agilent 7010D, GC-MS(QQQ) method to make exposome measurements in 50 µl of plasma. In a pilot study with 30 subjects, 10 Non-Hispanic Whites, 10 Mexican-Americans, 10 African Americans from the North Texas area, we measured over 400 pollutants (fungicides, insecticides, microbiocides, PCBs and PAHs). The most notable finding was that males had uniformly higher numbers of PCBs in their blood compared to females (100-132 vs. 21-96), across the three ethnic groups. We are currently measuring these pollutants in 550 subjects from the HABS-HD study, at both baseline and 2-years later time points, from Mexican-Americans and Non-Hispanic Whites.

Disclosures: D.C. German: None. **J. Richardson:** None. **R.F. Palmer:** None. **I. Chakraborty:** None. **D. Smith:** None. **J. McDonald:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.05/LBP005

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 5R25HG012702-03

Title: Exploring epigenetic mechanisms of alcohol tolerance: the role of Tip60 via CRISPR editing

Authors: *M. I. MORALES-QUEZADA[1], C. DEL VALLE-COLÓN[2], J. RODRIGUEZ-RIOS[2], A. MONTES-MERCADO[2], E. PENA[2], A. GHEZZI[2];
[1]Natural Sciences, University of Puerto Rico Rio Piedras Campus, San Juan, Puerto Rico;
[2]Biology, University of Puerto Rico Rio Piedras Campus, San Juan, Puerto Rico

Abstract: Sustained alcohol consumption alters neural circuitry through adaptive neurobiological processes that drive tolerance and dependence, ultimately contributing to the progression of Alcohol Use Disorder (AUD). This chronic brain condition affects nearly 56% of Puerto Ricans both on the island and in the U.S., underscoring its major public health burden. Tolerance reflects maladaptive plasticity within circuits governing reward, stress, and executive control, yet the molecular regulators of these neural changes remain poorly understood. Epigenetic remodeling has emerged as a key mechanism shaping alcohol-induced neural plasticity, with histone acetyltransferases such as Tip60 playing critical roles in regulating synaptic gene expression and neuronal function. In this study, we investigate Tip60 as a neuroepigenetic modulator of alcohol tolerance using the Drosophila melanogaster nervous system as a genetically tractable model. We developed a transgenic construct for targeted epigenetic editing that fuses the histone acetyltransferase (HAT) domain of Tip60 to a catalytically inactive CRISPR-dCas9 platform. Using Gibson Assembly, we successfully cloned the HAT domain into a dCas9 construct, validated its genomic incorporation, and established the framework for precise acetylation of alcohol-responsive genes within neuronal circuits. This approach enables us to manipulate chromatin states in a locus-specific manner, directly linking Tip60-mediated acetylation to neural gene regulation underlying alcohol tolerance. Future work will involve crossing the validated construct with gRNA-expressing Drosophila lines, followed by behavioral alcohol tolerance assays in the F1 generation. These experiments will test whether targeted epigenetic editing of neuronal genes alters the trajectory of alcohol tolerance, providing insight into how Tip60-driven chromatin remodeling contributes to maladaptive neuroplasticity and the pathogenesis of chronic alcoholism.

Disclosures: M.I. Morales-Quezada: None. **C. Del Valle-Colón:** None. **J. Rodriguez-Rios:** None. **A. Montes-Mercado:** None. **E. Pena:** None. **A. Ghezzi:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

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Program #/Poster #: LBP017.06/LBP006

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH Grant 1R01NS139914-01

Title: Novel compact promoters to drive cell type-specific transgene expression in the mouse brain

Authors: *C. E. GRONECK, T. UBINA, M. KARGINOVA, M. RICCOMAGNO; Molecular, Cell, and Systems Biology, University of California, Riverside, Riverside, CA

Abstract: Adeno-associated viruses (AAVs) are widely used in research and therapeutics because they enable robust transgene expression in vivo with low immunogenicity. However, their ~4.5-5 kb packaging limit poses a major challenge for incorporating regulatory elements that drive cell type-specific expression, particularly in the central nervous system (CNS). The goal of this project is to systematically identify and validate compact promoters to drive cell type-specific transgene expression in the mouse brain. If successful, our approach will address a critical gap in AAV-based research and therapeutics, allowing us to selectively target and manipulate diverse CNS cell types, including astrocytes and neurons. Using publicly available single-cell RNA sequencing atlases of the mouse brain from the Allen Institute and the NIH BRAIN Initiative Cell Atlas Network, we identified candidate genes with a high degree of expression and specificity in cell type clusters, including pan-neuronal, astrocytic, ependymal, and oligodendrocytes. As a proof-of-concept, we designed a panel of AAVs containing six candidate compact promoters predicted to drive enhanced green fluorescent protein (EGFP) expression specifically in astrocytes. After intracerebroventricular injection of viruses in postnatal day 0 (P0) mice, we observed a high degree of astrocyte-specific EGFP expression in two candidate compact promoters by assaying for co-expression with various cell type markers via immunohistochemistry (IHC) and flow cytometry, supporting the validity of our approach. Specifically, over 75 percent of EGFP-positive cells were co-positive for the astrocyte marker Aldh1L1 by IHC. Additionally, this high degree of astrocyte specificity was consistent between both neonatal (P0) and adult (>P21) injection time points. Future work will validate the specificity and robustness of our candidate short promoters, comparing them to an existing GFAP promoter for astrocyte-specific expression, using both EGFP reporter transgene expression and Cre-driven recombination of fluorescent reporters in vivo.

Disclosures: C.E. Groneck: None. **T. Ubina:** None. **M. Karginova:** None. **M. Riccomagno:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.07/LBP007

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: 5R00HG012593-04

Title: dCasRx-RBP: an in vivo splice modulation tool to study the role of alternative splicing in neurodevelopment

Authors: *N. BROWN;
Cellular Developmental Biology, Northwestern University, Chicago, IL

Abstract: Alternative splicing (AS) of precursor mRNAs is critical for increasing transcript diversity and for post-transcriptional gene regulation. More than 95% of all human genes undergo alternative splicing (AS). Neurodevelopment is characterized by widespread AS. AS is important for all aspects of neurodevelopment including neuronal differentiation, cell fate specification, migration, and synapse formation. Despite the central role of AS, few tools exist to selectively induce splicing of a specific RNA isoform in vivo. dCasRx, a catalytically inactive form of an RNA targeting CRISPR enzyme, and antisense oligos have been successfully used to trigger exon exclusion through steric hindrance of splice regulatory elements. Inducing exon inclusion, however, has remained challenging. Recently, several studies have reported dCasRx fused to RNA binding proteins (RBPs) such as RBM39, RBM25, and RbFOX1 as effective tools for splice modulation in vitro. However, the in vivo efficacy of these tools has not been tested. Here, we demonstrate the efficiency of alternative exon inclusion/exclusion of dCasRx-RBM25, dCasRx-RBM39, and dCasRx-RBFOX1 in zebrafish. As proof-of-concept, we successfully modulated the splicing of foxp1b, the zebrafish orthologue of FOXP1. Splice switching of FOXP1 is critical during neuronal differentiation in human and murine iPSCs. (Gabut et al., 2011). Mutations in FOXP1 that cause splicing defects are associated with neurodevelopmental disorders, including autism spectrum disorder. Using long read sequencing and qRT-PCR of foxp1b isoforms, we found that the splice switching behavior of foxp1b is conserved in zebrafish. Moreover, we showed successful modulation of foxp1b exons using dCasRx-RBM25. Efforts are underway to functionally characterize the effects of foxp1b splice modulation on zebrafish neurodevelopment. In conclusion, we have established dCasRx-RBPs as effective tools for in vivo splice modulation. These tools will prove invaluable in studying the role of alternative splicing in neurodevelopment.

Disclosures: N. Brown: None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.08/LBP008

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIMH Grant: U24 MH133236

Title: A Suite of Enhancer AAVs for Genetic Targeting of Specific Hippocampal Formation Cell Types

Authors: *W. CAO[1], E. VELAZQUEZ[2], J. T. TING[3], X. XU[4];
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Abstract: Despite the central role of the hippocampal formation (HF) in learning, memory, and spatial navigation, the functional dissection of excitatory neuron subclasses within this region has been constrained by a lack of cell-type-specific genetic targeting tools. Recently, enhancer adeno-associated viruses (AAVs) have emerged as a transformative approach for achieving cell-type-specific access. These tools offer flexible and cost-effective delivery and have cross-species utility and translational potential. While enhancer AAVs have been successfully developed for neocortical, striatal, spinal cord, and various non-neuronal cell types, efforts to generate comparable tools for the HF remain limited. To address this gap, we have developed and validated around 20 enhancer AAVs that drive expression of fluorescent reporters and Cre recombinase in defined cell types within the subiculum, the principal output structure of the HF. Our toolkit enables precise genetic access to subiculum subdomains across three major organizational axes—transverse, longitudinal, and radial axes. Notably, several of our enhancer AAVs selectively target transcriptomic subclasses and supertypes of excitatory neurons. Emerging evidence indicates that superficial and deep layers of the dorsal subiculum serve distinct roles in encoding spatial and object-related memories, yet the underlying circuit mechanisms remain poorly understood. Using our enhancer AAVs, we achieve selective labeling of these layers and reveal layer-specific input and output connectivity, providing new insight into their differential contributions to learning and memory. Collectively, our new suite of viral genetic tools may provide critical resources for cell-type-specific access and manipulation of HF neuron types based on their molecular identity, connectivity, and behavioral relevance.

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Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.09/LBP009

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NASA Grant 80NSSC20M0070
NASA Grant NNX13AB28A
NASA Grant 22-22EPSCoR-0018
COBRE Grant P20GM130443
INBRE Grant P20GM103395

Title: Comparative Analysis of AAV Serotype Transduction Efficiency and Cellular Tropism in the Arctic Ground Squirrel and Rat Brain

Authors: *N. B. CLARK[1], S. A. MEDBURY[2], B. W. LAUGHLIN[3], M. M. WELTZIN[1], L. E. FENNO[4], K. L. DREW[3], N. K. LAL[3];
[1]Chemistry, University of Alaska, Fairbanks, Fairbanks, AK; [2]Biology, University of Alaska, Fairbanks, Fairbanks, AK; [3]Institute of Arctic Biology, University of Alaska, Fairbanks, Fairbanks, AK; [4]Psychiatry & Neuroscience, University of Texas at Austin, Austin, TX

Abstract: Adeno-associated viruses (AAVs) are a cornerstone for gene delivery in neuroscience, yet their transduction profiles are highly dependent on serotype, species, and cell type and are often hard to predict. While extensively characterized in traditional laboratory models, their efficacy in non-model species, such as the arctic ground squirrel (AGS, *Urocitellus parryii*), a critical model for hibernation and metabolic regulation, remains largely unexplored. This study aims to systematically characterize the transduction patterns of four AAV serotypes in the arctic ground squirrel brain, using the rat as a canonical reference. Adult AGS (n = 3) and Sprague-Dawley rats (n = 3) received stereotaxic injections into the right lateral ventricle and the left and right frontal cortex. Lateral ventricle injections consisted of a cocktail of AAV1 and AAV2 and cortical injections were cocktails of either AAV1 and AAV2, right hemisphere, or AAV8 and AAV9, left hemisphere. All AAVs packaged a cassette driving the expression of either the fluorescent protein reporter GFP, AAV1 and AAV9, or tdTomato, AAV2 and AAV8, under the ubiquitous CAG promoter. After an 8 to 9-week expression period, animals were euthanized, and brain tissue was collected. Coronal sections will be processed via immunohistochemistry for immunofluorescence to co-localize fluorescent protein expression with canonical markers for neurons (NeuN), astrocytes (GFAP), tanycytes (vimentin), microglia (Iba1), or endothelium (CD31). We will present a comprehensive quantitative analysis of these experiments. Our data will characterize: (1) the spatial spread and overall transduction volume for each serotype in both species; (2) the cellular tropism of each AAV, quantified as the fluorescent intensity of transduced, co-labeled brain cells; and (3) a direct comparison of transduction efficiency and cell-type specificity between the AGS and rat brain. This analysis will highlight species-specific differences and identify the optimal serotypes for targeting distinct cell populations in the AGS

brain. This research will provide the first direct, comparative dataset on AAV performance in the AGS central nervous system. Our findings will establish a foundational toolkit for enabling sophisticated transgenetic manipulation in this unique model, thereby advancing studies into the neurophysiology of hibernation and altered metabolic states. Furthermore, this work will contribute to a broader understanding of how AAV vector biology varies across different mammalian species.

Disclosures: N.B. Clark: None. **S.A. Medbury:** None. **B.W. Laughlin:** None. **M.M. Weltzin:** None. **L.E. Fenno:** None. **K.L. Drew:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Be Cool Pharmaceutics, LLC. **N.K. Lal:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.10/LBP010

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NIH: R01 DC020212

Title: Heterogeneous stock rats show highly variable individual differences in reinforcement learning across sessions

Authors: *K. H. WATSON[1], A. R. SHIPP[2], L. C. SOLBERG WOODS[3], J. X. MAIER[4], K. T. KISHIDA[5];
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Abstract: Individual animals differ in the way they use information to learn and make choices. To test the hypothesis that computational models of reinforcement learning (RL) and choice behaviors may be used for phenotype-genotype mapping, we used heterogeneous stock (HS) rats (created from eight inbred founder strains, approximating the common genetic variation seen in humans[1,2]) and a multi-session, multi-day, taste-foraging task. In our task, rats freely choose between options that probabilistically yielded taste outcomes (i.e., sucrose, quinine, water). Outcome contingencies were stable within each 1-hour session but varied across sessions/days, requiring animals to adapt their behavior to maximize their preferred outcomes. Adaptive choice behaviors are inherently dynamic, with choices changing over time with learning. Computational models of RL are useful in characterizing dynamic learning behavior, but their validity as a *computational phenotype* is debatable[3,4,5]. A good computational phenotype ought to quantify the

process of interest (e.g., learning rate) with high reliability and reproducibility. Here, we begin to test the hypothesis that temporal difference reinforcement learning (TDRL) models – widely used to characterize dopamine-mediated learning and neurobiology – can be used as a computational phenotype in HS rats for phenotype-genotype mapping of learning and choice behaviors. HS rats learned to maximize appetitive outcomes and minimize aversive ones. As expected, HS rats demonstrated high variability in their behavior. For example, some animals strongly avoided quinine regardless of sucrose potential, while others did not. We fit choice behavior to a simple TDRL model and a softmax policy. This provided parameter-based estimates of 'learning rate' (α), 'temporal discounting' (γ), and 'choice volatility' (τ). Results show that parameters vary from day-to-day, suggesting that the simplest TDRL modeling approach may not be a reliable computational phenotype. However, future work will investigate more sophisticated models like OpAL[6], VPRL[7], or feature-specific RL[8]. This work sets the foundation for future studies aimed at understanding the genetic basis of learning and choice behaviors.
References1Solberg Woods, L., et. al., *Physiol. Genomics* 2014, 46, 81-90.2Solberg Woods, L., et al., *Methods Mol. Biol.* 2019, 233-247.3. Schurr, R., et al., *Nat. Hum. Behav.* 2024, *8*(5), 917–931.4. Mkrtchian, A., et al., *Comp. Psychiatry* 2023, *7*(1). 5. Vrizzi, S., et al., *Nat. Ment. Health* 2025, 1–13. 6. Collins, A., et al., *Psych. review*, 2014, *121*(3), 337.7. Sands, P., et al., *Sci. Adv.* 2023, *9*(48).8. Sousa, M., et al., *Nature*, 2025, 642 691–699

Disclosures: K.H. Watson: None. **A.R. Shipp:** None. **L.C. Solberg Woods:** None. **J.X. Maier:** None. **K.T. Kishida:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.11/LBP011

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Title: Ancestry-Stratified Genomic Insights into ADHD from the ABCD Cohort

Authors: *Z. AGHA[1], R. PATEL[2], S. WANG[3], J. B. WILLIAMS[4];
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Abstract: Common Variant Architecture and Transcriptomic Convergence in the Adolescent Brain Cognitive Disorders Cohort (ABCD) Zehra Agha[1], Shuai Wang[1], Rajvi Niraj Patel[1], Yana Shimanovich[1], Jamal B. Williams[1*]
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Address for correspondence: Dr. Jamal B. Williams, Assistant Professor, Department of

Psychiatry, State University of New York at Buffalo, Jacobs School of Medicine and Biomedical Sciences, Buffalo, NY 14203, USA.Email: jbwillia@buffalo.edu ADHD is a highly heritable neurodevelopmental disorder with a polygenic architecture. Most genomic studies to date have been conducted in European-ancestry cohorts, underscoring the need for ancestry-aware analyses. We hypothesized that ancestry-stratified analyses in the Adolescent Brain Cognitive Development (ABCD) cohort would reveal both convergent and ancestry-specific genetic risk for ADHD. We conducted multi-layered genomic analyses, including genome-wide association studies (GWAS), transcriptome-wide association studies (TWAS), functional annotation (FUMA), and copy number variant (CNV) burden analyses. GWAS identified genome-wide significant loci in the European (EUR) subset (n = 1,074 cases, 5,483 controls), including rs73146042 in *PLD5* on chromosome 1 ($P \approx 7\times10^{-11}$), and potential suggestively significant loci at other chromosomes. No SNP achieved genome-wide significance in the African (AFR) cohort (n = 379 cases, 1,734 controls), although nominal signals were observed. TWAS and meta-analysis across EUR, AFR, and iPSYCH childhood ADHD data implicated genes, including *ST3GAL3,* with high posterior inclusion probabilities in brain tissues. MiXeR modeling demonstrated substantial polygenic overlap between EUR adolescents and childhood ADHD (~2,100 shared variants; r_g> ≈ 0.36) but reduced overlap across ancestries (~300 shared variants; r_g ≈ 0.24). Functional annotation with FUMA mapped >1,000 EUR genes enriched for cortical and cerebellar expression, while only four mapped genes emerged in AFR. CNV analyses revealed no overall burden increase in EUR cases, but AFR ADHD cases carried significantly more large duplications (≥500 kb: OR ≈ 2.3, P = 0.024). Together, these results reveal both shared and ancestry-specific ADHD risk architecture, converging on brain-expressed genes and neurodevelopmental pathways. Our study highlights the value of diverse cohorts and multi-omic integration in psychiatric genetics. Limitations include a modest AFR sample size, which reduced discovery power.

Disclosures: Z. Agha: None. **R. Patel:** None. **S. Wang:** None. **J.B. Williams:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.12/LBP012

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: NEI Grant EY020485
NEI Grant EY026877

Title: Engineering Injury-Responsive Promoters for On-Demand Neuroprotection in the Retina

Authors: *Y. SITU[1], L. GUO[2,1,3], R. WEN[3], X. XIA[3], J. L. GOLDBERG[3], S. QI[1];
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Abstract: Precise control of transgene expression is essential to optimize the safety and efficacy of gene therapies. Constitutive expression from AAV vectors in gene therapy can lead to long-term toxicity, a critical barrier for treating chronic neurodegenerative disorders. To create safer and more adaptive therapies, we have engineered a synthetic promoter platform that activates transgene expression only in response to cellular stress. We dissected the architecture of endogenous ER stress-responsive CHOP promoter (pCHOP) and applied rational design principles, systematically truncating inhibitory regions and multimerizing key responsive motifs. This created a panel of compact, synthetic promoters with dramatically enhanced inducibility and low basal activity. Several variants demonstrated enhanced activation compared to the native promoter, both in vitro under chemical ER stress and in vivo following optic nerve crush in mice. Our work establishes a modular and tunable synthetic promoter system that harnesses endogenous injury pathways to drive therapeutic expression on-demand, offering a promising strategy for developing safer gene therapies for retinal and other neurodegenerative diseases.

Disclosures: Y. Situ: None. **L. Guo:** None. **R. Wen:** None. **X. Xia:** None. **J.L. Goldberg:** None. **S. Qi:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.13/LBP013

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: UM1 MH130994

Title: Gene Regulatory Dynamics in Human Brain

Authors: *Y. XIE[1,2], L. CHANG[1,2], J. RINK[3], C. T. BAEZ BECERRA[4], W. DING[5], K. LI[1], G. ZHONG[6], M. BEHRENS[7], J. R. ECKER[8], B. REN[1,2];
[1]New York Genome Center, New York, NY; [2]Department of Cellular and Molecular Medicine, University of California, San Diego, San Diego, CA; [3]Salk Institute for Biological Studies, La Jolla, CA; [4]Computational Neurobiology Dep, Salk Institute for Biological Studies, San Diego, CA; [5]GALE, Salk Institute for Biological Studies, San Diego, CA; [6]New York Genome Center, Jersey City, NJ; [7]CNL-B, The Salk Institute, La Jolla, CA; [8]PBIO-E, Salk Institute, La Jolla, CA

Abstract: The human brain comprises diverse cell types governed by distinct regulatory programs. While chromatin accessibility profiling has facilitated the identification of candidate regulatory elements, it provides only a limited, binary view of element activity. Here, we report joint single-cell multimodal profiling of transcriptomes and histone modification landscapes across 171 cell types from the human cerebral cortex, cerebellum, and pons. By integrating H3K27ac and H3K27me3 profiles with previous single cell maps of chromatin accessibility, DNA methylome and 3D genome architecture from the same donors, we reveal unprecedented details of heterogeneity in epigenome across brain regions and cell types. We utilized this

integrative dataset to annotate both active and PRC2-mediated repressive chromatin states for over 500,000 candidate cis-regulatory elements and infer their putative target genes and transcription regulators. Furthermore, we construct cell-type-specific gene regulatory networks and compile a comprehensive catalog of candidate transcription factors that define and drive cell identity. Finally, we trained a deep learning model leveraging multi-dimensional epigenomic features to achieve high prediction accuracy for functional risk variants and enhancer activity. In summary, the single cell epigenome atlas of the human brain helps to resolve regulatory heterogeneity across brain cell types and provide a foundation for studying gene regulatory mechanisms underlying the heterogeneity of the human brain.

Disclosures: Y. Xie: None. **L. Chang:** None. **J. Rink:** None. **C.T. Baez becerra:** None. **W. Ding:** None. **K. Li:** None. **G. Zhong:** None. **M. Behrens:** None. **J.R. Ecker:** None. **B. Ren:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.14/LBP014

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: Edward Scolnick Professorship (to X.W.)
Merkin Institute Fellowship (to X.W.)
Packard Fellowship (X.W.)
Sloan Research Fellowship (X.W.)
NIH 1DP2GM146245-01 (to X.W.)
Arnold O. Beckman postdoctoral fellowship in Chemical Instrumentation (to A.R.R.)

Title: Spatial single-cell transcriptome-translatome co-profiling reveals mouse brain aging signatures

Authors: *J. TIAN, J. GUO, A. R. ROY, X. WANG;
Broad Institute, Cambridge, MA

Abstract: Gene expression is regulated at both transcriptional and translational levels to fine-tune protein production and modulate cell identity and cell states. While spatial and single-cell transcriptomics excel at identifying cell types, they do not fully capture cell states, as post-transcriptional regulation can weaken the correlation between RNA abundance and protein synthesis. Meanwhile, when and where proteins are synthesized are controlled and reflected at the translatome level, which often provides a more direct and sensitive readout of functional cell state. However, existing methods typically measure either the transcriptome or the translatome in separate samples or cell populations, but not simultaneously in the same cell, making it challenging to deconvolve their respective regulatory contributions to cell state at the single-cell

level. Here, we introduce qRIBOmap, a new spatial multi-omics platform that enables co-profiling of transcriptome and translatome in the same cells with subcellular resolution. qRIBOmap enables highly specific detection of translating mRNAs and direct quantification of translation efficiency in situ. Applying qRIBOmap to brain tissue from young (2 months) and aged (21 months) male mice (N=3 mice per group), we co-profiled thousands of genes and uncovered widespread, cell type-specific transcription-translation shifts during aging. We found that the translatome exhibited stronger age-associated perturbation than the transcriptome especially in neurons and identified genes and pathways—particularly synaptic function and immune response—that undergo substantial translational remodeling. In addition, cell type- and region-specific subcellular analyses revealed dramatic alterations in the localized translation landscape in neurites and around various organelles such as mitochondria and endoplasmic reticulum. Together, qRIBOmap provides a subcellularly resolved, single-cell multi-omic perspective and a broadly applicable approach for interrogation of gene regulation along the central dogma.

Disclosures: **J. Tian:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); J.T. is an inventor on pending patent applications related to qRIBOmap. **J. Guo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); J.G. is an inventor on pending patent applications related to qRIBOmap. **A.R. Roy:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); A.R.R. is an inventor on pending patent applications related to qRIBOmap. **X. Wang:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); X.W. is an inventor on pending patent applications related to qRIBOmap, X.W. is a scientific cofounder of Stellaromics and Convergence Bio..

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.15/LBP015

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: 5UM1MH130994

Title: Single-Cell Analysis of Chromatin State and Transcriptome in Human Basal Ganglia

Authors: ***L. CHANG**[1], K. LI[1], Y. XIE[1], G. ZHONG[1], J. RINK[2], C. T. BAEZ BECERRA[3], A. BARCOMA[2], J. LIU[4], J. ARZAVALA[5], A. BIKKINA[2], M. MARRIN[2], J. WILLIER[2], K. RUSSO[2], S. CHO[2], C. YOUNG[2], Y. SANCHEZ[2], C. ROSE[2], S. ALT[2], Q. ZHU[6], T. WANG[7], X. XU[8], J. R. ECKER[9], M. BEHRENS[5], B. REN[1];
[1]New York Genome Center, New York, NY; [2]The Salk Institute, La Jolla, CA; [3]Computational Neurobiology Dep, The Salk Institute, San Diego, CA; [4]Computational Neurobiology

Labaratory, The Salk Institute, La Jolla, CA; [5]CNL-B, The Salk Institute, La Jolla, CA; [6]University Of California San Diego, La Jolla, CA; [7]Georgetown University Medical Center, Washington D.C., VA; [8]Anatomy and Neurobiology, Univ California, Irvine, Irvine, CA; [9]PBIO-E, The Salk Institute, La Jolla, CA

Abstract: The basal ganglia, a collection of interconnected subcortical nuclei, plays a central role in motor control, emotion, and reward processing. Dysfunctions in these circuits contribute to numerous neurological disorders, including Parkinson's disease, Huntington's disease, and various psychiatric diseases. While thousands of genetic variants have been associated with these diseases, most reside in non-coding regions of the genome and remain functionally uncharacterized. These risk variants likely influence disease by perturbing transcriptional regulatory elements in a cell-type-specific manner. However, the lack of comprehensive annotation of the cell-type-specific regulatory elements and their activity has prevented us from gaining a deeper understanding of the roles these non-coding risk variants play in disease pathogenesis. Here, we present a comprehensive joint single-cell atlas of histone modifications and transcriptome across eight basal ganglia regions from seven neurotypical adult human donors, generated by Droplet Paired-Tag. This dataset encompasses ~700,000 cells and covers three histone modifications—H3K27ac, H3K27me3, and H3K9me3. We identified 1,787 cell populations, 60 distinct cell groups, and annotated chromatin states for approximately 60% of the genome for each cell type. Our analysis revealed 1,430,938 active and repressive putative regulatory elements, many of which exhibit evolutionary conservation and consistent chromatin signatures in the mouse brain, underscoring their functional significance. We also investigated the distinct regulatory programs underlying the D1 and D2 subtypes of medium spiny neurons, which have divergent roles in movement regulation. To map regulatory activity in anatomical context, we also generated a spatial transcriptomic dataset and integrated it with the Droplet Paired-Tag dataset to investigate how gene expression patterns and regulatory logic are spatially organized across the basal ganglia. Finally, we leveraged this epigenomic atlas to find signaling pathways and gene regulatory programs in each cell type likely causal in neurological diseases, and developed deep-learning models to predict important cell-type-specific regulatory elements and the functional impact of disease risk variants. In summary, this single-cell histone modification atlas offers critical insight into cell-type-specific gene regulatory mechanisms in basal ganglia, improves the interpretation of non-coding disease risk variants, and lays the groundwork for more effective investigations into the molecular underpinnings of neurological and psychiatric disorders.

Disclosures: L. Chang: None. **K. Li:** None. **Y. Xie:** None. **G. Zhong:** None. **J. Rink:** None. **C.T. Baez becerra:** None. **A. Barcoma:** None. **J. Liu:** None. **J. Arzavala:** None. **A. Bikkina:** None. **M. Marrin:** None. **J. Willier:** None. **K. Russo:** None. **S. Cho:** None. **C. Young:** None. **Y. Sanchez:** None. **C. Rose:** None. **S. Alt:** None. **Q. Zhu:** None. **T. Wang:** None. **X. Xu:** None. **J.R. Ecker:** None. **M. Behrens:** None. **B. Ren:** None.

Late-Breaking Poster

LBP017: J.01. Molecular, Biochemical, and Genetic Techniques

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP017.16/LBP016

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA51100
NIH Grant EB022015

Title: Analyzing cerebrospinal fluid components contributing to electrochemical aptamer-based sensor drift

Authors: D. SOGBESAN, *T. E. KIPPIN;
Psychological & Brain Sciences, Univ California, Santa Barbara, SANTA BARBARA, CA

Abstract: Electrochemical aptamer-based sensors (EABs) support high-frequency, real-time measurements of dozens of molecular targets, including drugs and neurotransmitters, in various body compartments, including in the brains of freely-moving subjects. In vivo applications of EABs, like all sensing strategies, is challenged by biological fouling. While drift correction strategies for EAB measurements afford multi-hour measurements, they do not prevent the progressive signal loss which eventually negates meaningful measurements due to excessive deterioration of signal-to-noise. Given EABs do not exhibit drift in non-biological buffers, here we explore the nature of the biological components of cerebrospinal fluid (CSF) that produce drift. To do this, we applied molecular weight cut-off filters (MWCF) to remove proteins of specific sizes from commercially-available bovine CSF. Once filtered the CSF is reconstituted to serve as a buffer in which we perform in vitro voltammetric interrogation of EAB sensors for up to 8 hours. Unfiltered CSF resulted in greater than 50% signal loss over 8 hours which is similar to signal loss that is observed during in vivo measurements in brain tissue. Whereas measurements in CSF following application of 10 kDa MWCF, in artificial CSF, or in PBS buffers resulted in highly stable signal with losses < 10% over the same time periods. These studies indicate that the CSF proteins of molecular weights above 10 kDa are, in large part, responsible for EAB drift. In comparison, studies in blood using the same cut off approach indicate that EAB drift is due 100 kDa or larger proteins indicating distinct contributions of different biological systems to sensor fouling. These findings suggest that the longevity of intracranial monitoring using EABs may be enhanced by application of selective membranes but this strategy may negate the ability to monitor a few larger neuropeptides.

Disclosures: D. Sogbesan: None. **T.E. Kippin:** None.

Late-Breaking Poster

LBP018: J.02. Systems Biology and Bioinformatics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP018.01/LBP017

Topic: J.02. Systems Biology and Bioinformatics

Support: NIH Intramural Grant

Title: Proteomic and pathway analysis reveal synaptic roles of adhesion GPCR GPR110 in the hippocampus

Authors: B. X. HUANG, *M. MELKUMYAN, H.-Y. KIM;
NIH, Rockville, MD

Abstract: Adhesion GPCR GPR110 is the receptor for synaptamide (docosahexaenoylethanolamide), a docosahexaenoic acid (DHA)-derived lipid mediator in the brain. GPR110 activation by synaptamide stimulates cAMP/PKA signaling and CREB, promoting neurogenesis, synaptogenesis, and cognition. To define GPR110 function, we compared hippocampal proteomes of wild-type (WT) and GPR110 knockout (KO) mice using quantitative mass spectrometry and pathway analysis. Over 6,500 proteins were identified, with 300 showing significant changes in KO versus WT ($p < 0.05$, fold change ≥ 1.2; $n = 4$ WT, $n = 3$ KO). Of these, 200 were downregulated and 100 upregulated in KO hippocampus. Downregulated proteins were enriched in synaptogenesis and glutamatergic receptor pathways, including SLC6A17, SV2B, synapsin 2, glutamate transporters/receptors, and GABA-B receptor subunit 2. Additional decreases were observed in Eph receptor B1 and NCAM1 (synaptic formation/vesicle trafficking), MAPK1 (synaptic plasticity), and amyloid precursor-like protein 1 (synaptic adhesion). In contrast, ELFN1, which modulates presynaptic release probability, and TAB3, an NF-κB activator linked to immune regulation, were significantly increased. These findings identify GPR110 activation as a critical regulator of hippocampal proteome dynamics, linking DHA to synaptic pathways essential for neurodevelopment and cognitive function.

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

Late-Breaking Poster

LBP018: J.02. Systems Biology and Bioinformatics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP018.02/LBP018

Topic: J.02. Systems Biology and Bioinformatics

Support: (NIH) - 1R21NS135529
(AHA)- 25PRE1377051

Title: Blood-barrier transcriptomics of endothelial cells in the central and peripheral nervous system.

Authors: *A. PAL[1], A. WANGZHOU[2], M. HEMING[3], C. L. SOMMER[4], G. MEYER ZU HORSTE[3], T. J. PRICE[5], Z. QIN[6];
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Abstract: The central nervous system (CNS) and peripheral nervous system (PNS) are supported by an innervating vascular system that not only transports nutritional components but also protects them from circulating pathogens via their blood-barriers. While previous reports have solidified the impermeability of the blood-brain barrier (BBB) (CNS), limited information about these barriers at the PNS, especially in the context of humans, is reported. Here, we compile and characterize transcriptomic data for endothelial cells in the brain, dorsal root ganglion (DRG), and sural nerve ECs using single-nuclear RNA-seq analysis. First, we report the presence of heterogeneous groups of vessels that resemble large, intermediate, and small arterial and venous vessels in all three organs, as observed previously. These vessels express known canonical arterial, venous and capillary markers [PMID: **38987604]**, as well as some novel markers that are different between all the three organs. Interestingly, we find that the arteriovenous zonation of the enrichment of various tight junction proteins shifts from a venous (within CNS) to an arterial (within PNS) phenotype. Additionally, we find that the DRG and sural capillaries show a relatively low enrichment (to the brain) of canonical tight junction genes and negative regulators of non-specific endocytosis (eg, MFSD2A), as well as high expression of positive regulators of non-specific endocytosis (eg: PLVAP, FLT1) supporting its leaky phenotype. Finally, our interactome analysis reveals known and novel cell-cell communication pathways among endothelial and other cells in the CNS and PNS that are known to classically mediate barrier properties. This study provides novel insights into the transcriptomic blood-barrier properties within the CNS and PNS.

Disclosures: A. Pal: None. **A. Wangzhou:** None. **M. Heming:** None. **C.L. Sommer:** None. **G. Meyer zu Horste:** None. **T.J. Price:** None. **Z. Qin:** None.

Late-Breaking Poster

LBP018: J.02. Systems Biology and Bioinformatics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP018.03/LBP019

Topic: J.02. Systems Biology and Bioinformatics

Support: NIH UM1 HG009443
NIH UM1 HG012077
NIH U54 AG054349

Title: Direct RNA epitranscriptomic profiling of human brain cortex using the Dogme computational pipeline reveals transcript isoform-specific RNA modifications

Authors: *E. ABDOLLAHZADEH[1], A. MORTAZAVI[2];
[1]developmental and cell biology, Univ. of Irvine California, Irvine, CA; [2]developmental and cell biology, UC Irvine, Irvine, CA

Abstract: The role of RNA modifications in health and disease has been difficult to study because of the difficulty in measuring modification levels using traditional sequencing techniques. Oxford Nanopore Technologies (ONT) enables direct detection of RNA and DNA modifications from unamplified nucleic acids, providing unique insights into epigenetic and epitranscriptomic regulation. However, rapid updates to ONT basecalling models and evolving modification-detection tools pose challenges for reproducible analysis. To address these, we developed Dogme, which is a reproducible, Nextflow-based pipeline that automates ONT data processing, including basecalling, alignment, transcript annotation, modification detection, and transcript quantification, across direct RNA (dRNA), complementary DNA (cDNA), and genomic DNA (gDNA) datasets. Dogme supports diverse RNA modifications detectable by Dorado, including N6-methyladenosine (m6A), 5-methylcytosine (m5C), pseudouridine (Ψ), inosine (I), and 2'-O-methylation (Nm), as well as DNA methylation.
As part of the ENCODE project, we applied Dogme to four postmortem human cortex samples sequenced using ONT dRNA on promethION cells. We detected 42,469 known transcripts and 64,876 novel transcripts. We identified 1.4 M modification sites, with 254,092 consistently detected across all samples. We further analyzed modifications in an isoform specific manner to allow subsequent analysis and modeling. We found 2,467 differential sites in 1,340 transcript isoforms in 883 genes with differences in modification levels between isoforms of the same gene at the same position within the same samples. Sites that differ between isoforms generally show the highest prevalence of m6A (1,194 significant sites) compared to inosine (512), pseudouridine (487), m5C (431), and Nm (297). These differences in modification profiles of RNA isoforms from the same gene are candidates for regulation of their ultimate functions as mRNAs or non-coding RNAs.

Disclosures: E. Abdollahzadeh: None. **A. Mortazavi:** None.

Late-Breaking Poster

LBP018: J.02. Systems Biology and Bioinformatics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP018.04/LBP020

Topic: J.02. Systems Biology and Bioinformatics

Support: NIH Grant RF1MH128970
NIH Grant RF1MH133703
NIH Grant R01 AG066028

Title: Niche Trajectory Reference Map of Whole Mouse Brain

Authors: *W. WANG, S. SHIN, J. CHAVEZ, G.-C. YUAN;
Genetics and Genomic Sciences, ISMMS, New York, NY

Abstract: The complexity of brain functions is intricately connected with its anatomical and molecular structures. Recent cell-atlas mapping studies have provided important insights into such connections. However, existing studies are primarily focused on individual cell types in isolation, whereas a systems-level view of the brain microenvironment (ME) organization remains lacking. To address this issue, we have developed a novel, generally-applicable framework to represent the ME organization as a niche trajectory (NT), which delineates the spatially continuous variation of ME. The NT analysis framework differs from existing approaches in that treats a niche—a spatially localized group of cells—as its core unit. We therefore developed ONTraC, a graph neural network (GNN)-based algorithm specifically designed to reconstruct NTs from spatial transcriptomics data.By applying ONTraC to a recently generated whole mouse brain MERFISH dataset, we have created an NT map at the brain-wide scale. The resulting NT accurately recapitulated major anatomic structures while also revealing fine-grained variation within individual compartments. Guided by this map, we identified coordinated ME-dependent changes of gene expression, regulatory activity, and predicted cell-cell interactions. Together, these findings highlight the utility of NT analysis for uncovering both neural and glial dynamics across brain microenvironment.In summary, niche trajectory analysis provides a scalable and flexible framework for decoding ME variations. The whole-mouse-brain NT map may serve as a valuable resource for investigating the links between function and structural variations.

Disclosures: W. Wang: None. **S. Shin:** None. **J. Chavez:** None. **G. Yuan:** None.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP018.05/LBP021

Topic: J.02. Systems Biology and Bioinformatics

Support: UM1HG012077

Title: Characterizing cis and trans regulatory variation in the diencephalon and pituitary gland using diverse mouse strains at single cell resolution

Authors: *R. WEBER, A. MORTAZAVI;
Department of Developmental and Cell Biology, University of California, Irvine, Irvine, CA

Abstract: Variation in gene regulation influences brain cell-type diversity by orchestrating cell-specific expression programs. The genetic basis for gene expression variability can be explained by variants that impact cis-regulatory elements such as promoters and enhancers, and/or trans-acting transcription factors. As part of the IGVF Consortium, we generated a single-nucleus RNA-seq resource of ~15 million nuclei spanning 15 mouse genotypes, eight major tissues, and 105 cell subtypes. Here, we estimate cis- and trans-regulatory contributions to gene expression in the diencephalon and pituitary gland by leveraging the genetic diversity of the eight genetically diverse mouse strains, (C57BL/6J, A/J, NOD/ShiLtj, NZO/HlLtJ, 129S1/SvImJ, PWK/PhJ, WSB/EiJ, and CAST/EiJ), and seven F1 hybrids generated from crossing a C57BL6/J dam with sires from the seven other founder strains. Together, these genotypes provide a rich source of genetic diversity, collectively containing approximately 23 million unique single nucleotide polymorphisms (SNPs) and 350 million base pairs of structural variation compared to C57BL/6J. We sequenced diencephalon and pituitary gland samples from 10-week-old mice (4 males and 4 females per genotype) using single-nucleus RNA-seq, generating both total and allele-specific expression profiles at cell-type resolution. Here we report a cell-type-resolved atlas of allele aware gene regulation across major diencephalon and pituitary gland cell types. We detected ~14,000 expressed protein coding genes containing SNPs, which allowed us to quantify allele-specific expression. Among these, only ~1,000 genes were conserved across all tested cell types, while the remaining ~13,000 showed evidence of cis, trans, or cis-by-trans regulation in at least one cell type. We observe cell-type dependent switching of regulatory mode, notably between neuronal and glial cell types, including 40 genes that were classified as cis-regulated in glutamatergic neurons that switched to trans regulation in astrocytes. Across cell types, cis effects are more frequent than trans or cis-by-trans compensatory effects. Our study quantifies the impact of distinct mechanisms of natural genetic variation on cell-type-specific transcriptional regulation.

Disclosures: R. Weber: None. **A. Mortazavi:** None.

Late-Breaking Poster

LBP018: J.02. Systems Biology and Bioinformatics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP018.06/LBP022

Topic: J.02. Systems Biology and Bioinformatics

Title: Reimagining scholarship system renewal through a lens of non-visible dynamic trans-diagnostic disability in an age of Large Language Models: Implication for advancement of graduate education in the field of bio-medical public health research and advancement of graduate student well being

Authors: *P. S. PENNEFATHER[1,2], A. NIGAM[3];
[1]University of Toronto, Toronto, ON, Canada; [2]gDial Inc, Toronto, ON, Canada; [3]Institute of Medical Science, Collaborative Program In Neuroscience, University of Toronto, Canada, Toronto, ON, Canada

Abstract: The interoception dimension of our brain's ability to monitor and adapt to bio-physical and psycho-social stress has long been recognized but only recently seen much conceptual progress. Recent findings suggest that neuroplastic interoception sensitization may be at the core of nociplastic chronic pain (NCP). NCP is experienced as stressful, mood altering, pain that outlasts acute painfully salient signalling. NCP, is one example of a wider class of non-visible disabilities (NVDs). What previously had been described as general sickness behaviour is coming to be understood as a collection of phenomic signatures that potentially could be parameterized by measurable biomarkers. Recent emergence of natural language-based LLMs for interpreting narrative coded psycho-social affective temperament language descriptors combined with other forms of LLM technology omically trained on bio-physical process ontology language leads to the possibility of combining these two developments with the emergence of validated personal digital narrative dialectic health care interventions for diagnosed disability. This poster will discuss a framework for accommodations of dynamic interoception processing of NVD experiences by neuroscientist mentors and trainees living with NVDs and of renewing scholarship epistemology. This cohort is well suited to help generate a record of personal health care choices concerning stress related NVD syndromes tracked using neuroscience-based theories and frameworks concerning biophysical and psycho-social symptom causation, development, function and evolution. New health data privacy protection legislation allows explicit and tacit health system experiences grounded with patient specific health record data to be self-curated and owned by those patients and combined with patient- generated narrative records of their personal phenomic experiences. This phenomic data can then be used in collaboration with them under legal license, to build explicit learning system models of social and ecological determinants of interoception dependent phenomenology. Given the partial efficacy of pharmaceutical drugs in NVDs, the framework incorporates an additional feature of monitoring the impact of alternative creative health (music, dance, arts etc.) using emerging LLM technology to evaluate the efficacy of creative intervention and accommodations for NVDs experienced by neuroscience trainees and their mentors. The voices of people living with non-visible disabilities are precisely those needed to take advantage of new tools that are making "invisible" causation of NVDs, and of neuroscience training, visible.

Disclosures: P.S. Pennefather: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); gDial Inc. **A. Nigam:** None.

Late-Breaking Poster

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Topic: J.02. Systems Biology and Bioinformatics

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National Institutes of Health R01NS115484

Title: CEDNe: A unified graph-based platform for multi-omic modeling of nervous systems

Authors: *S. MOZA, Y. ZHANG;
Organismic and Evolutionary Biology, Harvard University, Cambridge, MA

Abstract: The advent of whole-organism level datasets, including anatomical connectome, gap-junction map, single-cell transcriptome, and neuropeptide-receptor distributions has led to several insights into nervous system development, structure, and function. However, a crucial next step is to integrate these diverse datasets with functional imaging and behavior into coherent, predictive models. To address this, we developed "CEDNe (s'Idni)", a platform that unifies, organizes and models neural data using content-enriched multi-relational graphs. We demonstrate CEDNe on *C. elegans*, the only organism with complete organism-level datasets, but the framework is general and extensible to other systems. CEDNe enables novel analyses, visualizations, and insights through cross-dataset integration. For accessibility, we provide both a Python-based, open-source library and an intuitive web-interface for visualization. We illustrate several insights and predictions enabled uniquely by CEDNe's cross-dataset integration capability. First, we integrated neurotransmitter ligand and receptor data with the anatomical connectome to predict putative neurotransmitter types for each connection. Then, we analyzed the structural properties of the connectome in context of these predictions. We found that chains of feedforward-loop motifs tile the worm connectome in the sensory-to-motor direction. These motif chains reveal a striking partitioning of the nervous system by glutamatergic, cholinergic and GABAergic connections. Next, we integrated simultaneous calcium-imaging and behavior data, and the neuropeptidergic connectome from open-access databases. By decomposing neural activity using unsupervised methods, we discovered functional modules of neurons that strongly corresponded to individual behavioral variables. CEDNe's integrated model narrowed down dominant neuropeptidergic pathways for these modules highlighting candidates for targeted experiments, some of which are validated using prior literature. Finally, we demonstrate CEDNe's simulation-optimization framework by combining the above datasets to build predictive models of the *C. elegans* nervous system. We propose CEDNe as a collaborative, evolving, data-driven framework, beginning with the *C. elegans* nervous system, and show its ready extension to other systems with available multi-omic datasets, such as *Drosophila melanogaster*.

Disclosures: S. Moza: None. **Y. Zhang:** None.

Late-Breaking Poster

LBP019: J.03. Anatomical Methods

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Program #/Poster #: LBP019.01/LBP024

Topic: J.03. Anatomical Methods

Support: Nakatani Foundation
AMED P-PROMOTE JP22ama221517

Title: Deep tissue penetration of oligo-conjugated antibody for three-dimensional staining of millimeter-thick brain tissues

Authors: *R. KURUSU[1,2], S. OCHI[3], N. OSUMI[3], E. A. SUSAKI[1,2,4,5];
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Abstract: Tissue clearing and light-sheet microscopy facilitated molecular phenotyping or connectomic analysis, in combination with various sample preparation methods, including 3D immunostaining and expansion microscopy. Several groups reported 3D immunostaining methods for the intact mouse brain, but these methods require specialized devices or empiric knowledge, which makes it difficult to reproduce in many laboratories. To establish simple and reproducible methods, we modeled immunostaining by diffusion-reaction theory and manipulated two major variables in the model. We termed this method as CUBIC-HistoVIsion2.0 (HV2.0) (Susaki, Kurusu+, in preparation). More recently, two groups reported whole-brain mRNA FISH methods (Kanatani+, Science 2024; Murakami+ BioRxiv 2025). These methods use hybridization chain reaction (HCR) to amplify FISH signals. Since HCR enables multiplexed imaging and signal amplification, the integration of HCR into immunostaining by oligo-conjugated antibodies will result in multiplexed, multimodal, and signal-amplified imaging. However, 3D immunostaining methods for oligo-conjugated antibodies have not been reported partly due to the notorious low penetration of oligo-conjugated antibodies. To achieve deep tissue penetration of oligo-conjugated antibodies, we modified our HV2.0 protocol. In the experiments using thin brain slices, we confirmed that dextran sulfate and salmon sperm DNA (ssDNA) reduced non-specific staining in the HV2.0 staining buffer. Based on dextran sulfate- and ssDNA-containing HV2.0 buffer, we found that 1) adding chemical X, 2) removing chemical Y, and 3) extending step Z improved antibody penetration. 2-mm thick hemi-coronal brain slices can be stained within 4 days with these modifications, while we observed rim-like staining without modifications. We also confirmed even antibody distribution in a half mouse brain after 2-3 weeks of staining with these modifications. Collectively, we first rationally designed a 3D immunostaining method that enabled deep tissue penetration of oligo-conjugated antibodies. This work provides a basis for multiplexed, multimodal, and signal-amplified imaging using HCR in the intact organs.

Disclosures: R. Kurusu: None. **S. Ochi:** None. **N. Osumi:** None. **E.A. Susaki:** A. Employment/Salary (full or part-time); CUBICStars, Inc..

Late-Breaking Poster

LBP019: J.03. Anatomical Methods

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Program #/Poster #: LBP019.02/LBP025

Topic: J.03. Anatomical Methods

Support: HHMI

Title: A new expansion microscopy strategy improves antibody signal linearity and reveals how protocol choice shapes accuracy and off-target staining

Authors: *B. MOHAR, A. MACRI, N. P. SPRUSTON, P. TILLBERG;
Janelia Research Campus, Ashburn, VA

Abstract: Expansion microscopy (ExM) extends fluorescence imaging into the nanoscale regime, enabling visualization of proteins and structures across diverse cells and tissues. Yet a central challenge remains: do immunostaining signals truly reflect endogenous protein levels and spatial distributions? Antibody staining can fail in two ways: loss of linearity at protein-positive sites and nonspecific signal at protein-negative sites (off-target). Protein loss during preparation compounds both, obscuring true localization and corrupting quantitative analysis. However, increasing fixation to prevent this loss leads to loss of antibody recognition. Without a way to quantitatively validate both abundance and localization, researchers risk drawing misleading biological conclusions and may spend significant time optimizing protocols without a clear benchmark. To address this, we developed a HaloTag-based platform that links endogenous abundance (HaloTag signal) to antibody fluorescence, enabling systematic tests of linearity, specificity, and retention across diverse workflows. Using knock-in mice expressing HaloTag fusions of PSD95 and GluA2 in fixed brain sections, we benchmarked 5 published ExM methods and a new variant, EXPAND, across a range of disruption conditions. In our benchmarking, EXPAND showed the highest antibody signal and the most linear relationship, while another (Ten-fold Robust Expansion Microscopy - TREx) achieved the best protein-to-antibody ratio and thus preserved biological signal most effectively. Both methods, however, exhibited high off-target staining at protein-negative sites without disruption, demonstrating the need for carefully tuned protocols. Other protocols showed poor accuracy and low precision, highlighting large differences in method reliability. Together these results highlight a principled way to match protocol choice to scientific goals: EXPAND for quantitative, linear detection and TREx for maximal biological signal, with both requiring sufficient disruption to minimize off-target binding. This framework converts ExM optimization from trial-and-error to measurement: it identifies protocol-specific operating points, flags conditions dominated by nonspecific staining or protein loss, and provides actionable guidance for method developers and users. Ground-truth referencing should generalize beyond PSD95 and GluA2 to other targets and tissues, improving the reliability of quantitative protein imaging in cells and tissues.

Disclosures: **B. Mohar:** A. Employment/Salary (full or part-time); HHMI. **A. Macri:** A. Employment/Salary (full or part-time); HHMI. **N.P. Spruston:** A. Employment/Salary (full or part-time); HHMI. **P. Tillberg:** A. Employment/Salary (full or part-time); HHMI.

Late-Breaking Poster

LBP019: J.03. Anatomical Methods

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Program #/Poster #: LBP019.03/LBP026

Topic: J.03. Anatomical Methods

Support: Austrian Science Fund FWF 35614

Title: Correction of air microscope objectives for use in solutions for tissue clearing

Authors: *H.-U. DODT;
Department of Life Sciences, University of Vienna, Wien, Austria

Abstract: Imaging of cleared tissue blocks, particularly whole mouse brains, has become widespread since the first demonstration of a cleared mouse brain (Dodt et al., Nature methods, 2007). Meanwhile, tissue clearing is also being applied to medical and diagnostically relevant specimens, and even centimeter-sized pieces of human brain have been successfully imaged. High-resolution imaging in clearing solutions requires the use of specialized immersion objectives. Among these, the immersion objectives with the largest field of view are typically 10× lenses, which provide imaging fields of about 1 mm. Imaging larger specimens therefore necessitates extensive stitching, a process that is time-consuming and often produces uneven results.For light sheet microscopy of large specimens, high-end zoom microscopes would be ideal, as they allow great flexibility in image acquisition. However, nearly all objectives for these microscopes are air objectives. When used with cleared samples, these are generally combined with simple immersion caps containing a plane glass window, which introduces significant aberrations, most notably spherical aberration.A simple, generally applicable solution for upgrading air objectives would thus be desirable. Our experiments show that nearly concentric meniscus lenses integrated into dipping cones provide excellent performance by effectively eliminating spherical aberration. While this approach does not match the optical quality of specially designed immersion objectives, minor adjustments to the lens design can also mitigate some residual aberrations.We evaluated this meniscus lens solution on two high-end zoom microscopes, the Nikon AZ100 and the Zeiss Axiozoom V16. In both systems, the meniscus lenses produced dramatically improved image quality compared to conventional plane-glass dipping cones. Furthermore, the working distance of the air objectives was preserved or even increased, depending on the meniscus lens design. Because such dipping cones can be retrofitted to existing air objectives, including large-diameter macroscope lenses with long working distances, this solution represents a practical and powerful tool for light sheet microscopy of large cleared samples.

Disclosures: H. Dodt: None.

Late-Breaking Poster

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Program #/Poster #: LBP019.04/LBP027

Topic: J.03. Anatomical Methods

Title: Portable automatic cryostat with integrated cooling, automated cutting, and sample collection

Authors: *J. A. DOMINGUEZ-RAMIREZ[1], R. BELTRAN-RAMIREZ[2], C. ROMÁN[3], X. M. BECERRA-GONZÁLEZ[1], J. MARTINEZ-MENDOZA[4], V. LOPEZ[3], F. RODRIGUEZ MENDOZA[3], C. MEDRANO[3], A. ESPARZA NUÑEZ[3];
[1]Universidad De Guadalajara, Zapopán, Mexico; [2]Sistemas de Informacion, Universidad de Guadalajara, Zapopan, Mexico; [3]Universidad de Guadalajara, Guadalajara, Mexico; [4]Periferico Norte, Centro Univericitario De Ciencias Economico Admin, Jalisco, Mexico

Abstract: Cryostat technology is essential for histological preparation, yet conventional devices are large, fixed, and dependent on external cryogenic systems, limiting their use in diverse laboratory or clinical environments. To address these challenges, we developed a patented portable automatic cryostat that integrates built-in cooling, automated sectioning, and independent sample collection modules. The device consists of a cylindrical structure housing a motor-driven screw mechanism that vertically displaces a sample base. A knife holder and an automated collection system operate synchronously through a cam-driven assembly, enabling precise tissue sectioning and deposition onto glass slides. Integrated Peltier-based cooling maintains chamber temperatures between -20 °C and -30 °C, while a dome-shaped cover provides isolation from external conditions and reduces contamination risks. A secondary thermal control directs a localized temperature gradient at the collection module, facilitating adhesion of tissue slices by differential cooling. All operations are electronically controlled through a user interface with programmable parameters, including temperature, slice thickness, and number of cuts. The system can be powered via direct current, rechargeable battery, or portable charger, ensuring true portability. Proof-of-concept tests confirmed that the cryostat produces uniform histological sections (10-30 μm) suitable for staining methods, while protecting sample integrity and improving efficiency. This portable automatic cryostat represents a novel methodological advance in tissue processing. By integrating compact refrigeration, automated cutting, and precise sample collection into a single protected framework, it provides a reliable, aseptic, and mobile solution for histological applications in neuroscience and biomedical research. Its patented design emphasizes reproducibility, contamination control, and accessibility, expanding the possibilities of frozen section analysis beyond traditional laboratory settings.

Disclosures: J.A. Dominguez-Ramirez: None. **R. Beltran-Ramirez:** None. **C. Román:** None. **X.M. Becerra-González:** None. **J. Martinez-Mendoza:** None. **V. Lopez:** None. **F. Rodriguez Mendoza:** None. **C. Medrano:** None. **A. Esparza Nuñez:** None.

Late-Breaking Poster

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Program #/Poster #: LBP019.05/LBP028

Topic: J.03. Anatomical Methods

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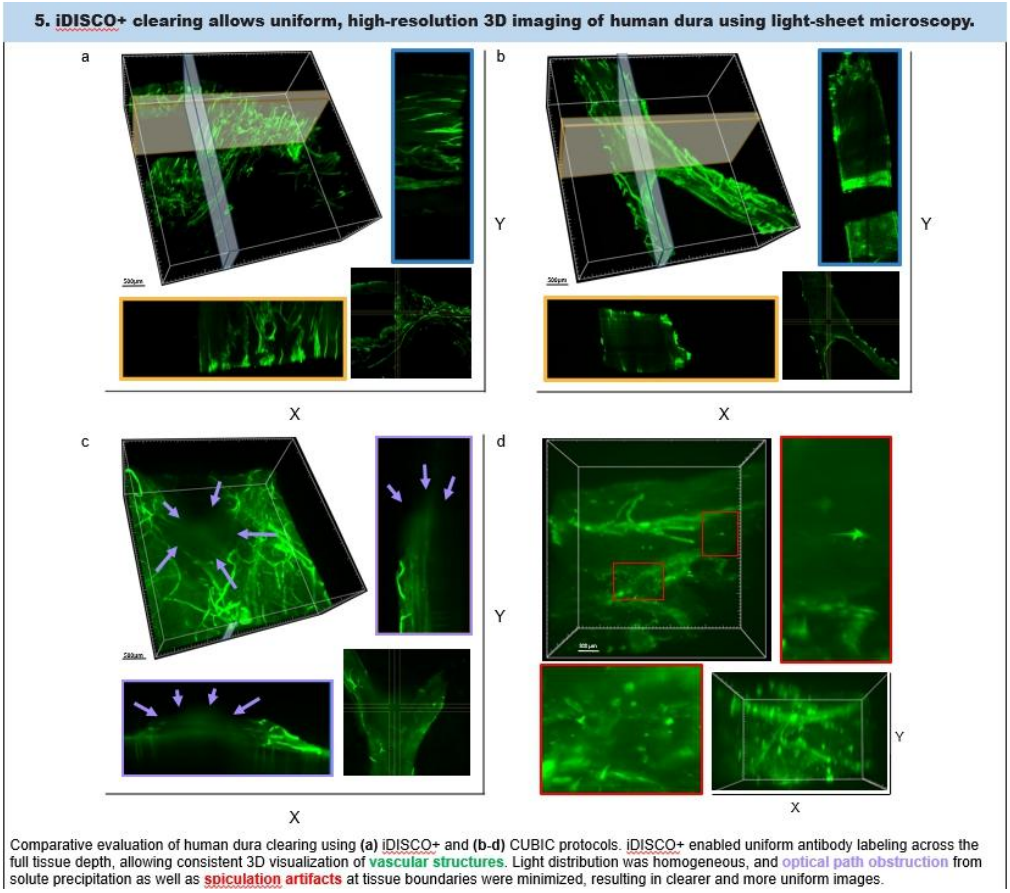
NRF Grants RS-2024-00349908
KHIDI Grant RS-2024-00405120
KBSI Grant RS-2024-004-4574

Title: Optimized imaging protocols for visualization of human dura mater

Authors: *M. PARK[1,2], D. KIM[1,2], I.-B. KIM[1], M.-Y. LEE[1,2], T.-R. T. RIEW[1,2];
[1]Department of Anatomy, The Catholic University of Korea, Seoul, Korea, Republic of;
[2]Department of Medical Sciences, College of Medicine, Graduate School of The Catholic University of Korea, Seoul, Korea, Republic of

Abstract: The dura mater is the outer most meningeal layer that envelops the brain and spinal cord. It consists chiefly of densely packed collagen bundles interwoven with fenestrated blood and lymphatic vessels, fibroblasts, immune cells, and nerves. Once viewed merely as a robust mechanical shield, it is now recognized as a critical interface for neuro-immune communication, suggesting its potential vital role in neurological diseases. However, despite this growing attention, the human dura remains poorly characterized due to a research landscape dominated by rodent models. Additionally, the dura's densely collagenous composition poses technical challenges for immunohistochemical analysis. In this study, we investigated postmortem human dura using a series of optimized immunohistochemistry (IHC)-based imaging protocols. We examined the effects of different paraformaldehyde (PFA) fixation concentrations on vascular endothelial immunolabeling and tested various fluorescence quenching strategies to reduce collagen-associated autofluorescence using confocal microscopy. These methodological advances allowed high-resolution visualization of key cellular components, including vascular and immune cells. To employ lightsheet fluorescence microscopy for volume imaging and three-dimensional reconstruction of the cellular composition of the dura mater, we compared two different tissue clearing methodologies and established an optimized protocol using a modified iDISCO method. Our findings establish a robust imaging framework for the human dura. This work offers foundational tools and perspectives for advancing research in neuroimmunology, CNS inflammation, and human meningeal biology.



Disclosures: M. Park: None. **D. Kim:** None. **I. Kim:** None. **M. Lee:** None. **T.T. Riew:** None.

Late-Breaking Poster

LBP019: J.03. Anatomical Methods

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Program #/Poster #: LBP019.06/LBP029

Topic: J.03. Anatomical Methods

Title: TARGA Imager: Unlocking Cellular Insights at Unprecedented Speed

Authors: *C. JAFFE;
Lumencor, Inc., Beaverton, OR

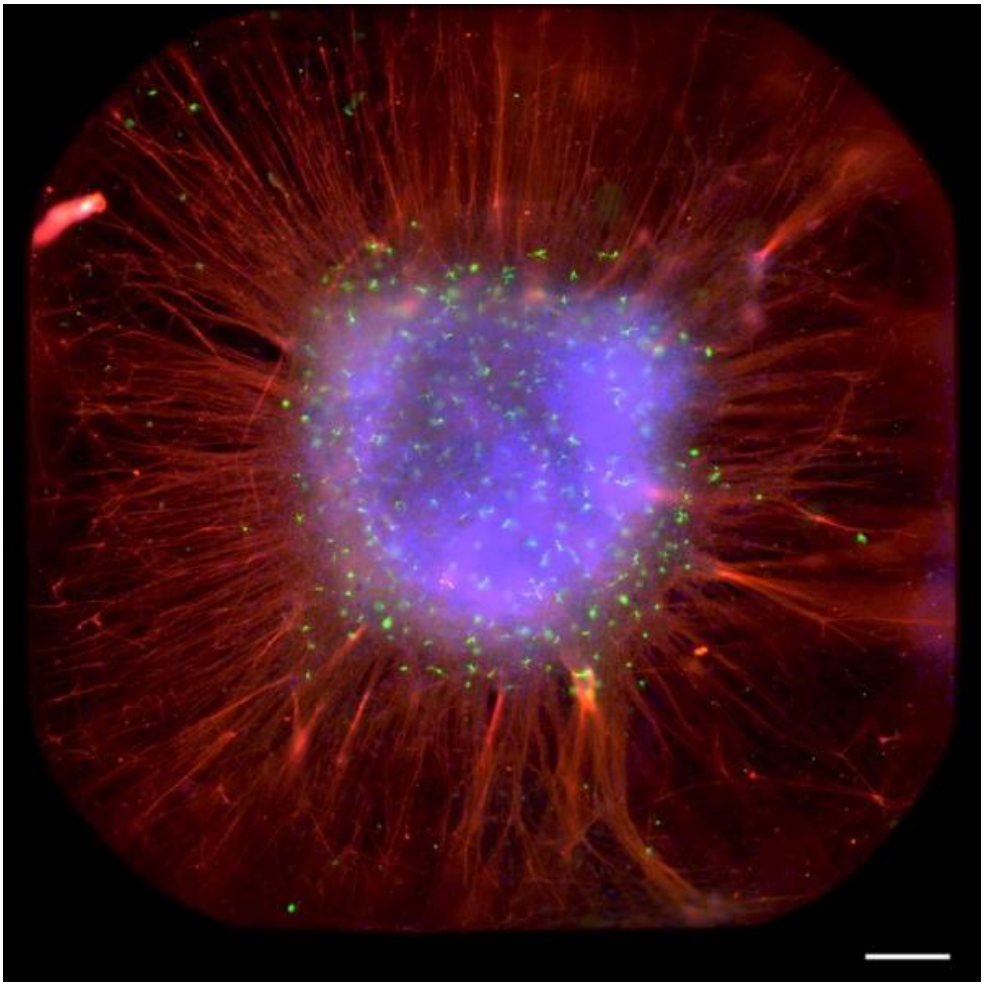
Abstract: Modern biomedical research, with applications ranging from disease modeling to personalized medicine, largely relies on fluorescent wide field and confocal microscopy. However, slow imaging misses crucial information along microsecond cellular processing timelines. Limited field-of-view requires tiled, stitched images for large tissues and organoids, further compromising data consistency and quality.

To overcome such technical challenges Lumencor developed the TARGA Imager. TARGA embodies all three essentials of high-performance imaging: speed, large field of view, sensitivity. This triumvirate enables visualization and measurement of intricate, multifaceted cellular structures as well as real-time function.

The De Vrij Lab, Department of Psychiatry at the Erasmus Medical Center [1], compared imaging the same neural organoid sample using both a Zeiss confocal microscope and Lumencor's TARGA. TARGA instantly images an entire well area reducing experiment time 10-fold. TARGA's fast multicolor light enables instantaneous imaging of numerous fluors in distinct brain cells and subcellular components. Moreover, dynamic neuronal properties, like short-term development and disease progression are observable.

Combining high-performance, solid-state lighting with sophisticated optics, illumination and detection, TARGA pushes past traditional imaging boundaries. Today's diverse biomedical research demands transformative hardware that offers performance tailored for diverse imaging specifications. TARGA best supports novel research by uncovering even the most subtle cellular features and phenomena.

Reference 1. van der Kroeg, Mark, et al. "Human adherent cortical organoids in a multiwell format." Elife 13 (2024).



Disclosures: C. Jaffe: None.

Late-Breaking Poster

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Topic: J.03. Anatomical Methods

Support: Innovate UK Knowledge Transfer Partnership 10070711
Research to Reward competition University of Bristol

Title: Development of next generation probes for correlative light and electron microscopy

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Abstract: Correlative light and electron microscopy (CLEM) is a powerful tool that combines the ability to undertake live cell imaging of fluorescence microscopy followed by fixation and imaging at sub-nanometer resolution using electron microscopy. This technique is particularly useful in highly dynamic and compartmentalised systems, such as the central nervous system. Currently, probes used for CLEM consist of antibodies conjugated with fluorophore and gold nanoparticles to enable detection of target proteins by fluorescence and electron microscopy respectively. However, the close proximity of the gold nanoparticle to the fluorophore quenches up to 95% of fluorescent signal, limiting the effectiveness of this technique. This project has developed novel probes consisting of antibodies conjugated to both gold nanoparticles and fluorophore, but with a structural design that prevents fluorophore quenching. Through use of spectrophotometry, fluorescence and electron microscopy we have optimised probes to prevent quenching of the fluorophore and therefore enable use of these probes in CLEM. These novel probes will enable study of protein localisation in the nanometer scale, for example linking cellular activity to the ultrastructure of the neuron. These novel probes will improve the accuracy and reliability of CLEM, enabling it to become a widespread technique in neuroscience and neurodegenerative disease research.

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Late-Breaking Poster

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Title: Finding a Needle in a Brainstack: Multimodal Pipeline for in vivo Patch-Clamp, Voltage Imaging, and EM Reconstruction

Authors: *D. R. BERGER[1], B. BOUAZZA AROSTEGUI[2], R. YUSTE[2], J. W. LICHTMAN[1]; [1]Harvard University, Cambridge, MA; [2]The NeuroTechnology Center, Columbia University, New York, NY

Abstract: The ability to generate multimodal datasets, in which the same neuron is studied with complementary imaging and recording approaches, opens new avenues for neuroscience. By combining dendritic voltage imaging, patch-clamp electrophysiology, and electron microscopy (EM) reconstruction of the dendritic tree, researchers can directly link neuronal function with ultrastructure and build mechanistic models of dendritic computation.

Here, we present a pipeline that enables targeted EM reconstruction of a neuron that was patch-clamp recorded and two-photon imaged in vivo in the mouse cortex. In anesthetized CD1 mice, we performed two-photon targeted patching in whole-cell configuration from layer 2/3 pyramidal neurons (Baz1a) of the somatosensory cortex, with simultaneous two-photon voltage imaging. After recordings, the pipette was carefully withdrawn along its trajectory, and the animal was perfused with aldehyde fixative. A punch biopsy containing the recorded site was prepared, and the core was embedded in low-melt agarose with a 100 micrometer brain section on top. This allowed us to carefully approach the pia of the biopsy core in the vibratome and to cut a ~600 micrometer thick pia-parallel section. This section was then prepared for electron microscopy and embedded in epoxy resin (ORTO protocol, Karlupia et al., 2023). Micro-CT imaging of the block revealed vasculature and the pipette tract, which guided precise trimming to the location of the recorded neuron. Finally, 2860 ultrathin sections (60 nm) were collected, imaged with a scanning EM, and computationally reconstructed into a 3D digital volume containing the patched neuron.

This correlative workflow establishes a “patch-to-EM” bridge, demonstrating the feasibility of linking in vivo electrophysiology and optical voltage imaging with ultrastructural reconstruction of the same neuron. Our approach opens the door to multimodal analyses that directly connect dendritic physiology to detailed synaptic architecture.

D. R. Berger and B. Bouazza Arostegui contributed equally to this work.

Reference: Karlupia, N., et al., 2023. Immersion fixation and staining of multicubic millimeter volumes for electron microscopy-based connectomics of human brain biopsies. Biological Psychiatry, 94(4), pp.352-360.

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Title: Microstructural axonal mapping for pathway activation models of deep brain stimulation

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Abstract: Pathway activation models of deep brain stimulation (DBS) depend on understanding the microstructural organization of white matter around the active electrodes. Current in vivo tractography techniques often lack the resolution needed to parameterize these models. Polarization-sensitive optical coherence tomography (PS-OCT) provides micron-scale measurements of birefringence and optic axis orientation, enabling direct visualization of axonal organization in ex vivo tissue. We developed a two-dimensional axon streamline tractography pipeline for PS-OCT that integrates complementary orientation and contrast information. First, orientation angles were extracted from the optical axis orientation (TEnAO: Tiled Enface Absolute Orientation) and the cross-polarization (TEnCr: Tiled Enface Cross Polarization) using morphological opening. Second, optimized high-confidence masks were generated by applying percentile-based thresholds on intensity, region size, and proximity-based bridging. Within these masks, orientation fields were fused such that morphology-derived angles from TEnCr were used in high-intensity regions, while TEnAO angles guided bridging areas. Third, adaptive brightness-dependent seeding was performed, yielding dense coverage in bright fiber-rich regions and sparser placement in low-contrast areas. Finally, streamlines were traced bidirectionally by Euler vector field integration, producing tractography maps with individual streamlines. Across multiple regions of interest, this method reconstructed coherent axonal trajectories that matched visible tissue structures of DBS targets including the subthalamic nucleus, globus pallidus, motor thalamus, and anterior limb of internal capsule. These results demonstrate that PS-OCT tractography can be used to generate quantitative orientation fields and streamline reconstructions at microscopic resolution. Our current work establishes a two-dimensional framework, and future efforts will extend this approach to three dimensions. A 3D PS-OCT axon tractography model will enable increased precision of DBS models that currently rely on

diffusion MRI tractography, providing a higher-resolution ground truth for studying white matter pathways relevant to DBS therapy.

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Title: Evaluation of Adeno-associated Virus 8 (AAV8) for Transneuronal Access in the Mouse Brain

Authors: *J. LAHR, M. R. WILLIAMS;
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Abstract: Adeno-associated viruses (AAVs) are frequently used to introduce genetic material into the mammalian nervous system, as well as for granting access to trace neural circuits. While some AAV serotypes have been shown to spread transneuronally at high viral titers, it has been unclear if this phenomenon is observed in AAV8, as current literature provides both evidence for and evidence against its spread. Therefore, we sought to determine if AAV8 spreads transneuronally in adult mice. We primarily utilized the M1 motor cortex to basal pontine nucleus (BPN) to cerebellar granule cell circuit as a model system. Stereotaxic injections of AAV8 were made into the BPN, while evidence of retrograde spread to M1 or anterograde spread to the cerebellum were observed. We utilized both viral and transgenic reporters of the transneuronal spread of AAV8: the expression of a fluorescent protein expressed by the AAV8 injected into the BPN and the induction of a Cre-dependent fluorescent protein reporter allele, or the induction of a Cre-dependent fluorescent reporter AAV. We report that AAV8 can spread anterogradely from the BPN to the cerebellum and that this spread appears to be dependent on the titer injected. We observed spread at 1E13 viral genomes per ml (GC/ml), as well as a low amount of spread at 1E12 GC/ml and none at 1E11 GC/ml. We did not observe robust fluorescence from the Cre-dependent fluorescent viral reporter in the cerebellum when saline was injected into the BPN. However, we observed some degree of Cre recombination of the reporter allele in the cerebellum with AAV8-td tomato Cre injection into the BPN and saline into the cerebellum. Interestingly, this spread of AAV8 does not appear to, or at least not solely, be spreading through a canonical neural circuit. When injecting AAV8-td tomato Cre into the contralateral V1 visual cortex of wild type mice, we observed recombination of the Cre-dependent reporter AAV in the cerebellum, despite the absence of canonical monosynaptic connections. Such long-distance apparent reporter recombination due to transneuronal spread of AAV8 may instead reflect spread through other extracellular spaces/routes. Given the widespread use of intersectional viral strategies for circuit tracing and manipulation, these results

suggest that an increased scrutiny to the exact conditions used may be necessary to critically interpret experimental findings.

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Title: Automated Segmentation of Volume Electron Microscopy Data Reveals Ultrastructural Correlates of Cognitive Decline in the Aged Common Marmoset

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Abstract: Understanding why cognitive decline emerges with aging remains an important question in neuroscience. One compelling hypothesis is that the function of synapses becomes dysregulated, which may be reflected by changes to the ultrastructure of synapses. Our recent study in layer III of dorsolateral prefrontal cortex (dlPFC) of common marmosets provided key evidence for this idea: through labor-intensive manual 3D electron microscopy reconstructions, we showed that an aged marmoset with working memory impairment lacked the tight size correlation between boutons and mitochondria - known as the ultrastructural size principle - which was observed in a young adult animal and an aged animal without working memory impairment. These results suggest that violation of the ultrastructural size principle may cause mismatches between synaptic demand and metabolic supply, leading to cognitive dysfunction. In this project, we extended these initial observations by generating high-throughput, automated ultrastructural segmentations across several electron microscopy datasets in multiple brain areas from the same three marmosets used in the above experiment: young adult, aged without impairment, and aged with working memory impairment. Our approach centers on a bootstrapping pipeline for training 3D-UNET segmentation models using the Pytorch Connectomics package: pretrained models are applied, corrected, and fine-tuned in cycles, yielding dataset-specific accuracy and reducing manual annotation needs.
We demonstrate successful automated segmentation of mitochondria, axonal boutons, and other synaptic structures in layer III dlPFC and the outer molecular layer of the dentate gyrus (DG) of the hippocampus. This approach not only completes the existing annotations of the dlPFC

datasets, but also extensd analysis to new, much larger volumes from the DG. The automated methods allow examination of the ultrastructural size principle at larger detail and scale than was previously possible with manual methods. Moreover, the abundance of automated annotations produced by the model further support detailed and specific comparisons, such as assessing mitochondrial size and density in excitatory versus inhibitory boutons, and determining whether the ultrastructural size principle is upheld to the same degree across distinct brain regions. These results provide substantial new evidence linking synaptic ultrastructure to cognitive decline, while demonstrating applicability of robust and scalable analysis methods.

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Topic: J.03. Anatomical Methods

Title: MouseCircuits.org: An open-source tool to study whole-brain connectivity in rodents

Authors: *S. TRIEU[1], K. C. O'REILLY[2], J. VEENSTRA-VANDERWEELE[3], K. R. ANDERSON[4], A. LIPSHUTZ[1], M. REIMERS[5], D. DUMITRIU[6];
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Abstract: Advances in rodent neural circuit manipulation have offered new opportunities to investigate how specific brain regions and pathways contribute to disordered affective states. However, much of the resulting circuit-mapping data exists as stand-alone findings across hundreds of publications, limiting accessibility and synthesis. To address this gap, we developed MouseCircuits.org, an interactive, open-source platform designed to centralize circuit-mapping studies and provide researchers with a tool for exploring whole-brain connectivity. During the initial database development, we systematically searched PubMed, Web of Science, Embase, MEDLINE, and Google Scholar for studies that used optogenetic or chemogenetic perturbations in mice or rats to examine “fear-like”, “anxiety-like”, and “depressive-like” behaviors, guided by the Research Domain Criteria (RDoC) framework. Each study was annotated for experimental design details including targeted regions or pathways, tracing methods, rodent strains, sexes, sample sizes, behavioral tests, and outcomes before inclusion into the database. Users can then interact with the database via a hierarchical edge-bundling connectome and a searchable interface for targeted exploration. Currently, MouseCircuits.org integrates data from over 200 studies published between 2010 and 2025, encompassing 51 distinct regions, 81 pathways, and

54 behavioral tests. While the initial focus of the platform was on stress-related behaviors, it has expanded to include other domains such as dominance, aggression, sociability, social reinforcement, and social memory. Across the integrated experiments, optogenetic approaches (62%) are more prevalent than chemogenetic approaches (38%). Additionally, there is a notable sex bias, with male rodents used in 82% of studies compared to female rodents (2%) or both sexes (15%), and a predominance of mouse studies (87%) over rat studies (13%). By consolidating data in this way, MouseCircuits.org enables researchers to identify such methodological biases and other knowledge gaps that are not apparent in isolated studies. This unified perspective also emphasizes the importance of examining whole-brain connectivity in addition to individual neural circuits when understanding disordered states. Moreover, by serving as a community-driven platform for sharing and integrating data, MouseCircuits.org fosters collaboration and promotes a more comprehensive understanding of how rodent circuit-mapping data translates to insights about the neural mechanisms underlying neuropsychiatric disorders.

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Title: BRAIN-XNAB: a new tool for integrating neural tracers with diffusion MRI data

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Abstract: A primary objective in neuroscience is to investigate the anatomical and functional organization of the cerebral cortex of human and non-human primates. To this aim, integration of data from non-invasive imaging modalities, such as functional and diffusion MRI (dMRI), with data from invasive experimental techniques analyzing serial tissue sections is extremely helpful. Whole-brain imaging facilitates the acquisition of 3D data at a macro-scale, whereas invasive methodologies provide morphological, anatomical, and electrophysiological information at a microscopical level. In this context, dMRI has emerged as a central tool for mapping the cerebral

white matter architecture. As this approach is under continuous refinement to improve resolution, sensitivity, and specificity, correlation with data from neural tracer injections in non-human primates (the golden standard for studying the primate connectome), can play a crucial role in testing and validating new algorithms and assessing possible improvements in accuracy. In the framework of a larger project aimed to establish new approaches for interactive multi-scale exploration of integrated 3D brain models, including imaging and histological data, we developed BRAIN-XNAB, a software for visualizing and comparing data from neural tracer injections with dMRI data obtained in the same animal. Digitized charts of histological sections, including cortical and region boundaries and labeled neuron positions and types, are non-rigidly registered to their corresponding blockfaces to build a 3D model of the cerebral cortex. Volumetric MRI data and tractograms are then fused through non-rigid registration. The combined model can then be explored and visualized through instruments that support complex predicates combining the interaction of fibers, neurons, and probes. We used BRAIN-XNAB to analyze data from a macaque brain in which connectional data from an injection of the retro-anterograde tracer Fluororuby (one injection, 1µl) in the ventral premotor area F5 were compared with different types of tractographic data obtained with ex vivo dMRI scanning of the same brain before cutting. We identified the tractograms originating from the injection site, placing ROIs in correspondence of the injection site and in the white matter where labeled axons were located. Loading the two data sets into the same native space allowed us to compare the number of labeled neurons and streamlines in each cortical sector. Accordingly, we propose BRAIN-XNAB as a powerful tool for multimodal anatomical and functional studies of the brain.

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Title: Designer indicators for two-photon recording of subthreshold voltage dynamics

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Abstract: Subthreshold voltage dynamics are critical for neuronal information integration, yet they remain understudied in vivo due to the limitations of current tools. While genetically encoded voltage indicators (GEVIs) offer a promising alternative, their application for deeper-layer voltage recording using two-photon (2P) microscopy—a preferred method for deep-tissue recording—has been hindered by insufficient sensitivity for detecting millivolt-scale subthreshold fluctuations. Here, we refined our multiparametric two-photon high-throughput screening platform to develop two novel GEVIs, JEDI3sub and JEDI3hyp, tailored explicitly for subthreshold voltage detection. Through fast 2P optical recording in awake, behaving mice, we demonstrated the superior sensitivity of JEDI3 indicators compared with JEDI-2P and state-of-the-art indicators. We also showed that JEDI3sub can monitor the subthreshold optical tuning of over one hundred cells simultaneously, while JEDI3hyp captured the subthreshold dynamics associated with sharp-wave ripple oscillations in hippocampal PV interneurons. Finally, JEDI3hyp facilitated extended imaging of brain-state-dependent, millivolt-scale subthreshold voltage changes across deep-layer somas, fine dendritic structures, and diverse cell types. By addressing the critical gap in 2P optical recording of subthreshold voltage dynamics, JEDI3 indicators open new avenues for studying neural information processing and its alterations in health and disease.

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Late-Breaking Poster

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Title: A positive-going indicator for sensitive two-photon voltage recording in vivo

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Abstract: Genetically encoded voltage indicators (GEVIs) offer a powerful, noninvasive approach for optically tracking neuronal membrane potential dynamics with high spatiotemporal resolution. However, large-scale recordings in dense tissue preparations remain challenging due to neuropil fluorescence contamination, limited sampling rates of existing microscopes, and insufficient photostability. Here, we present a new, unpublished family of green GEVIs with flipped response polarity, designed to increase fluorescence from a darker baseline during depolarization: Fluorescent Observers of Rapidly Climbing Electropotentials (FORCE). Among these, FORCE1s was engineered with optimized kinetics for compatibility across a wide range of imaging platforms, from conventional resonant scanning systems to advanced high-speed techniques. By reporting depolarizations with fluorescence increases, FORCE1s enhances signal-to-noise ratio in dense preparations, enabling more reliable multi-cell recordings. We demonstrate the advantages of FORCE1s across diverse experimental contexts, with a focus on deep-tissue two-photon imaging. We also compare the strengths of positive-response indicators, such as FORCE, with those of negative-response indicators, like JEDI, offering practical guidance for neuroscientists selecting tools for voltage imaging. Together, these advances mark a significant step toward scalable, high-fidelity voltage imaging in intact neural circuits.

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Title: Miniaturized widefield microscope for high-speed in vivo voltage imaging

Authors: *F. SPEED[1], C. SALADRIGAS[2], A. TEEL[3], M. ZOHRABI[4], E. MISCLES[2], L. BAKER[1], Y. ZHANG[5], G. FUTIA[6], I. KYMISSIS[5], V. BRIGHT[2], C. G. WELLE[7], D. RESTREPO[8], J. GOPINATH[2], E. GIBSON[9];
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Abstract: Miniature microscopes enable neuroscience researchers to study neural activity related to rodent behavior. Industry standard “miniscopes” record neural activity using genetically encoded calcium indicators (GECIs) and are therefore limited to inaccurate representations of underlying action potentials and subthreshold membrane potential oscillations. To directly record action potentials and subthreshold oscillations in a miniature device, MiniVolt was fabricated using off-the-shelf optics and a high-speed back surface illuminated (BSI) image sensor (Sony IMX568). This 16.4 g device provides high spike peak-to-noise ratio (PNR) voltage recordings with a numerical aperture (NA) of 0.6, 250 μm field of view (FOV) and 1.3 mm working distance. Recording from the full FOV at 530 Hz, MiniVolt provides comparable fidelity in Voltron2 recordings to a benchtop system with a Hamamatsu Orca Fusion-BT. Capable of recording above 1000 Hz with region-of-interest (ROI) cropping, MiniVolt showcases significant advancements in image sensor technology with significant relevance to the future of neuroscience research. This poster highlights the engineering advancements that differentiate MiniVolt from industry standard devices and showcases voltage imaging results with exceptional clarity in extracted neural signal.<!--EndFragment-->

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Title: Multimodal Ultrasound and Photoacoustic Imaging Biomarkers of Brain Cancer

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Abstract: Glioblastoma (GBM) is one of the deadliest brain cancers, with limited treatment options due to its aggressive nature and the presence of the blood-brain barrier (BBB), which restricts drug delivery to the tumor. The complex growth dynamics of gliomas and the interactions between tumoral tissue and the surrounding microenvironment present critical challenges in understanding glioma biology and advancing therapeutic strategies. Current imaging modalities often lack the necessary spatial and temporal resolutions to comprehensively map the tumor vasculature, functional hemodynamic changes, and molecular information in vivo. To address these limitations, we developed and validated a novel in vivo multimodal functional ultrasound and photoacoustic (fUSPA) brain imaging platform capable of mapping multiple imaging biomarkers of brain cancer (such as angiogenesis, echogenicity, hypoxia, vascular perfusion, and vasoreactivity) with high spatiotemporal resolutions. Our systematic in vivo fUSPA studies on orthotopic mouse models of glioblastoma (N=16) reveal that gliomas induce profound alterations in tissue architecture, hijack normal blood flow to sustain growth, and disrupt vascular perfusion, leading to ischemia in adjacent brain regions. We also observed significant impairment in cerebrovascular reactivity and functional brain responses, along with vascular changes such as vessel dilation, increased tortuosity, and the formation of abnormal capillary networks. Importantly, the fUSPA system allowed for concurrent visualization of both structural and functional vascular changes, providing a multi-dimensional perspective of glioma-

induced microvascular remodeling. These insights contribute to a deeper understanding of glioma pathophysiology and highlight the potential of advanced imaging technologies to guide precision medicine approaches for glioma diagnosis, monitoring, and treatment.

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Late-Breaking Poster

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HHMI

Title: Large-scale cellular-resolution read/write of activity enables discovery of cell types defined by complex circuit properties

Authors: *A. DRINNENBERG[1], A. ATTINGER[2], A. RAVENTOS[1], L. SIVERTS[3], T. L. DAIGLE[4], B. TASIC[5], H. ZENG[6], S. QUIRIN[1], L. M. GIOCOMO[2], S. GANGULI[7], K. DEISSEROTH[8];
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Abstract: The complexity of the mammalian brain's vast population of interconnected neurons poses a formidable challenge to elucidate its underlying mechanisms of coordination and computation. A key step forward will be realized with technologies that can perform large-scale, cellular-resolution monitoring and interrogation of distributed brain circuit activity in behaving animals. Here, we present an all-optical strategy for precise optogenetic activity control of $\sim 10^3$ neurons and simultaneous activity monitoring of $\sim 10^4$ neurons within and across areas of mouse cortex —an order-of-magnitude leap beyond previous capabilities. Tracking population responses following delivery of precisely-defined large-scale activity patterns to the visual cortex of awake mice, we were surprised to identify neurons robustly responsive to stimulation of diverse ensembles, defying conventional like-to-like wiring rules. These cells were primarily deep L2/3 somatostatin-positive (SST) interneurons with functional properties distinct from other SST neurons, and appeared to play a role in brain dynamics that could only have been identified through large-scale, cellular-resolution circuit interrogation. Our work reveals the value of measuring large-scale circuit-dynamical properties of functionally-resolved single cells, beyond genetic and anatomical classification, to define and explore the roles of cell types in brain function.

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Late-Breaking Poster

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Title: Detecting Nociceptive and Non-nociceptive Brain Activation Using Functional Near-Infrared Spectroscopy (fNIRS): A Pilot Study

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Abstract: Background and Aims Pain is a complex and multidimensional experience with both physiological and psychological components. A comprehensive understanding of its neural mechanisms is crucial for developing improved assessment methods and targeted interventions. Functional Near-Infrared Spectroscopy (fNIRS), a non-invasive neuroimaging technique, measures cerebral blood flow and oxygenation, offering a portable and robust method to monitor brain activity in naturalistic environments. This makes it especially suitable for studying the dynamic and distributed processes involved in pain perception. This pilot study aimed to explore the neural activation of nociceptive and non-nociceptive stimuli using fNIRS, with the goal of identifying potential hemodynamic biomarkers associated with pain. **Methods** Eleven healthy participants (4 males; mean age = 31.72 ± 8.49) were recruited for this study. Each participant underwent a 13-minute fNIRS recording session while receiving three types of somatosensory stimuli on the left hand: tap (8s), brush (8s), and thermal (46°C for 8s). Each stimulus type was presented in six blocks in a pseudo-randomized order. After each stimulus, participants rated their pain intensity using a visual analog scale (VAS, 0-200). fNIRS data were collected using the NIRScout system (NIRx Medical Technologies) with dual wavelengths (785 nm and 830 nm) at a sampling rate of 7.8 Hz. The montage included 32 sources and 32 detectors covering the whole brain. The separation distance between source and detector was 3 cm. Data acquisition was performed using NIRStar software, and preprocessing and analyses (GLM and group-level analysis) were conducted with Satori software. **Results** Participants reported tactile sensation without pain in response to the tap and brush stimuli, while the heat stimulus induced mild pain. fNIRS data revealed activation in several brain regions, including the right insula and secondary somatosensory cortex (S2), across all stimulus conditions. Notably, the painful heat stimulus elicited a greater number of activated channels in these regions compared to the other two conditions. Additionally, motor cortex activation was observed during the VAS rating period, corresponding to finger movement used for reporting. **Conclusion** These findings demonstrate

the feasibility of using fNIRS to detect brain responses to both nociceptive and non-nociceptive stimuli. The observed activation patterns are consistent with prior fMRI findings, supporting the utility of fNIRS as a promising tool for investigating pain-related brain activity in both research and clinical contexts.

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NIH Grant R00GM141450

Title: Anesthetic-Specific Coupling Between Calcium Fluorescence and Delta Oscillations Reveals Distinct Calcium Dynamics

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Abstract: General-anesthesia-induced synchronous activity provides a unique window into the neural mechanisms of unconsciousness. These large-scale rhythms reflect drug-specific disruptions of cortical communication that shape sedation and recovery. Clinically, synchronous activity serves as a biomarker of anesthetic depth and has been linked to postoperative delirium and cognitive decline. Identifying calcium-based proxies for local field potentials (LFPs) could simplify mechanistic and translational studies by reducing the need for combined optical and electrophysiological recordings.
While a previous, two-photon imaging study showed that calcium signals correlate with LFPs under isoflurane, we wanted to test if single-photon calcium fluorescence could serve as a proxy for the LFP, potentially simplifying future mechanistic studies.
We simultaneously recorded calcium fluorescence (UCLA Miniscope V4, 30 Hz) and LFPs (Neuralynx Digital Lynx SX, 2 kHz) from the prelimbic cortex in Sprague Dawley rats (n=6 per anesthetic, 3 male/3 female, 17.7-44.9 weeks). Subjects were administered dexmedetomidine (DEX) (high dose: 4.5 μg/kg/min; low dose: 0.3 μg/kg/min), propofol (0.8 mg/kg/min), and ketamine (2 mg/kg/min). Mean fluorescence from the cropped field-of-view was correlated with the LFP. Delta-band coherence (0.5-4Hz) and cross-correlation analyses were performed during

5+ minute baseline (non-anesthetic) and anesthetic periods.
High-dose DEX produced dramatic enhancement of calcium-LFP coupling. Delta-wave coherence increased 8.93-fold on average compared to baseline (0.025 ± 0.019 vs 0.225 ± 0.141, p=0.03125, Wilcoxon signed-rank test, Cohen's d=1.99). Peak cross-correlation rose 3.77-fold (0.096 ± 0.050 vs 0.363 ± 0.184, p=0.03125), with consistent positive time lags (0.111 ± 0.083 ms), indicating calcium signals lag electrical activity. Low-dose DEX reduced but maintained significant coupling (p=0.03125).
Strikingly, despite inducing robust delta oscillations in LFPs, neither propofol nor ketamine significantly altered calcium-LFP coherence (propofol: p=0.09375; ketamine: p=0.4375) or cross-correlation ($p > 0.05$). This dissociation suggests distinct relationships: DEX synchronizes cortical calcium dynamics with delta oscillations, while propofol/ketamine generate delta rhythms through pathways that lack coupling between calcium dynamics and population electrical activity.
These findings reveal anesthetic-specific synchronization between calcium and electrophysiological signals and establish that calcium imaging reliability as an LFP proxy depends critically on brain state and anesthetic choice.

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Late-Breaking Poster

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1R25GM132959-05

Title: A modular, headstage-agnostic, and comprehensive kit for electrophysiological implantations in rats

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Abstract: Electrophysiology enables the exploration of the relationship between neuronal activity and behaviour. This technology evolves rapidly and differs widely across manufacturers. Probes differ in size and form factors, recording systems with proprietary probes. This can cause problems for researchers when the equipment available to them is incompatible with available chronic implants as they are specific to a probe form factor. Chronic implants have several other complications, for example retention of high signal-to-noise ratio and the ability to withstand impaction over several days without breaking or the probe shifting. We sought a sturdy chronic implant for rats that could be adapted to different probes and was agnostic to headstages or recording equipment. To tackle this, we developed a comprehensive set of tools and protocols for implantation of electrode array silicon probes, including an adjustable chronic implant and a kit for assembly and testing.Besides addressing the complications previously mentioned, our implant allows probes to move vertically with precision using a screw and shuttle mechanism. It is also constructed using modular components which allows it to be easily modified for different equipment, namely headstages and probes. As a part of the kit, we have also developed a "screwdriver" which features a 24:1 gear ratio system which allows micrometer-level precision adjustments to probe depth.To test our implant kit, two separate adult rats were implanted with one Neuropixels probe each. The probes were adjusted over 2 weeks until a target DV of -5 mm was reached, in daily 48 um increments in the first week, and 300 um increments in the second. Afterward, one rat's neuronal activity was recorded 3 times a week to assess signal quality, with small 48 um adjustments in-between. We found that recordings remained stable with no detectable drift. Spikes remained detectable using a -80 uV threshold 82 days after surgery. An assessment of neuroinflammatory response was done on the second rat 23 days after implantation using Cd11b+c staining. Stain expression was less prevalent close to the target site suggesting that inflammation was avoided with slow adjustments.One limitation of the implant is that it is heavier and larger than some existing chronic implants. This can be remedied by using smaller probes (e.g. Neuropixels 2.0 instead of 1.0) and reducing the implant's size to fit them. Planned implant improvements include optimizing for probe retrieval, balancing build material, weight, and durability, and the inclusion of optical fibres for on-board optogenetic stimulation. Future studies will also use a u-CT scanner to assess probe location.

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Late-Breaking Poster

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Title: Magnetically Guided Neural Probe for Multi-scale Biosystems with In Vivo Electrophysiological Validation

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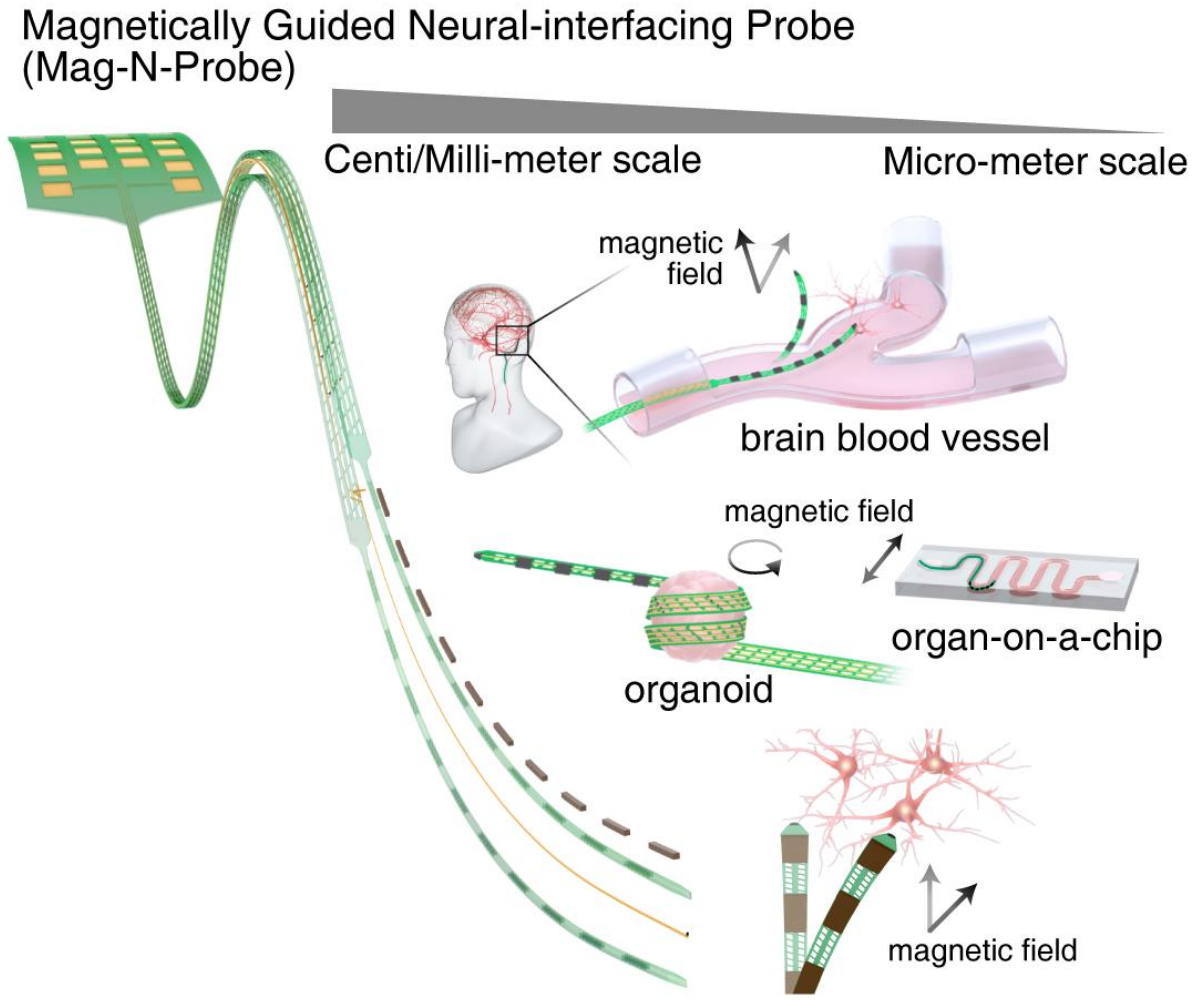
Abstract: Magnetically guided bioelectronic platforms functioning *in vitro* and *in vivo* hold promise for minimally invasive neural interfacing. We developed a flexible, magnetically guided neural probe (MagN-Probe) as a unified platform for navigation and electrophysiological recording. Using this probe, we demonstrate single-cell targeting and three-dimensional wrapping of cortical organoids *in vitro*, establishing precise neural control. We also validate navigation in vascular-mimicking channels with bifurcations, underscoring potential for endovascular guidance. Finally, we confirm capability for electrophysiological recordings in mouse brain *in vivo*. Primary cortical neurons were cultured and targeted by the probe, where external magnetic fields enabled micrometer-scale positioning and recording. Cortical organoids were cultured and magnetically actuated probes conformed around their 3D structures for multi-channel recordings. Navigation was assessed in vascular-mimicking channels under magnetic actuation. For in vivo validation, the probe was acutely inserted into the neocortex of anesthetized C57BL/6 mice using a shuttle. Electrophysiological signals were recorded at 20 kHz and analyzed post hoc for spike sorting. Single-cell recordings enabled selective targeting of neuronal compartments, soma and axon, with distinguishable waveforms. Organoid studies confirmed stable multi-channel spiking after magnetic wrapping, with ~75% active channels. *Ex vivo* navigation demonstrated robust trajectory control through bifurcating channels. Finally, *in vivo* cortical recordings revealed single-unit activity (peak-to-peak ~100 μV) within intact brain tissue, establishing feasibility of *in vivo* extracellular recording with the probe and highlighting its translational potential. This work validates the MagN-Probe as a multi-scale magnetic navigation platform bridging *in vitro* and *in vivo* brain models. Integration of magnetic actuation and electrophysiology demonstrates strong translational potential for minimally invasive neural interfacing.



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Late-Breaking Poster

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Topic: J.04. Physiological Methods

Title: Circuit electrophysiology from inside intact brain organoids reveals spiking periodicity, synchrony, and rich spontaneous activity patterns

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Abstract: Human brain organoids, derived from induced pluripotent stem cells, provide a powerful and scalable in vitro model for preclinical research. Yet, most electrophysiological approaches to date rely on planar electrodes that sample only surface activity, missing the deeper, circuit-rich interior. To harness the full potential of brain organoids, it is essential to probe their internal circuitry, enabling assessment of connectivity, disease-associated dys/function, and response to pharmacological intervention.We employed a fully automated system for inserting multi-channel silicon probes deep into intact organoids, achieving immediate, high-resolution recordings of spontaneous neural activity. We recorded circa 2,600 well-isolated single units and compared their temporal dynamics to those of hippocampal and cortical neurons recorded from freely moving mice. Similar to mouse neurons, most organoid neurons exhibited periodic spiking spanning a range of frequencies from sub-Hz to above 200 Hz. Spectral analysis of individual spike trains, computed from inverse inter-spike intervals and whitened to remove ~1/f background, revealed periodic firing at distinct frequencies. Organoid neurons exhibited a continuum of dominant frequencies, particularly within the sub-Hz to ~8 Hz range. CA1 units from freely moving mice showed rhythmic spiking with dominant frequencies near 0.25 Hz ("slow oscillations") and/or a sharp peak near 8 Hz ("theta oscillations"), but rarely in between. When multiple simultaneously-recorded units exhibited the same periodicity, spiking was synchronized between mouse units, but not between organoid units. Cortical organoids harboring Swedish/Indiana APP mutations showed dominant frequencies greater than 8 Hz, which persisted even with a drug treatment that effectively reduced amyloid-beta.While not synchronized in phase at a particular frequency, organoid units on spatially distributed shanks exhibited synchronized population events (PEs). These PEs manifested as transient increases in multi-unit activity, occasionally accompanied by low frequency, high amplitude extracellular voltage deflections corresponding to a current sink in a cellular layer. The spatial localization and consistent temporal ordering of multi-unit spiking during repeating PEs suggest localized, recurrent network activity rather than external, global activation.Our findings demonstrate that brain organoids generate spontaneous complex spiking patterns at both single-cell and network scales, offering a rich platform for functional phenotyping in disease modeling and drug discovery.

Disclosures: F. Wu: A. Employment/Salary (full or part-time); Diagnostic Biochips, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Diagnostic Biochips, Inc.. **A. Levi:** None. **B. Jamieson:** A. Employment/Salary (full or part-time); Diagnostic Biochips, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Diagnostic Biochips, Inc. **B. cakir:** A. Employment/Salary (full or part-time); Merck & Co., Inc. **R. Mathew:** A. Employment/Salary (full or part-time); Merck & Co., Inc.. **E. Stark:** None.

Late-Breaking Poster

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Title: Electrical stimulation reorganizes neural population activity in ex vivo human temporal neocortex

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Abstract: Neuromodulation is used clinically to treat a range of neurological and neuropsychiatric illnesses and is increasingly being explored to enhance cognition and memory. However, the network-level impact of electrical stimulation on circuit organization, and whether it can evoke plasticity-like reconfiguration reminiscent of learning, remains incompletely understood. We recorded single-unit activity at 20 kHz from 277 neurons across eight ex vivo human temporal neocortex specimens (layers I-VI) resected during epilepsy surgery. Recordings included a pre-stimulation epoch (median 300 s [IQR 180-600]) and a post-stimulation epoch (median 450 s [IQR 180-750]) separated by 15 minutes of focal electrical stimulation (bipolar square pulses, 200 μs per phase, 300 mV) applied in between. We characterized population geometry using Manifold Inference from Neural Dynamics (MIND), a nonlinear manifold-learning pipeline that estimates geodesic distances from state transitions and embeds high-dimensional spike activity into a low-dimensional latent subspace. The intrinsic dimensionality of the neural population was similar between epochs (pre 6.3 ± 1.0, median 6 [5.5-7.0]; post 6.1 ± 0.6, median 6 [6.0-6.5]). However, subspace structure changed significantly across all patients: pre- and post-stimulation manifolds were distinct (first principal angle: 79.9° ± 2.4°), with a shift in centroid ($\|\Delta\mu\| = 1.66 \pm 0.28$) and increased latent volume (Δvol = +320% [IQR +55% to +3224%]). UMAP projections of the MIND embeddings further demonstrated separation between pre- and post-stimulation geometries (mean silhouette score: 0.52 ± 0.25; median 0.51). To assess changes in population activity that might reflect synaptic reorganization, we constructed spike-time co-activity graphs by thresholding co-firing rates to define functional connections and identified neuronal communities using the Louvain algorithm. Partition stability was quantified using normalized mutual information (NMI) and the adjusted Rand index (ARI). In a representative patient, within-epoch consistency was high before stimulation but lower after (NMI: 0.923 ± 0.025 vs. 0.701 ± 0.112; ARI: 0.743 ± 0.060 vs. 0.507 ± 0.178), while cross-epoch similarity dropped markedly (NMI: 0.502 ± 0.049; ARI: 0.088 ± 0.042), suggesting network reorganization. Our results suggest that electrical stimulation alters the underlying geometry that coordinates population neural activity without changing its dimensionality and promotes reorganization of neuronal networks. This pattern is consistent with plasticity-like changes in which synaptic interactions are reconfigured.

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Title: Wirelessly powered mouse pup ECoG telemetry

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Abstract: Telemetry in small rodents is severely constrained by the limited lifespan and weight of conventional batteries, which impose trade-offs in sampling rate, resolution, channel count, experiment duration, and stimulation capacity. These limitations are particularly restrictive for studies involving young animals. To overcome this challenge, we implemented a first prototype with a wireless power transfer (WPT) system that eliminates the need for onboard batteries. Our design employs three orthogonal secondary coils mounted on the animal's head to maintain constant magnetic flux alignment with a primary coil positioned either inside or outside the cage. Despite the inherent efficiency loss due to the area mismatch between the coils, the system achieves reliable operation with a transmitter current below 50 mA.The system supports up to eight electrophysiological recording channels (24-bit, 250 samples/s), combined with LED stimulation and inertial sensing, all within a miniaturized implant. For neonatal applications, we further optimized the design by reducing power consumption from ~30 mA to ~5 mA through selective feature removal, including the LED driver and inertial sensor, and by lowering channel count and RF data rate. This reduction enabled the use of a single lightweight secondary coil, facilitating transmitter miniaturization to ~0.5 g—approximately 10% of body weight at postnatal day 6—while maintaining indefinite operational lifetime.To deliver power in this configuration, we relocated the primary coils into individually ventilated cages (IVCs) and implemented a circularly rotating magnetic field at 6.78 MHz, time-shared across three axes with two active axes switching every 10 µs. This approach ensures stable energy transfer to freely moving rodents. Our results demonstrate that WPT-based telemetry provides a practical solution for long-term, lightweight, and high-fidelity neural recording in both adult and neonatal rodents, overcoming the limitations imposed by traditional battery-powered systems.

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Title: Novel microfluidic chambers for longitudinal profiling of brain cortical organoids using graphene-based optical stimulation and microelectrode arrays

Authors: T. ZHOU[1], V. PRAGNA[2], H. HEMATI[1], E. MOLOKANOVA, PHD[2], A. R. MUOTRI[3], *A. SAVTCHENKO[4];
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Abstract: Human brain cortical organoids provide a powerful in vitro model to study human neural development and disease. We recently demonstrated that the optoelectronic properties of graphene—its ability to effectively convert light into a local electrical potential—can be integrated with neurons for non-invasive, non-genetic stimulation and modulation via a Graphene-Mediated Optical Stimulation (GraMOS) platform. When designing a closed-loop feedback system using Multi-Electrode Array (MEA) plates with our GraMOS platform for longitudinal monitoring of light-evoked electrical activity in organoids, we encountered technical challenges with the stability of the contact between larger, more mature organoids and the electrodes.
To overcome these challenges, we designed, lab-tested, and iteratively optimized multiple 3D-printed custom molds, fabricating two types of micro-chambers compatible with either 12- or 48-well MEA plates. These Polydimethylsiloxane (PDMS) micro-chambers enable precise positioning of brain cortical organoids at the center of the electrode array, significantly simplifying the plating procedure, accelerating organoid attachment, and enhancing long-term stability. Additionally, the micro-chambers are optimized for fluid dynamics to avoid disturbing organoids during media changes and to retain macromolecules near the organoid, making them ideal for therapeutic studies on MEA plates.
Using our micro-chambers, we demonstrated that brain organoids interfaced with graphene not only maintained excellent long-term viability but also exhibited increased spike frequency, enhanced burst coordination, and more robust network connectivity compared to controls. We further showed that the mini-chambers enable longitudinal, spontaneous, and light-evoked electrophysiological recordings under controlled conditions, providing reproducible and quantitative insights into the network dynamics of brain organoids. Their design supports scalable, high-resolution studies of complex 3D neural networks, pharmacological responses, and neuroengineering applications.

Disclosures: T. Zhou: A. Employment/Salary (full or part-time); NeurANO Bioscience. **V. Pragna:** A. Employment/Salary (full or part-time); NeurANO Bioscience. **H. Hemati:** A. Employment/Salary (full or part-time); NeurANO Bioscience. **E. Molokanova, PhD:** A. Employment/Salary (full or part-time); NeurANO Bioscience. **A.R. Muotri:** None. **A. Savtchenko:** A. Employment/Salary (full or part-time); Nanotools Bioscience.

Late-Breaking Poster

LBP020: J.04. Physiological Methods

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP020.14/LBP050

Topic: J.04. Physiological Methods

Support: Research supported by the Council for Higher Education Foundation

Title: Magnetic interfaces for neuronal uptake, targeting, and network activity recording

Authors: *D. R. LEVENBERG[1], C. MORDECHAI[2], Z. SHAPIRA[3], A. SHARONI[2], O. SHEFI[4];
[1]Bar-Ilan University, Ramat Gan, Israel; [2]Bar Ilan University, ramat gan, Israel; [3]Bar Ilan University, Ramat-Gan, Israel; [4]Bar-Ilan University, Ramat-Gan, Israel

Abstract: The ability to record individual neuron activity within a neural network is of great importance in understanding the brain in health and disease, with broad potential implications in therapeutics and in the development of nano-bioelectronic devices. Micro-electrode arrays (MEAs) enable extracellular monitoring of neuronal activity within networks. However, recordings are limited by cell migration, low electrode occupancy, and poor signal-to-noise ratio. To address these limitations, we developed a magnetic MEA platform that combines magnetically guided neurons with long-term extracellular recordings. Cortical neurons were magnetized by the uptake of magnetic nanoparticles and seeded onto micro-fabricated magnetic patterns or MEAs produced by multilayer photolithography and sputtering of ferromagnetic thin films. Simulations and experiments confirmed that the patterned magnets generated controlled field gradients capable of attracting and organizing magnetized neurons at predefined electrode sites. The magnetized neurons adhered, aligned, and formed viable networks that exhibited comparable spike and burst dynamics to unmodified controls, indicating that the magnetic process preserved fundamental electrophysiological properties. Results were replicated across multiple independent cultures (n = 3). In addition, the fabricated magnetic MEAs enabled stable and site-specific recording of neuronal activity, while maintaining the potential for drug delivery using functionalized magnetic particles. Together, these results demonstrate a novel bio-hybrid interface that integrates neuronal guidance and extracellular recording, providing a controlled read-and-write platform for studying network connectivity, neuroengineering applications, and future bioelectronic devices.

Disclosures: D.R. Levenberg: None. **C. mordechai:** None. **Z. Shapira:** None. **A. Sharoni:** None. **O. Shefi:** None.

Late-Breaking Poster

LBP020: J.04. Physiological Methods

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP020.15/LBP051

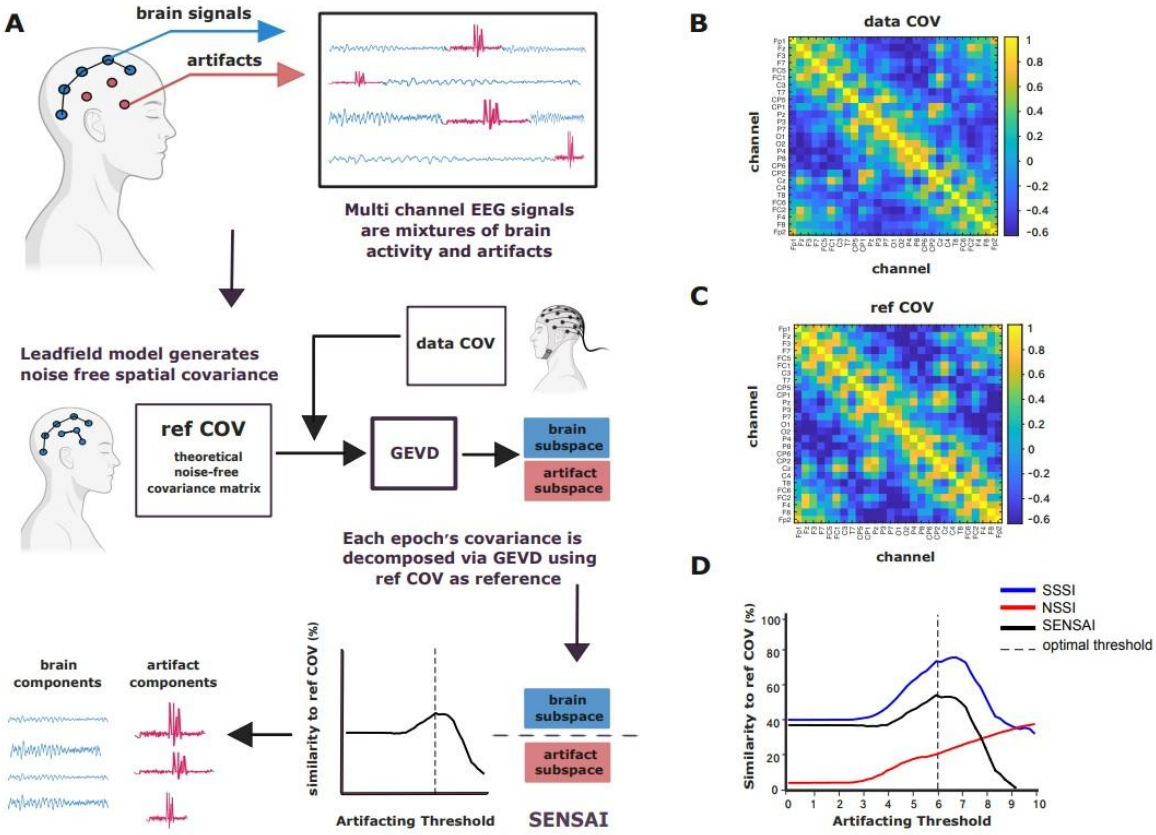
Topic: J.04. Physiological Methods

Support: Swiss National Science Foundation (SNSF), grant number 215712.

Title: Return of the GEDAI:Unsupervised EEG Denoising based on Leadfield Filtering

Authors: *T. ROS[1,2];
[1]Department of Clinical Neuroscience, University of Geneva, Geneva, Switzerland; [2]Center for Biomedical Imaging (CIBM), University of Geneva, Geneva, Switzerland

Abstract: The expansion of electroencephalography (EEG) to real-world settings is significantly hampered by contamination from non-cerebral artifacts, a challenge that current denoising methods struggle to overcome. To address the critical need for a fast, fully automated, and noise-agnostic solution, we developed GEDAI (Generalized Eigenvalue De-Artifacting Instrument), a novel algorithm based on Generalized Eigenvalue Decomposition (GEVD). GEDAI's innovation lies in its use of "leadfield filtering," where a theoretical reference covariance matrix derived from an EEG forward model defines the clean brain signal subspace. An automated algorithm, the Signal & Noise Subspace Alignment Index (SENSAI), then determines the optimal cutoff to separate neural from artifactual components. We benchmarked GEDAI against leading methods (ASR, ICLabel, MARA) on thousands of empirical and synthetic datasets across varying signal-to-noise ratios, temporal contamination levels, and artifact types. In these ground-truth simulations, GEDAI globally outperformed all other algorithms, showing particularly large effect sizes when removing complex mixtures of artifacts (NOISE+EMG+EOG) and in highly contaminated (up to 100%) or low SNR (-9 dB) conditions. This superior performance translated to neurobehavioral tasks, where GEDAI achieved the highest accuracy in both single-trial ERP classification and brain fingerprinting. By combining autonomy, speed, and noise-resilience in a single package, GEDAI provides a state-of-the-art tool that can enhance data quality in challenging real-world applications, including medical recordings, mobile EEG, and real-time brain-computer interfaces.



Disclosures: T. Ros: None.

Late-Breaking Poster

LBP020: J.04. Physiological Methods

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP020.16/LBP052

Topic: J.04. Physiological Methods

Support: JSPS KAKENHI grant 23H00413 (to T.S., T.M., I.H.)
JSPS KAKENHI grant 23K28420 (to T.K.)
JSPS KAKENHI grant 22K07323 (to Y.A.)
AMED grant JP24wm0625205 (to A.I.,T.S., T.M., I.H.)

Title: ECoG Recording from the Macaque Insular and Opercular Cortices with a Three-Dimensional T-Shaped Electrode Array

Authors: R. SAKATA[1,2], *Y. ADACHI[2], T. SUZUKI[3], T. MATSUO[4], A. IIJIMA[1,2,5], T. KAIJU[3,6], K. KAWASAKI[2], I. HASEGAWA[2];
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Physiology, Niigata University School of Medicine, Niigata, Japan; [3]Center for Information and Neural Networks, NICT, Osaka, Japan; [4]Department of Neurosurgery, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan; [5]School of Health Sciences, Niigata University, Niigata, Japan; [6]Human Informatics and Interaction Research Institute, AIST, Ibaraki, Japan

Abstract: Electrocorticography (ECoG) enables simultaneous recordings from extensive cortical surfaces. While we have previously reported methodologies for placing planar sheet electrodes within macaque cortical sulci (Matsuo et al. 2011), a challenge remains for sulci with complex three-dimensional structures. The intricate morphology of these deep regions, such as the lateral sulcus, which contains the insular cortex, impedes regular two-dimensional electrode placement with conventional planar sheets. To address this, we developed a three-dimensional, T-shaped composite of planar sheet electrodes. Individual sheet electrodes were fabricated with platinum contacts and wirings on 20-μm-thick Parylene-C films. Each recording contact was 0.38 mm in diameter and arranged at 2-mm center-to-center intervals. Two sets of these electrodes, containing 29 and 26 recording channels arranged in grids, respectively, were surgically implanted in a macaque monkey, placed within the right lateral sulcus to cover the frontal operculum and insular cortex. The electrodes were partially trimmed during surgery to conform to the specific intrasulcal structures. Postoperative computed tomography imaging, by visualizing platinum foil markers attached to the electrodes, confirmed the placement of the electrodes deep within the lateral sulcus. We evaluated the performance of these electrodes by recording under isoflurane anesthesia (< 0.5%) during auditory and tactile stimulation. As a result, from both opercular and insular surfaces, we recorded significant evoked responses ($p < 0.05$, sign permutation test, FDR-corrected) and event-related spectral perturbations ($p < 0.05$, permutation test, FDR-corrected) when compared to a pre-stimulus baseline period. This methodology enables ECoG electrode placement in anatomically complex intrasulcal structures, providing access to population-level cortical dynamics within deep sulcal regions previously inaccessible with conventional planar electrodes.

Disclosures: R. Sakata: None. **Y. Adachi:** None. **T. Suzuki:** None. **T. Matsuo:** None. **A. Iijima:** None. **T. Kaiju:** None. **K. Kawasaki:** None. **I. Hasegawa:** None.

Late-Breaking Poster

LBP020: J.04. Physiological Methods

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP020.17/LBP053

Topic: J.04. Physiological Methods

Support: ERC grant 101001448

Title: Low-power neuromorphic system for real-time compression of large-scale neural recordings

Authors: *H.-P. LIAW[1], Y. HE[2,3], P. RUSSO[2,4], J. LIU[2,5], **Y.-H. LIU**[2,4,6];
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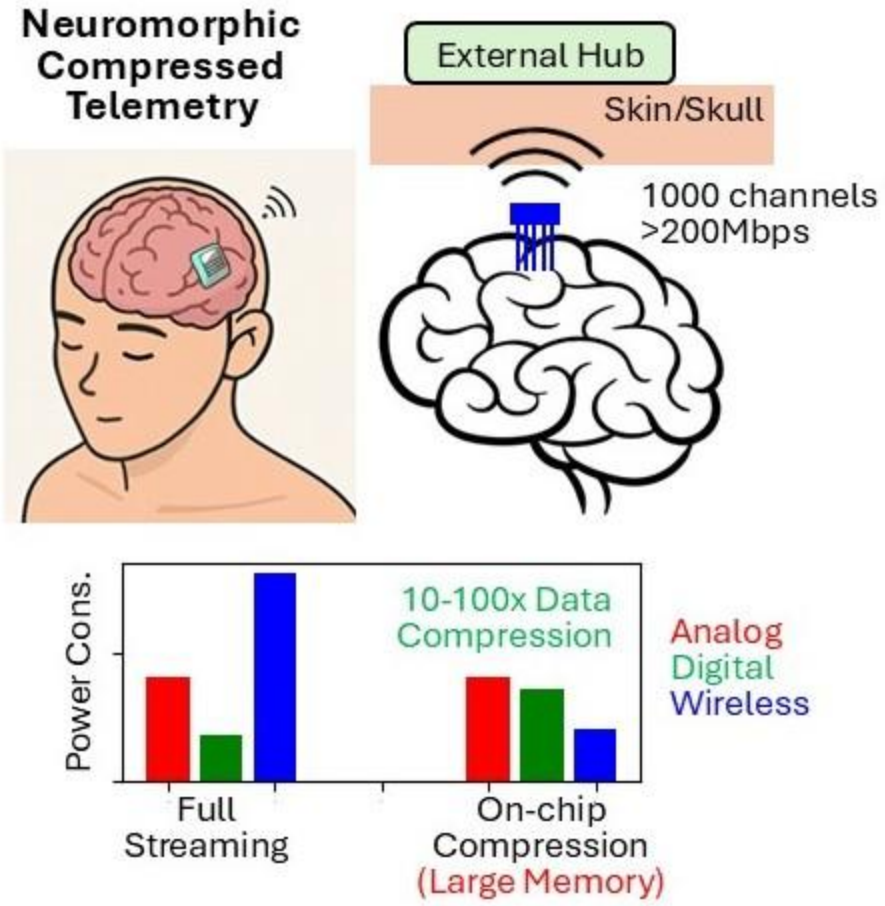
Abstract: Brain-computer interfaces (BCIs) have gained significant interest in their clinical potential to improve life quality of patients with neurological disorders and beyond. To unleash it fully capability, high-density electrodes arrays are often used to capture single units activities from the brain. However, transmitting this large volume of neural data wirelessly remains a major challenge due to strict power and safety constraints. An energy-efficient, real-time data compression method is urgently needed for BCIs.

Our system, Neuromorphic Compressed Telemetry (NCT), is designed to efficiently compress and transmit large-scale neural recordings with minimal loss of signal quality. The compression process involves two key steps. First, the delta-modulation that compares the signal between different timestamps, i.e., temporal delta, and outputs the difference. Second, a biologically inspired spiking neural network that selectively compresses the most relevant features, such as action potentials, while preserving the fidelity required for downstream analysis like spike sorting.

NCT operates in multiple modes: it can prioritize high-fidelity waveform reconstruction during training mode, switch to efficient real-time compression during compress mode, and monitor signal changes over time to adapt to biological variability like electrode drift during monitor mode. A novel event-based transmission protocol efficiently packages the outputs of different modes for wire or wireless communication.

Tested on real neural recordings, NCT achieves over 80× data compression while maintaining signal quality comparable to the noise level of typical recording systems. The compact chip (1.5 x 3 mm) consumes less than 1mW when processing data from 384 channels. This enables scalable, wireless BCIs that can record from multiple brain areas without causing tissue overheating or requiring bulky hardware.



Disclosures: H. Liaw: None. **Y. He:** None. **P. Russo:** None. **J. Liu:** None. **Y. Liu:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.01/LBP054

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

Title: EEG/ERP Signatures of Cortical Dysfunction and Treatment Response to Ketamine in Major Depressive Disorder

Authors: *A. MEGHDADI[1], C. BERKA[1], P. KLEINE[2], S. HUANG[3], C. CUSIN[4], S. MCEWEN[5];
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Abstract: Many patients with major depressive disorder (MDD) experience recurrent episodes despite treatment. Ketamine is a promising rapid-acting antidepressant, yet its neurophysiological mechanisms are unclear. Trial endpoints rely on self-report/clinician ratings which are subjective and prone to placebo effect. EEG/ERP provide objective biomarkers of cortical function that may clarify ketamine's mechanism and serve as reliable efficacy endpoints. In this single-dose, open-label study, adults with recurrent MDD (n=20; ages 19-48; 55%F) receiving standard care ketamine with prior partial response, completed EEG at baseline prior to infusion (BL), early post-dose 12-48 hours (+1d), and 2 weeks post-dose (+2w). Depressive symptoms were assessed with validated scales (QIDS-C/HAMD6). EEG protocol included resting with eyes open/closed (EO/EC) and two ERP tasks: auditory oddball (AO) and emotional faces (EIR). EEG spectral power, aperiodic slope, Lempel-Ziv complexity, AO P300, EIR N170 to emotional faces and slow wave potential (SWP) were measured. Data were compared to age-matched healthy controls (HC). Between group differences (Welch's t-test) and within-subject treatment effects (paired t-test) were assessed. G_{ch} denotes the effect size (Hedges g) at the most significant channel. At BL, compared to HC, patients showed increased Beta/Gamma power (G_{T5}=0.9, p<.001, EO), reduced aperiodic slope (G_{T5}=-0.64, p<.05, EO), increased complexity (G_{O1}=0.84, p<.01), reduced AO P300 amplitude (G_{T6}=-0.54, p<.05) and faster reaction time (G=-0.57, p<.05). In EIR, they showed increased N170 to sad faces (G_{T3}=0.33, p<.05), enhanced Sad-Neutral bias (G_{P4}=0.69, p<.01), reduced SWP (G_{T6}=-0.73, p<.05). Post-dose, Theta power decreased globally +1d (G_{T5}=-0.55, p<.01) and +2w (G_{Poz}=-0.37, p=.01). Aperiodic slope increased +1d in EC (G_{Poz}=0.41, p<.01) and decreased +2w in EO (G_{O1}=-0.38, p<.05). Complexity decreased +1d in EC (G_{Fp1}=-0.44, p<.05) and a nonsignificant increase in EO +2w (G_{F8}=0.54, p=.07). P300 increased +2w (G_{C3}=0.46, p<.05). EIR N170 amplitude to sad faces marginally increased +1d (G_{T4}=0.8, p=.05) , +2w (G_{T6}=0.3, p=.05), Sad-Neutral bias did not change significantly. SWP increased +1d: (G_{Fp2}=0.41, p<.05) and +2w (G_{Cz}=0.47, p<.05). EEG/ERP in MDD revealed baseline abnormalities and post-ketamine improvements in resting EEG and ERP response. These findings support EEG/ERP as objective biomarkers for both trait abnormalities and treatment effects and offering insight into neurophysiological mechanisms underlying ketamine's rapid-antidepressant action. Results need replication in larger sample size.

Disclosures: A. Meghdadi: A. Employment/Salary (full or part-time); Advanced Brain Monitoring Inc. **C. Berka:** A. Employment/Salary (full or part-time); Advanced Brain Monitoring Inc. **P. Kleine:** A. Employment/Salary (full or part-time); Atai Life Sciences. **S. Huang:** A. Employment/Salary (full or part-time); Massachusetts General Hospital. **C. Cusin:** A. Employment/Salary (full or part-time); Massachusetts General Hospital. **S. McEwen:** A. Employment/Salary (full or part-time); Atai Life Sciences.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.02/LBP055

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

Title: Developing EEG-based Biomarker Systems in Rodents and Primates for Drug Response Evaluation: Deep Learning-Based Prediction Model Construction

Authors: Y. YAWATA[1], A. MASUDA[2], N. TAKAI[1], S. HIROYAMA[1], *K. TAKASU[1], K. HAYASHIDA[2], K. OGAWA[1];
[1]Shionogi & Co., Ltd., Toyonaka, Japan; [2]Drug Safety Laboratories, Shin Nippon Biomedical Laboratories, Ltd., Kagoshima-city, Japan

Abstract: Drug development for central nervous system (CNS) disorders is often hindered by the low success rates of clinical trials, frequently due to insufficient drug efficacy in achieving the intended therapeutic effects. This highlights the need for a predictive biomarker that reliably assesses drug efficacy across species. Despite progress in electroencephalography (EEG) research, including auditory event-related potentials (AERP), translational research is limited by species-specific constraints. Mice provide homogeneity and ease of sample size acquisition but lack extrapolative applicability. In contrast, non-human primates like cynomolgus monkeys offer superior extrapolation potential but pose challenges due to limited sample availability and pronounced individual variability. Comprehensive cross-species EEG studies are rare and typically focus on specific indices. Our study addressed to bridge this gap by developing robust EEG measurement systems for both mice (n = 16 mice) and cynomolgus monkeys (n = 6 monkeys), evaluating the same drugs using consistent measurement protocols across both species and conducted a comparative analysis. Specifically, we evaluated resting-state EEG and AERP signals, including auditory habituation (AH), mismatch negativity (MMN), and auditory steady-state response (ASSR), following the administration of MK-801, an NMDA receptor antagonist. We analyzed the ability of EEG data to predict pharmacological effects, focusing on the differences and similarities between the species. We confirmed increased high-gamma power in the resting-state EEG, decreased N1 amplitudes in the AH and MMN tasks, and a decreased phase-locking index in the ASSR task. Using deep learning models, we achieved prediction levels of 84.1% accuracy in classifying EEG data according to different treatment conditions, namely, saline, low-dose MK-801, and high-dose MK-801 treatment. At the same time, we succeeded in prediction of species (mice or monkeys) with an accuracy of 95.1% using the same models. The analysis of learned representations demonstrated reduced inter-species distances at similar plasma concentrations of MK-801, as well as unique label distributions. Moreover, we introduced the predictive contribution score (PCS), which facilitated identification of proof-of-mechanism markers, classification explainability, and the generation of inter-species hypotheses. Our findings have the potential to significantly advance CNS drug development by providing insights that improve clinical trial strategies and elucidate the neurophysiological mechanisms of drug action.

Disclosures: Y. Yawata: A. Employment/Salary (full or part-time); Shionogi & Co., Ltd.. Other; This study was supported by research funding from Shionogi & Co., Ltd. **A. Masuda:** A. Employment/Salary (full or part-time); Shin Nippon Biomedical Laboratories, Ltd.. Other; This study was supported by research expenses provided by Shionogi & Co., Ltd. **N. Takai:** A. Employment/Salary (full or part-time); Shionogi & Co., Ltd.,. Other; This study was supported by research expenses provided by Shionogi & Co., Ltd. **S. Hiroyama:** A. Employment/Salary (full or part-time); Shionogi & Co., Ltd. Other; This study was supported by research funding from Shionogi & Co., Ltd. **K. Takasu:** A. Employment/Salary (full or part-time); Shionogi & Co., Ltd.. Other; This study was supported by research expenses from Shionogi & Co., Ltd. **K.**

hayashida: A. Employment/Salary (full or part-time); Shin Nippon Biomedical Laboratories, Ltd.. Other; This study was supported by research expenses provided by Shionogi & Co., Ltd. **K. Ogawa:** A. Employment/Salary (full or part-time); Shionogi & Co., Ltd.,. Other; This study was supported by research expenses provided by Shionogi & Co., Ltd..

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.03/LBP056

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

Support: RS-2022-KH129545

Title: Positive modulation of NMDA receptors in the hippocampus ameliorates Alzheimer's disease phenotypes via IL-33/ST-2/OPN signaling in APP/PS1 mice.

Authors: *S. CHUNG[1], E.-E. JUNG[2], J. JEONG[3], Y. KIM[4];
[1]Physiology, Yonsei University College of Medicine, Seoul, Korea, Republic of; [2]Yonsei University College of Medicine, Seoul, Korea, Republic of; [3]BNH Research R&D Center, Goyang-si, Korea, Republic of; [4]BNH Research R&D Center, Gyeonggi-do, Korea, Republic of

Abstract: Alzheimer's disease (AD) still lacks curative therapy: currently available symptomatic agents offer only modest, transient benefit and do not alter disease progression. Recently approved antiamyloid monoclonal antibodies—exemplified by lecanemab (Leqembi)—lower brain amyloid burden and produce moderately less cognitive decline versus placebo, but their safety profile reflects modality-specific liabilities, notably amyloid-related imaging abnormalities (ARIA) and infusion reactions; ARIA is recognized by the FDA as a class effect of antibodies targeting amyloid and is highlighted with a boxed warning on the Leqembi label. Accordingly, there is a critical need for brain-penetrant small-molecule therapeutics that avoid antibody-driven adverse events while simultaneously suppressing pathogenic Aβ deposition and restoring depressed synaptic plasticity. Identifying targets that couple Aβ reduction with enhancement of Hebbian plasticity in hippocampal-cortical circuits—and developing small-molecule modulators to control those targets precisely—will be essential to overcome current treatment limitations. We, therefore, developed BNH-015B, a positive NMDA modulator targeted at a GluN2B-binding site. Orally-administered BnH-015B enhanced synaptic strength and LTP induction at the Schaffer collateral input to CA1 hippocampus in a dose-dependent manner, with a maximum dose of 10 mg/kg in 15-month APP/PS1 mice. The effect of BnH-015B was nearly entirely prevented by applying R0-25-6981 (5 μM), a GluN2B-selective antagonist, via intraventricular infusion. In addition, BnH-015B also decreased the amyloid-beta deposit in the cortex and hippocampus of 15-month APP/PS1 mice. In terms of a molecular mechanism for the BnH-015B effect, BnH-015B significantly increased expression of IL-33, but decreased osteopontin (OPN) expression in the hippocampus in 15-month-old APP/PS1 mice, which was significantly hindered by the blockade of GluN2B-containing NMDA receptor with

R0-25-6981. In addition, the effects of BnH-015B on the LTP and amyloid beta deposit were suppressed considerably by intraventricular infusion of ST-2 protein, an IL-33 decoy receptor, in 15-month APP/PS1 mice. Finally, BnH-015B-treated mice exhibited significantly improved performance of hippocampus-dependent spatial learning and memory compared to vehicle-treated controls. These results suggest that Positive modulation of NMDA receptors in the hippocampus may rescue Hebbian synaptic plasticity and cognitive deficit, as well as amyloid-beta deposit via IL-33/ST-2/OPN signaling in the rodent Alzheimer's disease model.

Disclosures: S. Chung: A. Employment/Salary (full or part-time); BnH Research. Co., Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BnH Research. Co., Ltd. **E. Jung:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BnH Research. Co., Ltd. **J. Jeong:** A. Employment/Salary (full or part-time); BnH Research. Co., Ltd.. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); BnH Research. Co., Ltd. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BnH Research. Co., Ltd. **Y. Kim:** A. Employment/Salary (full or part-time); BnH Research. Co., Ltd.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BnH Research. Co., Ltd..

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.04/LBP057

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

Support: NIH Grant U01NS114156
NIH Grant ZIAHG200409
NIH Grant P30DK020579

Title: Diagnostic and Therapeutic Applications of the Glycan Biomarker H3N2b in GM1 Gangliosidosis

Authors: *X. JIANG;
Washington University School of Medicine, Saint Louis, MO

Abstract: GM1 gangliosidosis is a rare, progressive lysosomal storage disorder caused by mutations in the *GLB1* gene, resulting in β-galactosidase deficiency and accumulation of GM1 ganglioside and related glycoconjugates. Clinical manifestations vary by age of onset and severity, with the infantile form being the most severe. Current diagnostic approaches—enzymatic and genetic testing—have limitations that delay diagnosis and treatment. We identified two pentasaccharides, H3N2a and H3N2b, as disease-associated glycan fragments elevated in GM1 gangliosidosis. To quantify H3N2b in plasma and urine, we developed liquid

chromatography-tandem mass spectrometry (LC-MS/MS) assays using a synthetic H3N2b standard and a deuterated internal analog. Diagnostic performance was evaluated in a cohort of GM1 gangliosidosis patients, healthy controls, and individuals with other lysosomal storage disorders. Additionally, H3N2b levels were monitored in patients receiving intravenous AAV9 gene therapy. H3N2b levels were significantly elevated in both plasma and urine of GM1 gangliosidosis patients compared to controls. The assays demonstrated 100% sensitivity (plasma) and 99.17% sensitivity (urine), with 100% specificity for both matrices. H3N2b also showed excellent specificity when tested against 15 other lysosomal storage disorders. Following AAV9 gene therapy, H3N2b levels declined in treated patients, and plasma H3N2b concentrations were inversely correlated with serum β-galactosidase activity, indicating its potential as a pharmacodynamic biomarker. H3N2b is a highly sensitive, specific, and non-invasive biomarker for the diagnosis of GM1 gangliosidosis. Its robust performance across biofluids and disease contexts supports its application in diagnostic workflows and as a tool for monitoring treatment efficacy, including gene therapy interventions.

Disclosures: X. Jiang: None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.05/LBP058

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

Title: Nanoparticle-based Labeling of Catecholaminergic Neurons: A Novel Tool for assessing neuronal activity

Authors: *A. MURUGAN[1], Y.-J. CHUANG[1], A. PALANIYAPPAN[1], S. M. MOHANKUMAR[2], P. S. MOHANKUMAR[3];
[1]UNIVERSITY OF GEORGIA, Athens, GA; [2]Veterinary Biosciences and Diagnostic Imaging, University of Georgia, Athens, GA; [3]Dept Pathobiol & Diagnostic Invest, University of Georgia, Athens, GA

Abstract: Measuring catecholaminergic activity is a crucial step in assessing changes in neuroendocrine function. Currently, we use a variety of methods including micro dialysis or push-pull perfusion in combination with HPLC-EC or cyclic voltammetry. These techniques are invasive, require skill, are labor intensive and require the use of expensive analytical tools. Imaging agents can be used to non-invasively assess catecholaminergic neuronal function over time. However, this has been a challenge since there are no imaging agents that can effectively cross the blood brain barrier (BBB) to reach these neurons. To overcome this issue, we have developed a novel nanoparticle (NP), SGER9102, which, when administered intravenously, can cross the BBB and specifically target catecholaminergic neurons. We have previously shown that NP uptake can be monitored by high-resolution magnetic resonance imaging (MRI). In the present study, we validated the localization of the nanoparticles in catecholaminergic neurons

using immunohistochemistry. Four-month-old, male F344 rats were intravenously injected with PBS or SGER9102 NP and euthanized 4 hours post-injection. Their brains were fixed with 10% neutral-buffered formalin, cryoprotected in graded sucrose and sectioned at 30 μm thickness using a cryostat. Sections were analyzed by double immunofluorescence for tyrosine hydroxylase (TH) immunoreactivity and the NP using confocal microscopy. TH is the rate-limiting enzyme for catecholamine biosynthesis and serves as a marker of catecholaminergic neurons. Both PBS- and NP- treated rats exhibited robust TH immunoreactivity in the A1, A2 and A6 noradrenergic nuclei and the arcuate, substantia nigra (SN) and zona incerta (ZI) dopaminergic nuclei. Importantly, rats injected with the NP displayed co-localized fluorescent signals within TH-positive neurons, confirming specific uptake of the NP by catecholaminergic neurons. These findings demonstrate that SGER9102 successfully crosses the BBB and selectively labels catecholaminergic neurons in vivo. This approach represents a promising non-invasive strategy for assessing catecholaminergic neuronal activity over time.

Disclosures: A. Murugan: None. **Y. Chuang:** None. **A. Palaniyappan:** None. **S.M. Mohankumar:** None. **P.S. Mohankumar:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.06/LBP059

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

Support: L.K. Whittier Foundation at the HMRI
R01MH110438 (National Institute of Mental Health)

Title: A longitudinal multi-omics pilot analysis of CSF reveals changes in cell-matrix adhesion protein levels associated with cognitive impairment.

Authors: *J. JOSE[1], N. ASTRAEA[2], X. WU[2], R. BUTLER[3], A. QUACH[4], O. CHOI[4], S. KHOSRAVIAN[5], A. NOLTY[5], R. KLONER[6], A. VASUDEVAN[7], A. FONTEH[1];
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Abstract: Introduction: Cell-matrix adhesion proteins are vital for cognitive function, mediating cell-extracellular matrix communication and influencing neuronal development, synaptic plasticity, and contributing to neurological disorders. Therefore, we hypothesized that fluctuations in CSF cell-matrix adhesion protein levels are associated with cognitive impairment.**Method:** In the context of an aging study, we determined cognitive function using a

comprehensive neuropsychological battery with neuropsychologist determination of cognitive status. For this project, participants were identified as cognitively unimpaired (CU) at baseline, and cognitively impaired (CI) 4-5 years later. CSF samples were collected at both visits after an overnight fast, and using a high-resolution mass spectrometer operated at data dependent acquisition (+/-) ddMS2, peptides were detected, and proteins were identified. Variations in proteins levels were compared between baseline visits with all CU and follow-up visits with all CI, using GraphPad Prism and MetaboAnalyst 6.0.**Results:** Detailed clinical conferencing and examination of key neuropsychological domains revealed that all the 8 CU participants became CI in the follow-up visit. Analysis of protein data revealed that levels of lumican, matrilin-2, desmoglein-2, protocadherin-17, transmembrane glycoprotein NMB, Vasorin, VSP10 domain containing receptor SorCS3, thrombospondin-4, neuroligin-1 and Noelin were significantly higher, and ephrin-1, Chondroadherin, amyloid-beta precursor protein, cell adhesion molecule 3, neutral cell adhesion molecule 1, cell adhesion molecule 3, LINGO3 and sodium channel subunit beta-2 were significantly lower with cognitive impairment. Further analysis showed a strong correlation between these proteins.**Conclusions:** These data establish an association between cell-matrix adhesion proteins and cognitive impairment. These findings suggest that cell matrix adhesion proteins are important in pathology and may be potential biomarkers of cognitive impairment associated with Alzheimer's disease.

Disclosures: J. Jose: None. **N. Astraea:** None. **X. Wu:** None. **R. Butler:** None. **A. Quach:** None. **O. Choi:** None. **S. Khosravian:** None. **A. Nolty:** None. **R. Kloner:** None. **A. Vasudevan:** None. **A. Fonteh:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.07/LBP060

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

Support: Bridge Proof of Concept 40B1-0_214621
Pioneer fellowship PIO-03 22-2
Gebert Rüf Stiftung GRS-032/23
Innosuisse 113.845 IP-LS

Title: Closed-loop movement-paired transcutaneous auricular vagus nerve stimulation for upper-limb rehabilitation: a feasibility study

Authors: *C. LHOSTE[1,2], M. QUAST[1,2], A. RONCO[1,2], A. VOGEL[1,2], M. BRANSCHEIDT[1,3], O. LAMBERCY[1,2,4], P. VISKAITIS[1,2], D. DONEGAN[1,2];
[1]ETH Zurich, Zürich, Switzerland; [2]Rehabilitation Engineering Laboratory, ETH Zurich, Zurich, Switzerland; [3]Center for Research and Neurorehabilitation, cereneo, Weggis, Switzerland; [4]Future Health Technologies, Singapore-ETH Centre, Campus for Research Excellence and Technological Enterprise (CREATE), Singapore, Singapore

Abstract: Neurological injuries, including stroke and spinal cord injury, are leading causes of disability worldwide [1]. A common consequence is upper-limb impairment, with persistent deficits in up to 50% of stroke survivors even six months after [2]. One promising approach to improve recovery is therapy combined with transcutaneous auricular Vagus Nerve Stimulation (taVNS) paired with movement. While taVNS-combined therapy has shown promise for improving upper-limb function in stroke, a remaining challenge is the labour intensive setup and triggering of taVNS by therapist-controlled buttons or by electromyography (EMG)-sensor systems [3]. In this study, we introduce SmartVNS, a fully wireless, wearable system that automatically delivers movement-paired taVNS using a wrist-worn inertial measurement unit (IMU) for movement detection. We evaluated SmartVNS in a four week, 20 session, clinical feasibility study involving nine individuals with stroke or spinal cord injury during conventional therapy. Despite a wide range of baseline upper-limb function in patients (ARAT scores 0-47), the system demonstrated a consistent stimulation rate between sessions and patients, averaging 14.7 stimulations/min with a low variability (SD = 3.4 stimulations/min; n=9). The IMU-based movement detection algorithm achieved stimulation precision comparable to manual therapist triggering (precision: SmartVNS: 76.3±11.9%, therapists: 82.4±10.1%, video analysis used a ground truth), while delivering stimulation in twice more movements (recall: SmartVNS: 50.4±19.5%, therapists: 23.4±18.1%). The system demonstrated high usability (patients and therapists rated UMUX: 85±12%) and was well-tolerated by participants, with patients able to self-apply the device. Exploratory clinical outcomes showed consistent functional improvements across participants. These findings support the feasibility and usability of SmartVNS as a scalable neuromodulation platform for neurorehabilitation. This work provides valuable insights and paves the way to larger, controlled studies.
[1] Bhat, S.G. et al. "Upper extremity asymmetry dueto nerve injuries or central neurologic conditions: a scoping review". Journal of NeuroEngineering and Rehabilitation 20(1) (2023)
[2] O'Flaherty, D., Ali, K.: "Recommendations for upper limb motor recovery: An overview of the UK and european rehabilitation after stroke guidelines (2023)." Healthcare 12(14) (2024)
[3] Austelle, Christopher W et al. "Vagus nerve stimulation (VNS): recent advances and future directions." Clinical autonomic research : official journal of the Clinical Autonomic Research Society vol. 34,6 (2024): 529-547

Disclosures: C. Lhoste: None. **M. Quast:** None. **A. Ronco:** None. **A. Vogel:** None. **M. Branscheidt:** None. **O. Lambercy:** None. **P. Viskaitis:** None. **D. Donegan:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.08/LBP061

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

Title: QSAR design, syntheses, and in vitro assessment of bridged polycyclic alkyl aryl amines as uncompetitive nmda receptor antagonists for treatment of neurodegenerative disorders

Authors: *B. STANLEY[1], I. DIALLO[2], B. CHIN[3], A. EYSSALENNE[3], A. ADEJARE[3]; [1]Chemistry and Biochemistry, Saint Joseph's University, Philadelphia, PA; [2]Biology, Saint Joseph's University, Philadelphia, PA; [3]Pharmaceutical Sciences, Saint Joseph's University, PHILADELPHIA, PA

Abstract: The N-Methyl-D-Aspartate Receptor (NMDAR) is an ionotropic glutamate receptor which plays a critical role in the pathophysiology of many Central Nervous System (CNS) disorders. Overactive NMDARs occur through excessive glutamate binding, leading to cytotoxic effects and neurodegeneration. To address this issue, uncompetitive NMDAR antagonism continues to be a worthwhile pursuit, as demonstrated by FDA approval of three compounds in that class - memantine for treatment of Alzheimer's Disease (AD), amantadine for treatment of Parkinson's Disease (PD), and the recent approval of Ketamine for treatment resistant major depressive disorder. However, the potencies of the compounds in this class are known to be correlated with undesirable side effects - such as hallucination, dissociation, and elevated levels of aggression, indicating a desirable therapeutic window or "goldilocks" zone for uncompetitive NMDAR inhibition. We report an exploratory structure-activity relationship (SAR) study of novel aryl adamantylamines and arylbicyclo[2.2.2]octylamines designed to probe conformational restriction and steric modulation on NMDAR binding affinities. Thirty target compounds were synthesized in general good yields overall (18-84%) and structures were confirmed using melting point, NMR, HPLC, and MS. Binding affinities at the NMDAR PCP site, measured via [^{3}H]-MK-801 radioligand assays, ranged from 679 nM to 10,000 nM. SAR analysis revealed that N-substitution significantly improved potency, and replacement of a benzene ring with thiophene further enhanced activity. Preliminary 2D QSAR model studies demonstrated strong predictive performance amongst the training and test set compound series ($R^2 = 0.84$, $Q^2 = 0.76$), while molecular docking was used to gain further insight into SAR relationships within the PCP binding site. These results establish bridged polycyclic alkyl aryl amine scaffolds as promising uncompetitive NMDAR antagonists and provide new insight into strategies for developing therapeutic agents targeting neurodegenerative disorders.

Disclosures: B. Stanley: None. **I. Diallo:** None. **B. Chin:** None. **A. Eyssalenne:** None. **A. Adejare:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.09/LBP062

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

Support: NIH U01 AI163064
NIH R01AI168044
DP1DK130660
NIH PO1AG078106
P30DK052574

T32HL007081
SPARK grant from the Department of Pathology & Immunology

Title: Depth-Variant Deconvolution Applied to Widefield Microscopy for Rapid Large-Volume Tissue Imaging

Authors: *D. D. LEE;
Pathology and Immunology, Washington University School of Medicine, Saint Louis, MO

Abstract: Depth-Variant Deconvolution Applied to Widefield Microscopy for Rapid Large-Volume Tissue Imaging
Daniel D. Lee[1*#], Kevin A. Telfer[1*], Mark. A. J. Koenis[2], Yim K. Lee[3], Kevin W. Namink[2],Brian T. Saunders[4], Heyun Lee[1], Hailey K. Kelley[1], Heather S. Ruiz[1], Joseph P. Gaut[1],Gwendalyn J. Randolph[1#], Bernd H. Zinselmeyer[1#1]Department of Pathology & Immunology, Washington University School of Medicine, SaintLouis, MO, USA.[2]Scientific Volume Imaging B.V., Hilversum, Netherlands[3]Independent Scholar, Saint Louis, Missouri, USA [4]Zeiss Microscopy, Saint Louis, Missouri, USA*These authors equally contributed.#Corresponding authors: Daniel D. Lee, Gwendalyn J. Randolph, Bernd H. ZinselmeyerEmail: ldaniel@wustl.edu; gjrandolph@wustl.edu; bzinselmeyer@wustl.edu
Advances in tissue clearing and 3D imaging have deepened our understanding of brain structure and pathology, yet broad adoption remains constrained by time-intensive workflows and dependence on advanced imaging systems. Although widefield microscopy is fast and accessible, its lack of intrinsic optical sectioning has limited its role in 3D neuroscience applications. Here, we combine depth-variant deconvolution using a commercial algorithm that we optimized for large-scale, high-resolution imaging of cleared tissues. To overcome depth-related resolution loss, we implemented prefiltering and z-brick segmentation, enabling subnuclear axial resolution through 500 μm of tissue in multi-tile datasets. We applied this approach to two relevant neuroinflammatory disease models. In thick sagittal brain slices from a mouse model of cerebral amyloid angiopathy (CAA), we visualized amyloid-beta deposition along penetrating arterioles and small vessels with resolution comparable to confocal microscopy, revealing the 3D spatial relationship between vasculature and pathology. In a separate model of ileitis, we observed associated inflammatory changes. To explore translational potential, we extended this workflow to human clinical samples, imaging hundreds of z-planes in cleared kidney biopsies. While outside the CNS, this illustrates applicability to human tissues that are difficult to prepare transplant-relevant timelines. Our results demonstrate that widefield imaging, when coupled with robust computational deconvolution, offers an accessible and scalable approach for high-resolution 3D imaging of neurodegeneration, vascular disorders, and brain-immune interactions.

Disclosures: D.D. Lee: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Leinco Inc..

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.10/LBP063

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

Support: National Science Foundation (NSF) – 2123971

Title: Localized and Deep Brain Release of Molecules with Photosensitive Nanovesicles and Mechanoluminescent Nanoparticles

Authors: *H. TAJARENEJAD[1], A. PAL[2], M. MALINAO[3], A. DEANDA[4], K. SHARMAH GAUTAM[5], X. GE[6], S. ACHILEFU[5], G. HONG[7], Z. QIN[8];
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Abstract: Title:
Localized and Deep Brain Release of Molecules with Photosensitive Nanovesicles and Mechanoluminescent Nanoparticles**Authors and affiliations:**H. Tajarenejad[1], A. Pal[2], M. Gil Malinao[3], A. DeAnda[2], K. Sharmah Gautam[4] X. Ge[1], S. Achilefu[4], G. Hong[3], Z. Qin[1,2,4]*1Department of Mechanical Engineering, University of Texas at Dallas, Richardson, TX, USA[2] Department of Bioengineering, University of Texas at Dallas, Richardson, TX, USA[3]Department of Materials Science and Engineering, Stanford University, Stanford, CA, USA[4] Department of Biomedical Engineering, University of Texas Southwestern Medical Center, Dallas, TX, USA***Abstract:**
Noninvasive, localized, and deep brain delivery of molecules holds transformative potential for neuromodulation and targeted drug delivery. We have previously developed light-responsive liposomes, termed azosomes, to enable precise molecule release via azobenzene-modified lipids *(Xiong et al., Nano Research, 2023).* One limitation of light activation is the limited tissue penetration of external light sources. To overcome this, we propose a novel strategy that leverages mechanoluminescent nanoparticles (MLNPs), which can store light energy and emit it upon focused ultrasound excitation *(Jiang, S., Wu, X., Yang, F. et al. Nat Protoc 2023)*. We hypothesize that ultrasound-triggered emission from MLNPs can activate azosomes, enabling localized release of encapsulated molecules deep within brain tissue. To test this, we conducted in vitro experiments using dye-loaded azosomes and co-localized MLNPs, stimulated by focused ultrasound pulses at 0.2 to 0.8 MPa for 20 to 100 seconds (1 Hz). Release dynamics were monitored in real time using fiber photometry to record fluorescence intensity before, during, and after stimulation. In addition, we used azosomes encapsulating deschloroclozapine (DCZ), a

chemogenetic ligand, to activate fluorescent responses in hM3Dq-expressing cells transduced with lentivirus. The results show that DCZ release from azosomes, triggered by emission from MLNPs under focused ultrasound pulses, successfully activated the cells. These findings demonstrate a promising approach for ultrasound-gated, light-mediated molecular delivery to deep brain regions and lay the groundwork for future noninvasive neuromodulation and therapeutic interventions.

Disclosures: **H. Tajarenejad:** A. Employment/Salary (full or part-time); University of Texas at Dallas. **A. Pal:** None. **M. Malinao:** None. **A. DeAnda:** None. **K. Sharmah Gautam:** None. **X. Ge:** None. **S. Achilefu:** None. **G. Hong:** None. **Z. Qin:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.11/LBP064

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

Support: NIH AI093504

Title: Delivery of a Diphtheria Based Reporter Construct to Cortical Neurons

Authors: T. G. WENTZ[1], *J. A. CLEARY[1], P. M. MCNUTT[2];
[1]Wake Forest Institute for Regenerative Medicine, Winston-Salem, NC; [2]Wake Forest Inst. for Reg. Med., Wake Forest School of Medicine, Winston-Salem, NC

Abstract: Delivery of protein therapeutics to the neuronal cytosol requires the ability to selectively target and enter neurons. Bacterial AB-type biological toxins have evolved two functional units to effect intracellular delivery: a domain for cell binding and endosomal uptake and a domain to facilitate translocation of cargo into the cytosol. Botulinum neurotoxins (BoNTs) selectively bind and enter motor neurons but have limited flexibility in terms of cargo. In contrast, diphtheria toxin (DTX) can translocate diverse protein cargoes into the cytosol but is promiscuous in terms of cell specificity. Here we leverage the neuronal specificity of BoNT and the pliability of DTX to create a recombinant delivery vehicle (BDTX) with the unique ability to selectively deliver therapeutic cargo to neurons. Recombinant BDTX was produced and purified from E. coli and tested for its ability to deliver a fused reporter cargo, comprised of a split-luciferase (HiBit) and conditionally fluorescent (HaloTag) tags, to the cytosol of primary rodent neurons. Dissociated rat cortical neurons were transduced to express cytosolic LgBit and, upon maturity, neurons were treated with 1 μM BDTX, the BoNT binding domain alone carrying the reporter construct (HcA), or HiBit alone. Luminescence was monitored over 8 hours post-treatment, and cells were subsequently fixed, stained and imaged for fluorescence. BDTX treated cells were observed to produce significantly greater luminescence during the 8 h post-treatment relative to HcA ($p = 0.0447$) and HiBit alone ($p = 0.002$). In a separate experiment, treating cells prior to and concurrently with 0 or 200 nM BafalomycinA1 (BafA1), a vacuolar V-ATPase

inhibitor, resulted in a significant ($p = 0.0002$) reduction in luminescence from BafA1 treated cells receiving 2 μM BDTX, a modest reduction in luminescence from BafA1 treated cells receiving HcA ($p = 0.0450$), and no significant difference ($p = 0.9209$) in cells receiving HiBit alone. Fluorescence microscopy of the fixed cells 8 h post treatment indicated association of BDTX & HcA with the cortical neurons. Collectively, these studies demonstrate neuronal uptake and cytosolic translocation of BDTX and demonstrate the utility of a cell-based platform in reporting complex mechanistic steps essential to cytosolic drug delivery. This platform will be used to test the compatibility of diverse cargos with BDTX, determine the effect of iterative modifications to the BDTX vehicle, and enable the study of additional neuronal delivery vehicles.

Disclosures: T.G. Wentz: None. **J.A. Cleary:** None. **P.M. McNutt:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.12/LBP065

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

Support: Yantao Xing
Yang Yang
Xiang Li
Hongwei Cai
Zhuhao Wu
Zheng Ao
Chunhui Tian
Jack Crystal
Taylor Woodward
Heather Bradshaw
Junhua Xu

Title: An intelligent device for rapid reversal of opioid overdose

Authors: *V. NIU[1], F. GUO[2], K. MACKIE[3];
[1]Indiana University, Bloomington, IN; [2]IU, Bloomington, IN; [3]Psychol & Brain Sci, Indiana University Bloomington Department of Psychological and Brain Sciences, Bloomington, IN

Abstract: Opioids provide highly effective and dependable pain relief, but overdose can induce respiratory failure and lead to death. Naloxone, an opioid antagonist, is the standard treatment for opioid overdose. Its effectiveness, however, relies on timely administration to avoid asphyxiation, which is often difficult to achieve in real-life situations. To address this challenge, we developed an intelligent device capable of rapidly detecting opioid overdose and automatically administering naloxone. This device involves a patch with an acoustic delivery

patch for active and on-demand transdermal delivery of naloxone. When tested in a mouse model of opioid overdose, the device demonstrated successful treatment of fentanyl overdose, with a naloxone delivery rate of ~0.55 mg/min. Compared to conventional methods, this treatment method exhibited reduced detection time, as well as reduced duration and severity of overdose episodes when compared with conventional methods. Additionally, we collected ~780 respiratory datasets from 78 mice, which was then used as data to train an AI model in classifying respiratory depression. Using AI-guided respiratory sensing, we were able to adapt the device to operate for closed-loop treatment. This allows for the device to be used for real-time detection and intervention of opioid overdose. Overall, we believe this technology offers a promising route towards personalized healthcare and digital therapy against acute disease.

Disclosures: V. Niu: None. **F. Guo:** None. **K. Mackie:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.13/LBP066

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

Title: First-in-Human Transplantation of Hypoimmunogenic iPSC-derived RPE for Age-related Macular Degeneration

Authors: *F. XU[1], Q. WANG[1], S. YUAN[2], J. WANG[1], G. CHEN[3];
[1]HELP Therapeutics Co., Ltd, Nanjing, China; [2]Nanjing Medical University, Nanjing, China; [3]Zhuhai UM Science & Technology Research Institute, University of Macau, Macau, Macao

Abstract: First-in-Human Transplantation of Hypoimmunogenic iPSC-Derived RPE for Age-related Macular Degeneration

Qian Wang[1,2], Faxiang Xu[2], Songtao Yuan[3], Jianxian Wang[2], Guokai chen[1]
[1]Faculty of Health Science, University of Macau, Macao;[2]HELP Therapeutics Co., Ltd., Nanjing, China; [3]Nanjing Medical University, Nanjing, China

AbstractBackground: Age-related macular degeneration (AMD) causes central vision loss through primary dysfunction or loss of retinal pigment epithelium (RPE) and secondary photoreceptor degeneration. RPE replacement is promising but constrained by limited cell sources and immune rejection. We engineered hypoimmunogenic human induced pluripotent stem cells (iPSCs) via targeted gene editing and differentiated them into hypoimmunogenic RPE to mitigate alloimmune responses.**Methods:** We established GMP-compatible manufacturing for hypoimmunogenic iPSCs generated by gene editing, followed by lineage-specific differentiation to RPE. In-process analytics included qPCR during differentiation. We comprehensively benchmarked three cell types—conventional iPSC-derived RPE (RPE), hypoimmunogenic RPE, and fetal RPE—assessing purity, immunofluorescence marker expression, phagocytosis, and immunogenicity. Single-cell RNA sequencing profiled RPE and fetal RPE. An initial clinical application involved subretinal transplantation of hypoimmunogenic iPSC-derived RPE in one

AMD patient with serial assessments at baseline and 4, 11, 18, 34, and 62 days postoperatively.**Results:** The manufacturing process yielded hypoimmunogenic iPSCs and RPE meeting predefined quality attributes, with typical morphology and RPE marker expression. Comparative analyses across RPE, hypoimmunogenic RPE, and fetal RPE demonstrated high purity, preserved phagocytic function, and reduced immunogenicity in gene-edited cells. Single-cell transcriptomics indicated convergence of iPSC-RPE toward fetal RPE signatures. The clinical procedure was completed with predefined longitudinal safety and ophthalmic evaluations through 62 days.**Conclusions:** We present an integrated platform to produce gene-edited, hypoimmunogenic iPSC-derived RPE and report initial clinical experience from a single-patient transplantation. These data support further evaluation of immune-evasive allogeneic RPE replacement as a therapeutic strategy for AMD.
J Pain ReliefISSN: 2167-0846 JPAR an open access journaFibromyalgia 2016June 15-16, 2016Volume 5, Issue 3(Suppl)Page 40

Disclosures: F. Xu: A. Employment/Salary (full or part-time); Faxiang Xu is a full-time employee of HELP Therapeutics. **Q. Wang:** A. Employment/Salary (full or part-time); Qian Wang is a full-time employee of HELP Therapeutics. **S. Yuan:** 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.; Songtao Yuan is the PI of this clinical study. **J. Wang:** A. Employment/Salary (full or part-time); Jiaxian Wang is a full-time employee of HELP Therapeutics.. **G. Chen:** None.

Late-Breaking Poster

LBP021: J.05. Biomarker, Drug Discovery, and Experimental Therapeutics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP021.14/LBP067

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

Title: Identification and characterization of microglial immunomodulatory compounds by high-throughput proteomics: insights from quantification of 1000 proteins in a >6,500 sample screen

Authors: *A. ROSENBLOOM[1], K. EDWARDSON[2], N. ROBICHAUD[3], N. RASHIDI[3], M. DAGHER[3];
[1]Nomic Bio, Woodinville, WA; [2]Nomic Bio, Toronto, ON, Canada; [3]Nomic Bio, Montreal, QC, Canada

Abstract: Microglia are critical for maintaining neural homeostasis. However, under pathological conditions, they can adopt a pro-inflammatory M1 phenotype characterized by the release of IL-12, IL-1β, TNF-α, and IL-6. Chronically, the M1 state contributes to neurodegenerative diseases including Alzheimer's, Parkinson's, and multiple sclerosis (MS). Identifying potential therapies requires capturing the breath of inflammatory proteins produced by microglia, and signals of potential toxicities to minimize adverse events (AEs).

The high cost of capturing these diverse signals at scale limits typical drug discovery efforts to simple low-plex readouts. To address this gap, we previously described the Nomic platform, a proteomics tool capable of quantifying >1000 proteins simultaneously. Here, we leverage the Nomic's Omni 1000 to screen 510 bioactive small molecules in microglia stimulated with LPS to mimic a pro-inflammatory state, generating >6,500 samples and >6.5 million data points.
LPS led to expected increased expression of TNF-alpha, IL-1β, and IL-6, as well as ISG15 and IL-12 p40, indicators of chronic inflammation associated with neurodegenerative diseases. Approximately 1/3 of the compounds screened blocked inflammation, of which ¼ presented clear signs of toxicity, characterized by leaking of intracellular content into the supernatant. To further assess potential toxicities, we treated cardiomyocytes and hepatocytes with these compounds, identifying expected and novel drugs with promising properties. For example, Berberine (BBR) is being developed to revert M1 microglia to M2 by blocking NF-κB signaling. We observed significantly reduced IL-12 p40, IL-10, and CXCL6 upon addition of BBR, with minimal signs of toxicities. Methylprednisolone (MP), a synthetic glucocorticoid, is used for inflammatory flares in MS. Here, MP significantly reduced TNF-α, IL-6, IL-1β, and IL-12 p40 in LPS-treated microglia. However, in hepatocytes, MP led to increased SAA, CXCL11, and CXCL9, consistent with clinical reports of hepatic AEs with high MP exposure.
Our results demonstrate the value of high-throughput proteomics to simultaneously identify immunomodulatory compounds and characterize their efficacy and safety profile.

Disclosures: A. Rosenbloom: A. Employment/Salary (full or part-time); Nomic Bio. **K. Edwardson:** A. Employment/Salary (full or part-time); Nomic Bio. **N. Robichaud:** A. Employment/Salary (full or part-time); Nomic Bio. **N. Rashidi:** A. Employment/Salary (full or part-time); Nomic Bio. **M. Dagher:** A. Employment/Salary (full or part-time); Nomic Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Nomic Bio.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.01/LBP068

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

Title: Neuroimmune Crosstalk in Systemic Inflammation: Insights from a Vascularized Human Brain-Lung Multi-Organ-On-Chip Model

Authors: S. GAIKWAD, J. ROSANO, *G. FEWELL;
SynVivo, Inc., Huntsville, AL

Abstract: Severe respiratory infections, including COVID-19, trigger systemic inflammation that propagates to the central nervous system (CNS), driving encephalopathy, stroke, and cognitive impairment. Mechanistic understanding of neuroimmune crosstalk under physiologic flow remains limited. Microphysiological systems (MPS) are now being used as predictive *in*

vitro platforms for studying neuro-immune interactions during acute systemic inflammation. In this study, we developed a unique brain-lung multiorgan organ-on-chip (OOC) model incorporating whole, human blood, enabling real-time assessment of leukocyte endothelial interactions following inflammatory insult. The vascularized brain-lung multi-OOC model was made using SynVivo's perfused microvascular platform. Human lung (dual-culture) and blood-brain barrier (BBB; tri-culture) tissues were established in interconnected vascular compartments. The tissues were then perfused with whole human blood containing peripheral blood mononuclear cells (PBMCs) to mimic *in vivo* conditions. Systemic inflammation was induced via a cytokine cocktail (TNF-α, IL-1β, IFN-γ) applied to the lung compartment. Once inflammation was induced, PBMC adhesion/migration were quantified, and effluents were analyzed by multiplex cytokine profiling. Both lung and BBB microvasculature formed intact lumens with low baseline permeability under physiological flow. Cytokine challenge of the lung triggered a spatiotemporal cascade of inflammatory mediators (IL-6, IL-8, CCL2, IL-10) that propagated to the brain. Coordinated cytokine surges, particularly at 3h, confirmed systemic signaling. PBMC adhesion was significantly elevated across inflamed lung and brain endothelium, with heightened trafficking in brain tissue exposed to lung-conditioned media. This integrated brain-lung OOC recapitulates systemic inflammatory cascades and immune-endothelial interactions, providing a novel human-relevant model of neuroimmune crosstalk. The platform enables mechanistic insight into leukocyte-mediated endothelial dysfunction during severe infections and serves as a translational tool for evaluating therapeutic strategies to mitigate CNS sequelae and off-target neuroimmune effects of candidate drugs.

Disclosures: S. Gaikwad: A. Employment/Salary (full or part-time); SynVivo Inc. **J. Rosano:** A. Employment/Salary (full or part-time); SynVivo Inc. **G. Fewell:** A. Employment/Salary (full or part-time); SynVivo Inc..

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.02/LBP069

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

Support: NIH grant R01MH062349
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Neuronex NSF 2015276

Title: Large Sag Conductance Masked by Low Input Resistance in Parvalbumin Interneurons: A Patch-seq analysis

Authors: *Y. JIN, J. H. MENG, A. LAI, X.-J. WANG;
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Abstract: Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels generate the H current, which influences resting potential and integrative properties. A common way to quantify HCN channel function is by measuring sag amplitude or sag ratio during hyperpolarizing current steps. In cortical interneurons, parvalbumin (PV) interneurons (INs) display a smaller sag amplitude than somatostatin (SST) INs. However, this sag amplitude difference is not reflected by the expression level of HCN encoding genes in a V1 patch-seq dataset collected by the Allen Institute. Surprisingly, HCN channel encoding genes are more highly expressed in PV INs, a result which seemingly contradicts the observed difference in the sag amplitude. We hypothesized that differences in leak conductance, which are higher in PV than in SST cells, could explain this mismatch between sag amplitude and HCN expression. Increased leak conductance can reduce the relative contribution of H current to hyperpolarizing responses, thereby masking sag despite higher HCN expression. To test this hypothesis, we constructed a minimal conductance-based model including only leak and HCN currents, which confirmed that sag amplitude reflects the interplay between leak and HCN conductance rather than HCN alone. To disentangle this relationship, we developed a multi-feature optimization method that estimates sag conductance from voltage traces and validated its robustness with pseudo-data generated from ground-truth parameters. Applying this method, we confirmed that the recovered sag conductance correlates strongly with both HCN1 and HCN2 expression in the V1 Patch-seq dataset, consistent with their established role as molecular determinants of H current. In addition, in about 80% of cells, including a K_{ir} current was essential for achieving accurate fits, consistent with the expression of corresponding KCNJ genes. We also identified upstream regulators, such as DGKZ, that may shift the half-activation voltage of HCN gating variable. In summary, our findings reconcile discrepancies between sag-based physiology and HCN transcriptomic profiles, underscoring the limitations of using sag amplitude as a direct proxy for HCN conductance. Instead, our results suggest that the sag amplitude reflects the interaction of HCN, leak and K_{ir} currents. We further predict cell type differences in K_{ir} conductance and upstream regulatory pathways, providing testable hypotheses for future electrophysiological experiments.

Disclosures: Y. Jin: None. **J.H. Meng:** None. **A. Lai:** None. **X. Wang:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.03/LBP070

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

Title: Prioritizing and validating regulators of neuronal health and axon degeneration: a machine learning guided approach

Authors: *J. REED[1,2], A. WESTERHAUS[1], R. IHRY[1];
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Abstract: Neuronal health is controlled by complex genetic regulators, many of which remain poorly characterized in the context of neurodegenerative diseases. SARM1 is a key driver of axon degeneration through its NAD+ depletion activity, which can be activated by metabolic toxins such as Vacor. To identify regulators of SARM1 dependent axon degeneration, we performed a genome wide CRISPR-screen on the Neuron Factory. NGN2 neurons were treated with Vacor to induce axon degeneration via SARM1 activation, then screened for genes that suppress degeneration and promote neurite outgrowth and survival. From the hits from this screen, we prioritized cross-disease regenerative targets for experimental follow-up using machine learning and quantitative phenotyping. This approach prioritized top candidates which showed strong disease relevance and performance across various neurodegenerative disorders. By integrating CRISPR screen data with pathway analysis, disease linkage, and machine learning-driven prioritization, we provide a scalable framework for discovering targets to block axon loss in neurodegenerative diseases.

Disclosures: J. Reed: Other; Novartis Summer of Science Intern- Undergraduate Research. **A. Westerhaus:** A. Employment/Salary (full or part-time); Novartis full-time. **R. Ihry:** A. Employment/Salary (full or part-time); Novartis full-time.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.04/LBP071

Topic: G.03. Stress and the Brain

Title: AI-Driven Innovation in Mental Health: Research Initiatives of The Global Center for AI in Mental Health

Authors: T. KHASHAN[1], D. HAZAPIS[2], J. BOSWELL[2], A. JOSHI[1], A. NITZA[2], *S. DURA-BERNAL[1];
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Abstract: The Global Center for AI in Mental Health (GCAIMH) is pioneering a suite of interdisciplinary projects that leverage generative artificial intelligence (GenAI), machine learning (ML) and multiscale mechanistic modeling of the brain to address gaps in mental health care and treatment of brain disorders, especially in underrepresented populations.
First, GCAIMH is developing a novel AI chatbot for Psychological First Aid (PFA), in collaboration with IBM, designed to be deployed in disaster zones to train and support humanitarian personnel and assist disaster survivors. Compared to existing generic tools, this disaster-specific AI LLM is trained specifically on data relevant to real-world disaster response scenarios and is built on evidence-informed intervention models such as PFA and other principles of trauma-informed care. Moreover, it incorporates both text and real-time speech, allows offline functionality, and is culturally and linguistically adaptive.

Second, GCAIMH collaborates with Google to develop Ther-Assist, a generative AI multimodal tool to help psychotherapists deliver personalized, evidence-based treatments for anxiety, depression, and related disorders. Ther-Assist harnesses generative AI to provide therapists with real-time insights into the patient's emotional and cognitive status and recommend treatment pathways aligned with evidence-based therapies during and in-between sessions.
Lastly, GCAIMH is developing Brain Digital Twins for precision mental health care. A Brain Digital Twin is a virtual replica of an individual's brain that integrates multimodal data, such as from wearables, clinical records, and genetics, and leverages AI and advanced modeling to simulate scenarios, predict outcomes, and guide personalized treatments. We propose leveraging AI-driven multiscale biophysical modeling to develop Brain Digital Twins that revolutionize mental healthcare and treatment of brain disorders. To this end, we are developing a suite of detailed models of brain neuronal circuits—linking genetic and molecular changes to measurable neurophysiological biomarkers such as EEG—as the building blocks of Brain Digital Twins. These models are trained and informed by extensive genetic, neurophysiological, and clinical datasets, can generate realistic brain recordings, and accurately simulate the effect of pharmacological and neurostimulation interventions. Combining mechanistic simulations with AI will enable prediction of disease risk, progression, and treatment response for conditions such as schizophrenia, Alzheimer's, depression, epilepsy and amyotrophic lateral sclerosis (ALS).

Disclosures: T. Khashan: None. **D. Hazapis:** None. **J. Boswell:** None. **A. Joshi:** None. **A. Nitza:** None. **S. Dura-Bernal:** None.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP022.05/LBP072

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

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Georgia CTSA KL2 (KL2TR002381)
Georgia CTSA (UL1TR002378)

Title: A whole-brain connectme-constrained model of subcallosal cingulate deep brain stimulation evoked potentials

Authors: *P. SARIKHANI[1], R. J. BUTERA[1], H. S. MAYBERG[2], C. J. ROZELL[1], A. WATERS[2], S. ALAGAPAN[1];
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Abstract: Deep brain stimulation (DBS) of subcallosal cingulate cortex (SCC) is an emerging intervention for treatment resistant depression (TRD). The electrophysiological effects of SCC DBS are non-linear across timescales (Alagapan et al., *Nature*, 2023, Cha et al., *Molecular Psychiatry*, 2024) suggesting an adaptive process at the circuit level. The mechanisms through which SCC DBS exerts its effects are now emerging, but not yet fully understood. Given the limitations in current experimental techniques to dissect human neural circuits in vivo, electrophysiological readouts, particularly scalp electroencephalography (EEG), offer a non-invasive scalable alternative tool to provide insights on underlying mechanisms. In this study, we present a computational framework that integrates biophysical modeling and machine learning (ML) to bridge anatomical and cellular mechanisms with electrophysiological observations of DBS effects measured with stimulation-induced cortical evoked potentials (EPs). Our methodology involves constructing a whole-brain, connectome-constrained biophysical model using structural connectivity data from the Human Connectome Project. Neural dynamics in each region are simulated using the extended Jansen-Rit neural mass model and a forward head model is used to simulate 256-channel stimulation-induced EPs. Implementation in PyTorch allows efficient parameter estimation through automatic differentiation by fitting the model to experimental stimulation-induced EPs. We preprocessed the single trial EP data to reject stimulation artifact using independent component analysis. We evaluated model performance using averaged stimulation-induced EP data from TRD patients undergoing SCC DBS. The trained model achieved a correlation coefficient of 0.84±0.01 between simulated and experimental functional connectivity matrices, and a cosine similarity of 0.85±0.03 between simulated and experimental stimulation-induced EP across five runs. The model also generalized to unseen data: stimulation amplitude sweeps produced experimentally consistent increases in evoked potential amplitude, waveform width, and peak latency. In conclusion, our biophysically grounded, connectome-constrained modeling framework enables quantification of DBS-induced electrophysiological changes in EPs and demonstrates a robust fit and generalizability to experimental EP data. By enabling systematic perturbation and inference of neural components, this approach further supports hypothesis-driven exploration of SCC DBS mechanisms.

Disclosures: P. Sarikhani: None. **R.J. Butera:** None. **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. **C.J. Rozell:** F. Consulting Fees (e.g., advisory boards); Motif Neurotech, Inc.. **A. Waters:** None. **S. Alagapan:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.06/LBP073

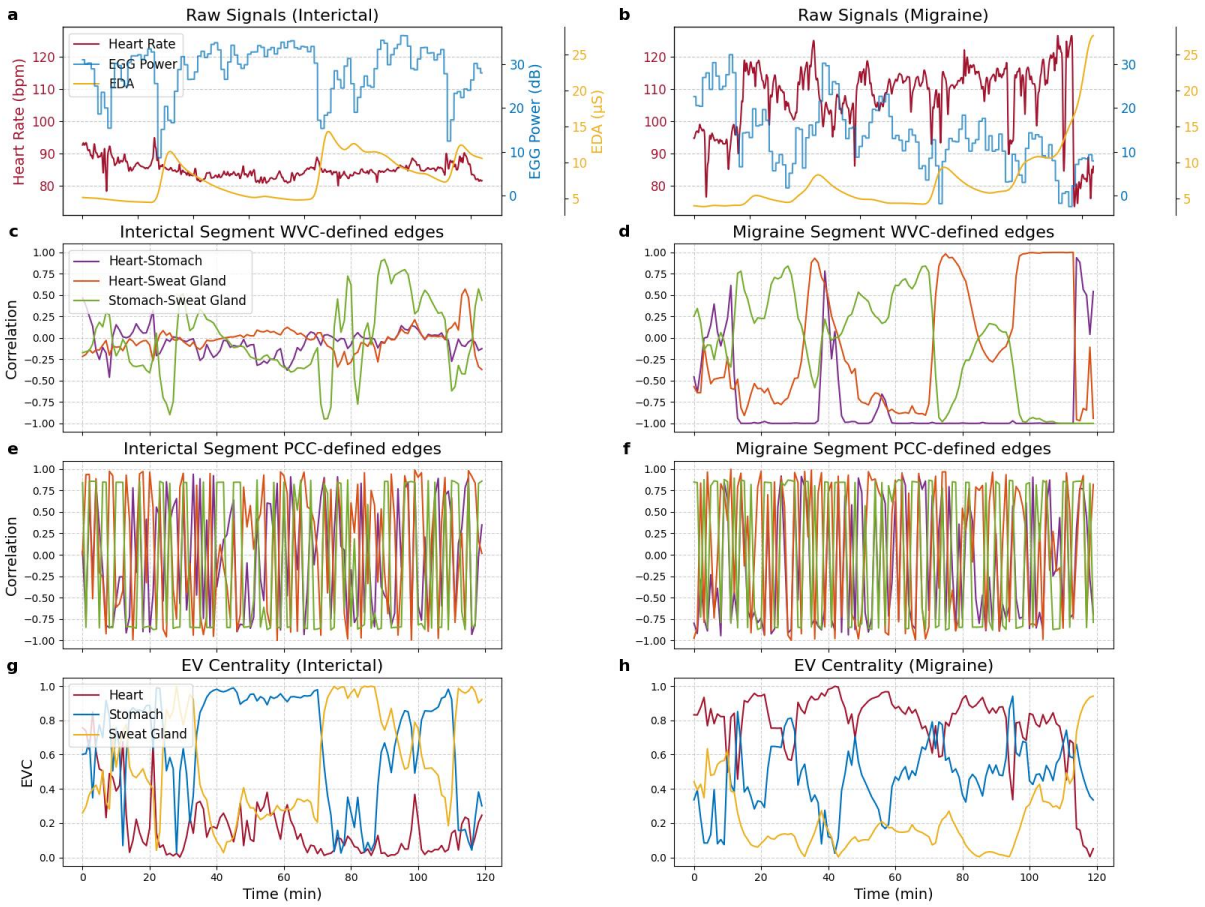
Topic: J.06. Computation, Modeling, and Simulation

Support: Schmidt Science Fellows Postdoctoral Fellowship
L'Oreal USA For Women in Science Fellowship

Title: Modeling dynamic multi-organ autonomic functional connectivity in migraineurs during migraine and interictal periods

Authors: J. MOHAN[1], S. MACKEY[3], *S. SUBRAMANIAN[2,4];
[1]Electrical Engin. and Computer Sci., [2]Computat. Precision Hlth., Univ. of California, Berkeley, Berkeley, CA; [3]Div. of Pain Med., Stanford Univ., Redwood City, CA; [4]Univ. of California, San Francisco, San Francisco, CA

Abstract: Purpose: We aim to investigate the dynamic network structure of the autonomic nervous system (ANS) by modeling time-varying interactions between multiple organs using heterogeneous physiological signals. Specifically, we aim to capture nuanced differences in dynamics over time for a single person, in this case comparing migraine and interictal periods for one chronic migraineur. Methods: Using 72-hour multivariate time series data from the heart (instantaneous mean heart rate computed from electrocardiogram or ECG), sweat glands (tonic electrodermal activity or EDA), and stomach (normalized high-resolution electrogastrogram or HR-EGG power around 0.05 Hz) collected at home from one 55-year-old female chronic migraineur, we constructed functional connectivity networks for 1-minute windows where nodes represent each organ (heart, sweat gland, stomach) and edges describe their connections. To quantify weighted, undirected edges between such heterogeneous nodes with varying generative mechanisms and periodicities, we developed a windowed variance-correlation (WVC) metric and compared it to Pearson correlation (PCC). The eigenvector centralities (EVC) of the nodes were computed over time to track node importance. We compared 2-hour interictal and migraine segments, time-matched across different days. Results: Our defined ANS network clearly exhibits different dynamics between interictal and migraine states for this patient. The network structure is dynamic interictally, with all nodes increasing and decreasing in EVC (Fig. 1g). By contrast, during the migraine episode, the network becomes rigid with the heart being most central consistently (Fig. 1h). The WVC-defined edges are more stable than PCC (Fig. 1c-f), which fails to meaningfully capture dynamics due to volatility. Discussion: This exploratory work proposes a new multi-organ network model of the ANS that captures personalized dynamics over time. Traditional methods like PCC fail because they do not adapt to heterogeneous nodes. Our framework can personalize ANS-related diagnoses and treatments.



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Location: SDCC Hall B

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Program #/Poster #: LBP022.07/LBP074

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

Support: P50MH109429

Title: The next-generation Human Neocortical Neurosolver: biorealistic cell models reveal the importance of dendritic spiking dynamics in interpreting EEG/MEG

Authors: *K. DUECKER[1], S. PUGLIESE[2], N. TOLLEY[1], A. E. SOPLATA[1], D. DANIELS[1], T. JONES[3], S. R. JONES[4];
[1]Brown University, Providence, RI; [2]University of Washington, Seattle, WA; [3]University of Illinois at Urbana-Champaign, Wilmette, IL; [4]Department of Neuroscience, Brown University, Providence, RI

Abstract: Electro- and Magnetoencephalography (E/MEG) are fundamental tools to study fast-timescale human brain activity in health and disease. However, their utility in understanding neural function is limited by a lack of interpretability at the cell and circuit level. The Human Neocortical Neurosolver (HNN) is a user-friendly computational neural modeling software tool, designed to develop and test hypotheses on the neural generators of E-/MEG signals such as brain oscillations and event-related potentials (ERPs). The foundation of HNN is a laminated neocortical column model, consisting of excitatory pyramidal neurons and inhibitory interneurons in supragranular and infragranular layers, with synaptic input from exogenous thalamic and cortical sources. While the cellular elements were originally informed by somatic dynamics in rodents, recent advances and open-source data on the physiology of human cells provide unprecedented details to retune the model. Here, we present an updated HNN network, tuned to in vitro data from human pyramidal neurons and inhibitory interneurons. The retuning closely matches known human cell physiology, including dendritic dynamics associated with parallel processing in layer 5 pyramidal neurons and corresponding extracellular fields. Simulations in the updated model reveal that dendritic calcium activity in the pyramidal neurons produces large currents clearly detectable in the extracellular fields that are consistent with prior reports in rodents. Importantly, the dendritic calcium spikes generate strong inward currents toward the soma that have dominating effects on the scalp potentials. This finding has implications for their role in generating correlates of perception in ERPs. Our modeling work further suggests that calcium events may contribute to the waveform shapes of oscillatory dynamics, for instance, short events in the beta-band.
Overall, the updated HNN model provides a tool validated with human cell physiology, providing unique insight into the neural mechanisms underlying ERPs and oscillations. Detailed examination of cellular dynamics during functionally meaningful signals can help uncover their causal role in perception and cognition, and potential disruption in neuropathology. The tuned model and corresponding tutorials will be openly shared with the HNN software to facilitate future research on the neural generators of E/MEG signals.

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Late-Breaking Poster

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Program #/Poster #: LBP022.08/LBP075

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

Support: NIH F32DC018225

Title: Towards embodied brain emulations: A Drosophila connectome-constrained brain model accurately predicts neural activity and controls behavior in a virtual environment

Authors: S. HARRIS[1,2], A. SINHA[2], ***P. SHIU**[2];
[1]Ophthalmology, UCSF, San Francisco, CA; [2]Eon Systems, San Francisco, CA

Abstract: Creating accurate computational models of brain activity is a major goal of neuroscience. Embodying virtual brains in virtual bodies and environments is essential for full understanding of how the brain generates behavior. To this end, we have combined existing brain models (Shiu et al., 2024; Lappalanein et al., 2024) with existing biophysical body simulations (Wang-Chen et al., 2024) of Drosophila, the animal with the most complete adult brain connectome data to date. These combined brain-body models can accurately recapitulate the behavior of their biological counterparts. We first created a leaky integrate-and-fire model of the Drosophila brain based on the Flywire adult connectome (Shiu et al., 2024, Nature). This model accurately predicts neural activity, for example, identifying a novel aversive taste modality (Ir94e), and accurately predicting over 90% of the 164 empirical predictions tested.
We next embedded this brain model within the "NeuroMechFly" biophysical fly model (Wang-Chen et al., 2024). We used information from the underlying MuJoCo physics simulator to activate specific sensory inputs. For example, visual input into the eyes activated the visual system, as in Wang-Chen et al., 2024 and Vaxenburg et al., 2024, while virtual taste information activated gustatory receptor neurons. Other information like olfactory information, virtual temperature information, or physical forces would activate other appropriate sensory neurons. We then used the activity of known descending neurons that control various behaviors, such as aDN1 and aDN2 for antennal grooming (Hampel et al., 2015); the BB, FG and BRK halting neurons (Sapkal et al., 2024); and DNa02 and DNg13 for turning (Rayshubskiy et al., 2025), etc. to control behavior of the virtual body. Motion capture data has been used to create models of various behaviors (Vaxenburg et al., 2024; Wang-Chen et al., 2024). One challenge is relating the exact activity levels of these descending neurons to the probability of generating the behaviors they control, as these often are unknown. We used a combination of handtuning and reinforcement learning to arrive at DN activity levels that generated behaviors at reasonable probabilities.
We find that this combined brain-body-environment framework can generate realistic behaviors, often "straight out of the box." For example, appetitive taste information causes appropriate turning towards food cues and stopping, while grooming signals cause grooming, which was hand-tuned, but also correctly promotes stopping as well, which was not. Further refinement of these models will allow for accurate embodied, whole brain emulations of whole adult animals.

Disclosures: S. Harris: A. Employment/Salary (full or part-time); Eon Systems. F. Consulting Fees (e.g., advisory boards); Eon Systems. **A. Sinha:** A. Employment/Salary (full or part-time); Eon Systems. **P. Shiu:** A. Employment/Salary (full or part-time); Eon Systems. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Eon Systems.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.09/LBP076

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

Title: An enhanced transformer architecture with dynamic memory, attention and self-programmable control for brain computer interfaces

Authors: *M. SARAFYAZD, B. HAN;
BrainCo Inc, Somerville, MA

Abstract: We present a novel transformer architecture that extends the transformer paradigm with dynamic memory, dynamic attention mechanisms, and self-programmable control systems for applications with large neural data. Unlike conventional transformers that process sequences with fixed computation patterns, our model introduces: (1) an integrated dynamic memory system, (2) adaptive computational control that dynamically modulates information flow between attention, memory, and feed-forward components, and (3) cyclic computation with self-programmable weight modulation. This architecture, inspired by both (1) computational and systems neuroscience principles, and (2) advanced computing architectures, enables more efficient modeling of long-range dependencies and complex temporal dynamics. We demonstrate the model's effectiveness primarily on neural spike sequence data from brain recordings (selected 2000 neurons), showing significant improvements in prediction accuracy compared to conventional transformers. Our enhanced architecture achieves better performance with reduced computational requirements while maintaining state across longer sequences; a critical capability for advanced brain-computer interfaces.

Disclosures: M. Sarafyazd: A. Employment/Salary (full or part-time); BrainCo Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainCo Inc. **B. Han:** A. Employment/Salary (full or part-time); BrainCo Inc. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); BrainCo Inc.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

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Program #/Poster #: LBP022.10/LBP077

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

Support: NIH BRAIN Initiative (R01NS104925: The self-tuning brain: cellular and circuit mechanisms of behavioral resilience)
Simons Collaboration for the Global Brain (542975SPI Simons Foundation)
University of Washington super computing cluster, Hyak

Title: Self-organizing integration

Authors: *D. BELL[1], A. DUFFY[2], A. L. FAIRHALL[2];
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Abstract: Integration—the accumulation of information over time—is a fundamental computation in navigation, decision-making, and memory. The dominant circuit model, the continuous attractor neural network (CANN), explains integration through finely tuned, symmetric connectivity that supports marginally stable states. However, data from systems such as Drosophila central complex suggest that real connectivity is heterogeneous, implying that symmetry may only exist in a coarse-grained sense, if at all. One class of models explains this heterogenous connectivity by evoking supervised learning which can enforce coarse-grained symmetry at the expense of extensive trial and error learning or by employing biologically unrealistic learning rules. Another class employs only local learning rules, but this approach typically fails when circuit connectivity or tutoring inputs become sufficiently heterogeneous. Here, we attempt to bridge this gap by taking a machine learning approach (meta-learning) to identify local learning rules that can organize integration dynamics in heterogeneous networks of excitatory and inhibitory neurons. The learned rule is parameterized as the Taylor expansion of an arbitrary function that depends on synapse size as well as eligibility traces of pre and post synaptic activity and input from other cell types. We discover rules that form bump attractors given only weak spatial priors and integration inputs. In a simpler two-neuron system, we find rules that generate line attractor dynamics. A shared feature across both learned rules is anti-Hebbian spike-timing-dependent plasticity (STDP), in which synapses supporting sequential activity are depressed. This rule flattens the energy landscape of the attractor manifold, creating multiple stable states that support integration. We further test whether learned plasticity rules can compensate for structural heterogeneity by varying the strength of global inhibition across excitatory neurons. In both bump and line attractor models, meta-learned plasticity successfully constructs continuous attractor dynamics despite heterogeneity. Together, our results suggest that unsupervised local plasticity rules, particularly those that include anti-Hebbian STDP, may provide a biologically plausible mechanism for the self-organization and robustness of integration circuits.

Disclosures: D. Bell: None. **A. Duffy:** None. **A.L. Fairhall:** None.

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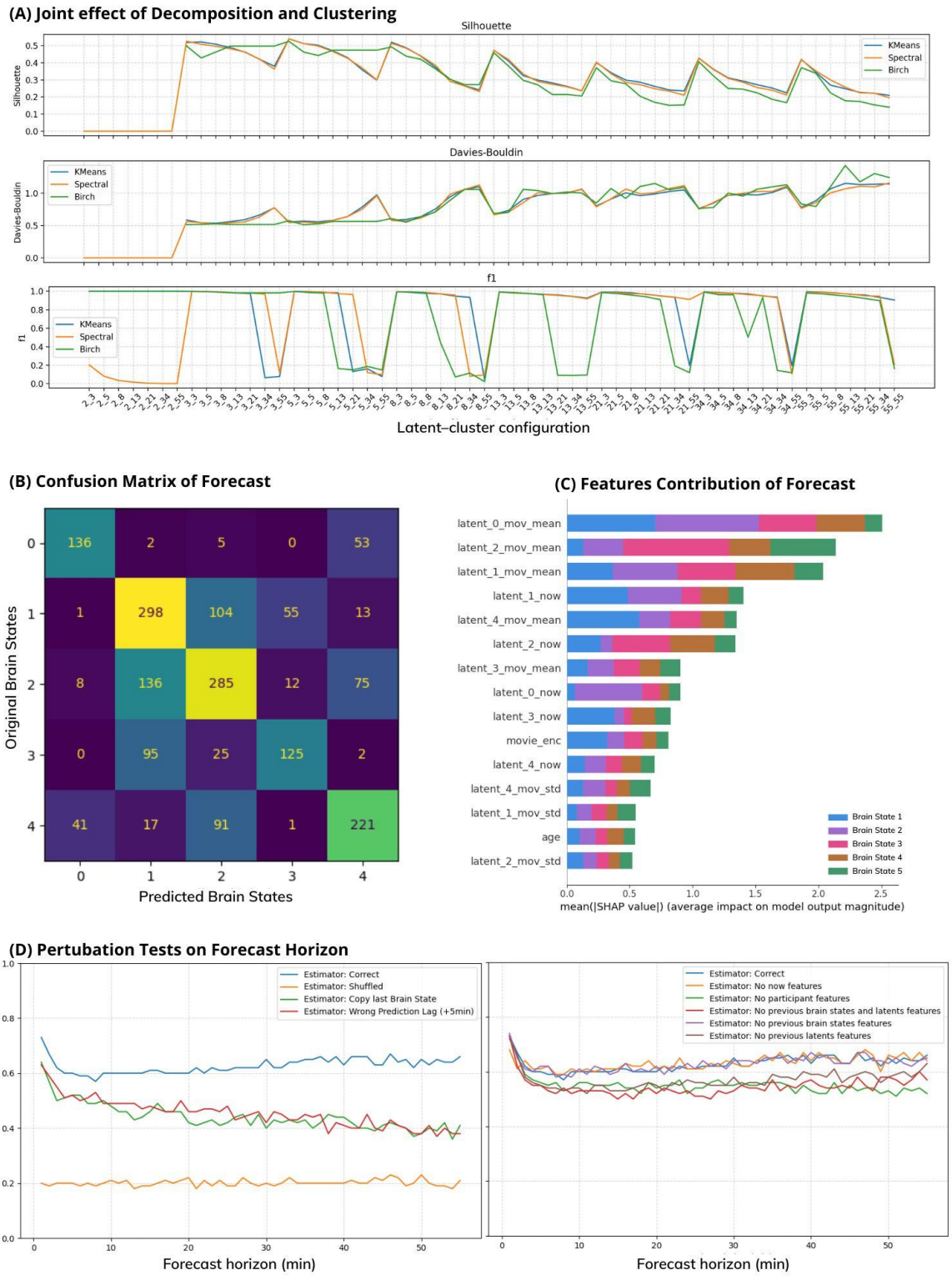
Program #/Poster #: LBP022.11/LBP078

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

Title: Dynamic Functional Connectivity Decomposition - A benchmark for forecasting brain states under naturalistic stimuli

Authors: *T. CORREA MARCAL[1], P.-J. TOUSSAINT[2], A. C. EVANS[3];
[1]McGill, Montreal, QC, Canada; [2]McGill University, Montreal, Montreal, QC, Canada; [3]Dept Neurol, Montreal Neurol Inst, Montreal, QC, Canada

Abstract: Monitoring brain responses to naturalistic stimuli is a powerful way to understand brain circuit dynamics. Movie-watching paradigms offer rich, ecologically valid stimuli that capture complex temporal patterns of neural activity. However, current studies have yet to fully decompose brain signals during movie-watching using agnostic, data-driven approaches. We hypothesize that temporal dependencies on the signal create stable dynamic patterns, with prior Dynamic Functional Connectivity (DFC) of an individual serving as a predictor of their future brain states. We address this by decomposing the DFC and developing a forecast model of future brain states. We analyzed data from the Naturalistic Neuroimaging Database, derived from 86 participants who watched 10 full-length movies (average duration of 117 minutes). DFC was estimated using a sliding window approach, computing connectivity every 5 minutes with overlapping windows. An autoencoder was then applied to achieve DFC decomposition, followed by clustering to identify groups of similar connectivity patterns, referred to as brain states. Finally, to probe the stability of brain state dynamics, we forecasted the next 5 to 50 minutes of brain activity based on previous states, latent components, movie, age, and gender. Our findings show that brain states were best obtained using 3-5 latent dimensions combined with 5-13 clusters, showing complete encoding of latent variables with high separation between brain states and low variation within them. When forecasting future brain states, the model showed a predictive power of 62.7% (±0.03). The moving averages of the first three latent variables of the DFC decomposition emerged as the most important predictive features. These findings highlight that the DFC incorporated into the forecast model, captured both group-level and individual-specific brain dynamics. Our framework provides a new benchmark for modeling brain activity under naturalistic stimuli. Thus, it points the way for future research on temporal dependences and forecasts of brain operations.



Disclosures: T. Correa Marcal: None. **P. Toussaint:** None. **A.C. Evans:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

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Program #/Poster #: LBP022.12/LBP079

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

Title: Linking Mesoscopic and Neuron Level Two-Photon Mouse Imaging to Identify Cortical Area

Authors: *M. ABIJAOUDE;
Washington University in St Louis, st louis, MO

Abstract: The human brain can be divided into functional networks that identify interactive brain regions and provide insight into neuronal communication throughout the brain. This provides a platform to examine how functional connectivity relates to human behavior and how this organization may be altered in neurodegenerative disease. Many tools are used to analyze this relationship in human and in animals. Functional connectivity (FC) analysis has gained prominence in human neuroimaging studies utilizing functional magnetic resonance imaging (fMRI) as a tool in mapping spontaneous brain activity. Large field-of-view two-photon microscopy and genetically encoded calcium indicators can be used to examine FC at both the neuron level and the mesopic level in mouse models. In human FMRI Voxel-by-voxel FC maps can be analyzed to identify large-scale brain regions; these regions can be grouped spatially distributed large-scale networks that subserve human cognition. Accurate identification of cortical areas - functional groupings of voxels- is a primary goal of modern systems neuroscience. These rsFC boundary map- derived parcels provide information about the location and extent of human cortical areas. There are individual-specific parcellation methods. RsFC networks are primarily consistent between individuals. Individual variability in network organization has also been stable within participants across scanning sessions and day. We aim to follow this method to generate mouse specific parcellations. Imaging neurons using TPM the field of view is limited. Thus, to identify where you are imaging you rely on the vasculature and a structural capture at a wider field of view. However, this only tells you where you are in the image and not which cortical area. Parcellation techniques analyze the similarity between the FC maps at neighboring seed regions. Together these tools enable location specific analysis at the neuronal level in mouse models. Using a custom large FOV TPM, and a 4x objective (NA 0.28) we first obtain a structural image of the mouse brain. A smaller ROI is imaged with a 10x objective (NA 0.5). This provides neuron level analysis as expected. From the same microscope we can also map mesoscopic functional connectivity. Using the 4x objective, we smooth the data using a 30-micron gaussian (FWHM). Pixel-to-pixel FC maps and map the spatial derivative in both dimensions, thus finding borders between functional regions and generate parcels. The parcels label a mouse specific atlas. Then linking back to vasculature - we can identify these across mouse imaging sessions and consistently specific region of interest.

Disclosures: M. Abijaoude: None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.13/LBP080

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

Title: Neural Coding in the Kemeny Rank Space

Authors: D. HSU, ***Y. ZHOU**;
Fordham University, New York, NY

Abstract: Rank-based neural representation has been suggested as a method for encoding sensory information. For instance, in vision, this method is known as rank-order coding (ROC), where visual stimuli are represented by the ranking of responses from a population of visual neurons. Previously, a decoding method using a look-up table (LUT) trained on natural images could achieve a recognizable recovery with a signal-to-noise ratio (SNR) of up to 15dB. More recently, evidence indicates that the olfactory system might use a "primacy code" to encode odorant information, which relies on the ranking of responses across glomeruli in the olfactory lobe. This type of representation offers two main advantages. First, It does not require the absolute response amplitude, making it well-suited for biological systems inherently subject to neuronal noise. Second, sorting a large number of items can be easily achieved by the order of the spike arrival time. However, the full representational capability of rank-based representation has not been fully established, particularly regarding whether information is lost by exclusively using the rank of a neuronal population.
The presented work addresses these questions by introducing the Kemeny rank space as a framework for signal representation. We formally investigate the relationship between continuous stimuli and their discrete representation using the ranks of a neuronal population. We formalize the encoding process by using the notion of a scoring system that includes a score function, a derived rank function, and a rank-score function (RSF). We then derive reconstruction algorithms for recovering the input stimuli from full rank function, partial rank function as well as under noisy conditions. We demonstrate that, with ~44,000 neurons - the same number of neurons as in the LUT-based algorithm - natural images can be recovered with an 80dB SNR, almost loss-free. Importantly, this is accomplished without the need for any training. We show that the representation in the Kemeny space can be considered as a simultaneous discretization and quantization scheme, and the SNR increases log-linearly as the number of neurons increases. Furthermore, we demonstrate that the representation is robust to noise. The result we obtained here suggests that under appropriate conditions, rank function of the population response can be used to faithfully represent sensory stimuli in the absence of an exact score function. This opens new avenues for understanding neural processing within the Kemeny rank space representation.

Disclosures: D. Hsu: None. **Y. Zhou:** None.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP022.14/Web Only

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

Support: Stanford HAI Hoffman-Yee Research Grant

Title: Neuro-symbolic decoding of compositional structure in human fMRI

Authors: *J. HSU[1], Y. WANG[2], E. ADELI[1], J. WU[1];
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Abstract: Human cognition is thought to rely on compositional representations that integrate entities and their relations across distributed cortical networks. However, it remains unclear how such structured meanings are reflected in neural activity. We present NEURONA, a neuro-symbolic framework for neural decoding, which tests whether human fMRI signals exhibit predicate-argument structure when viewing complex visual input. We leveraged paired fMRI-stimulus data from two large datasets: BOLD5000, where participants viewed naturalistic images, and CNeuroMod, where participants watched episodes of a television series. Each visual stimulus was parsed with a vision-language model into symbolic expressions, such as "holding(person, baseball-bat)," which capture both predicates (relations) and their arguments (entities), and aligned to fMRI responses parcellated into cortical networks. We then asked whether such predicate-argument structures could be encoded in neural responses across networks. Specifically, we compared hypotheses that varied in how representations were distributed: (i) single-region localization, (ii) multi-region co-activation, and (iii) argument-guided co-activation, where subject and object entities guided which networks were recruited. Across both datasets, argument-guided models substantially outperformed unguided models and prior approaches. On BOLD5000, argument-guided decoding achieved 0.710 decoding accuracy, compared to 0.648 unguided and 0.477 prior best; on CNeuroMod, results were 0.719, 0.616, and 0.464, respectively. These improvements were especially notable for relational expressions involving actions and positions. Qualitative analyses further showed that the same predicate was associated with activity in different networks depending on its object (e.g., holding a kite versus a surfboard), suggesting that object context modulates relational representations, while also showing consistent associations with prefrontal and attentional networks linked to cognitive control. Our findings provide evidence that neuro-symbolic decoding offers a framework for mapping structured meaning to human fMRI, and reveals how information about entities and relations can be distributed across cortical networks.

Disclosures: J. Hsu: None. **Y. Wang:** None. **E. Adeli:** None. **J. Wu:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

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Program #/Poster #: LBP022.15/LBP081

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

Support: 1F32NS138250-01
Center for Theoretical and Computational Neuroscience (CTCN) at WUSTL
Postdoctoral Fellowship

Title: Testing Quasicriticality in The SORN Model

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Abstract: The brain criticality hypothesis posits that there exists a homeostatic set point for optimal function, known as the critical point. This means that there is a set of parameters (e.g., synaptic strength, membrane threshold, refractory period) that are optimal for information processing. Signs of brain criticality are found in all studied species, but their critical signatures (scaling exponents) vary across species, individuals, and states of consciousness (Hengen & Shew, 2025). The quasicriticality hypothesis (qCH) provides a theoretical framework that allows and even predicts the possibility of multiple optimal set points (Williams-Garcia et al., 2014). It predicts that the optimal set points always occur near peaks of maximal susceptibility, where the network is maximally sensitive to input and information processing is optimized. However, the models used to test this hypothesis lack key adaptive mechanisms that can show the transient behavior of a network adapting to a set point as well as excitatory and inhibitory interactions. We used a biologically plausible neural model, Self-Organized Recurrent Network (SORN), which incorporates these features, to bridge the gap between theory and biology. This model has been shown to replicate key learning behaviors (Wang et al., 2017), neural dynamics (Hartmann et al., 2015), and has been shown to reach criticality independently of initial synaptic strengths for certain learning tasks (Del Papa et al., 2017). We explored a wide range of the model's parameter space to see if the network would adapt to different set points as predicted by the qCH. Model simulations revealed network dynamics that were not apparent in the more simplistic models, such as multiple susceptibility peaks correlated with network-wide oscillations, and a smaller peak that correlated with the signatures of criticality observed in biological neural networks. Moreover, testing different types of perturbations did not change the scaling exponents dramatically, but other parameters did, such as target firing rate. The susceptibility peak correlating with other signatures, such as branching ratio (balance of activity propagation) and Pearson correlation (neural activity covariance), confirms the homeostatic set point that gives rise to critical dynamics.

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NIH grant RF1NS100440
NIH grant R21DC021557
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Title: How the brain predicts and corrects our speech: disentangling neurocomputational mechanisms using simulation based inference on individuals with and without cerebellar damage

Authors: *A. L. PONGOS[1], K. S. KIM[2], B. PARRELL[3], J. GAINES[4], V. RAMANARAYANAN[5], K. BRENT[6], S. NAGARAJAN[7], J. F. HOUDE[8];
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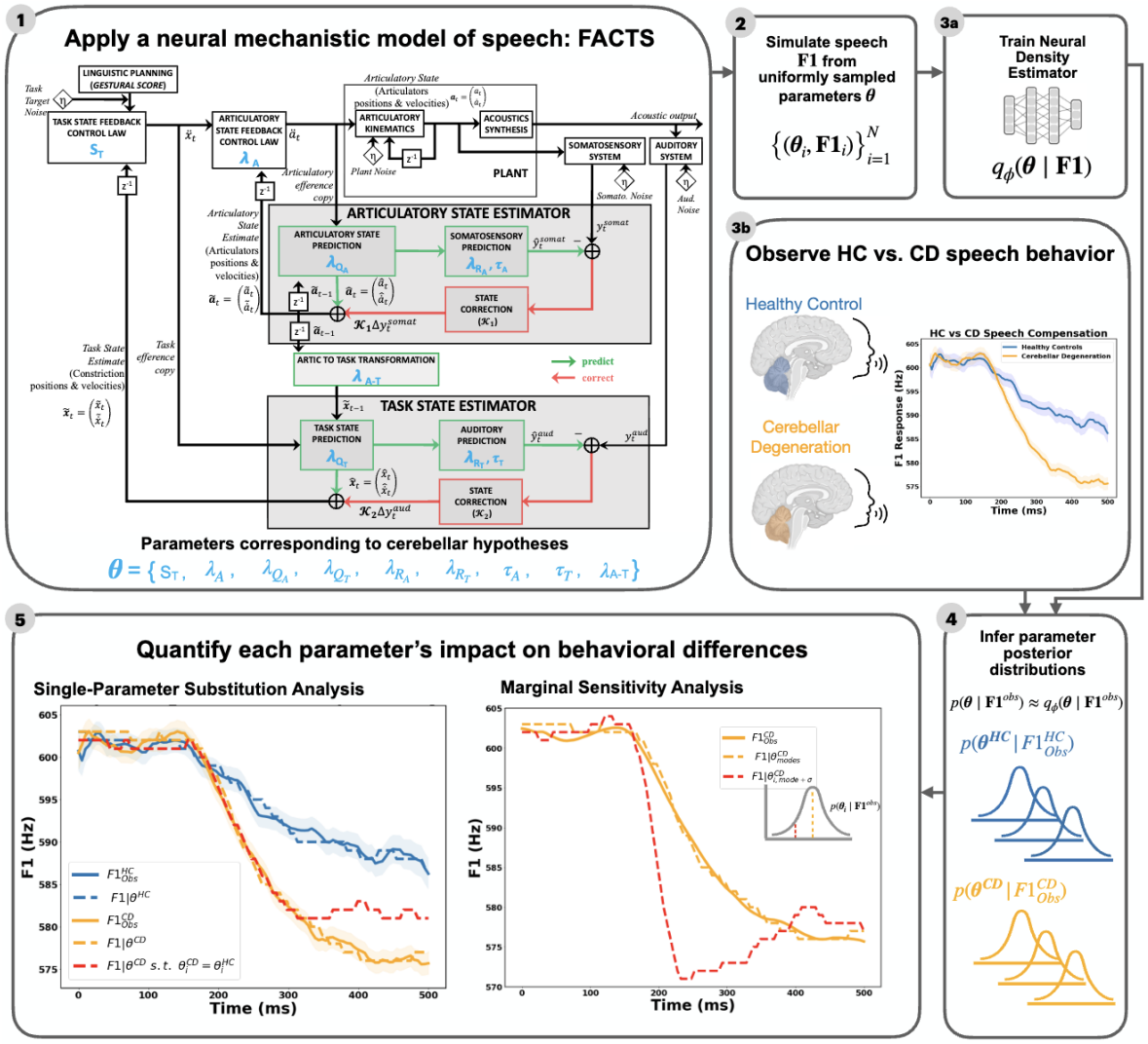
Abstract: Motivation/Problem Statement: When we speak, our brains continuously predict what our voice should sound like and quickly correct mistakes. Although the cerebellum has been implicated in such processes, disentangling predominant cerebellar mechanisms and quantifying the contribution of these mechanisms remains to be investigated.
Methods Approach: We used a computational model of speech and simulation based inference to explore how the cerebellum helps us speak accurately. We focused on people with cerebellar degeneration (CD), a condition that affects motor coordination and speech, to compare to healthy controls (HC). We infer over 9 parameters that map to 5 predominant cerebellar theoretical frameworks (internal modeling, error detection & correction, temporal processing, movement kinematic modeling, and multi-modal interaction). We apply parameter posterior analysis to quantify parameter certainty and effect sizes, single-parameter substitution analysis to quantify the extent that each parameter drives behavior, and marginal sensitivity analysis to quantify how parameter variation affects speech trajectory.
Results: By comparing CD speech to that of healthy individuals, and simulating tens of thousands of possible brain control settings, we show that 3 out of 9 hypothesis-driven control parameters are disrupted, and quantify the extent each mechanism affects behavior. The group with cerebellar damage differed in internal forward modeling, movement kinematics modeling,

and timing.

Conclusion: Our results highlight the power of this research paradigm to help disentangle age-old debates about brain function and behavior.



Disclosures: A.L. Pongos: None. **K.S. Kim:** None. **B. Parrell:** None. **J. Gaines:** None. **V. Ramanarayanan:** None. **K. Brent:** None. **S. Nagarajan:** None. **J.F. Houde:** None.

Late-Breaking Poster

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Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.17/LBP083

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

Title: Cortical reciprocity reflects functional specialization

Authors: M. NORUIŠIS[1], ***M. S. KANG**[2], P. VILIMELIS ACEITUNO[3];
[1]ETH Zurich, Zürich, Switzerland; [2]KAIST, Daejeon, Korea, Republic of; [3]Inst. of Neuroinformatics, ETH Zurich, Zürich, Switzerland

Abstract: Cortical networks exhibit a wide range of nonrandom features that are thought to be relevant for computation. Among these, the reciprocity level, or the presence of bidirectional connections between neurons, differs across the cortex. For example, visual and prefrontal cortices tend to exhibit an overabundance of reciprocal connections, whereas barrel cortex and middle temporal gyrus show reciprocity levels closer to those expected in random networks. Timescale- and memory-based accounts describe how recurrent structure can lengthen integration windows and support maintenance (Marti et al., PRE 2018; Brunel, Nat Neurosci 2016), but they do not explain the nonreciprocal microcircuitry reported in the human temporal cortex (Peng et al., Science 2024). We propose a complementary perspective: reciprocity selects a circuit's frequency passband and thereby shapes signal processing and functional specialization. As reciprocity increases, eigenvalue spectra compress toward the real axis and power concentrates at low frequencies, yielding a narrower low-pass response, while decreasing reciprocity broadens spectral support and preserves higher frequencies (Aceituno et al., iScience 2020).
Guided by this frequency framework, we used reservoir computing to test whether reciprocity predicts computation relevant to each area and inductive bias. Prefrontal-like evidence accumulation improved monotonically with higher reciprocity, matching a low-pass regime that preserves slow components and attenuates fast fluctuations. Visual-like temporal stabilization with framewise jitter benefited from more reciprocal networks, which suppressed high-frequency perturbations and improved classification, consistent with stronger low-pass filtering. In models aligned with the temporal cortex, networks with lower reciprocity performed better on spoken digit recognition, in line with a broader passband that tracks rapid spectral modulations. Performance on a barrel-like texture classification task improved with lower reciprocity, reflecting enhanced transmission of higher-frequency components.
Together, these results suggest that reciprocity is a computational primitive that selects which frequencies are transmitted, rather than the time window over which signals are integrated. This framework links microcircuit motifs to frequency-selective computation, provides testable predictions across areas, and helps bridge theory and biological data. However, current support is based on cross-species studies, so a priority is to test these proposals across different cortical areas within a single species.

Disclosures: M. Noruišis: None. **M.S. Kang:** None. **P. Vilimelis Aceituno:** None.

Late-Breaking Poster

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Program #/Poster #: LBP022.18/LBP084

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

Title: Embedded Intelligence: Inheritance and Resurgence Across AI Large Language Models

Authors: *C. A. DE LA ROSA[1,2,3];
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Abstract: Large Language Models (LLMs) have demonstrated the ability to generate coherent logical structures and novel inferences that were not explicitly programmed. We introduce the conceptual framework of **Embedded Intelligence**, which posits that the accumulated human language collection carries embedded logical contents, rules, and meanings that are inherited during model training and can resurge during inference. This framework offers an explanatory path for understanding how LLMs produce unplanned logical chains and associations.This work represents a **second step** in the development of the Embedded Intelligence framework, expanding upon our original presentation at the *31st Institutional Research Congress* (Universidad El Bosque, Colombia). While the first report of this study introduced the concept, here we extend the analysis further by conducting comparative experiments across multiple platforms (**ChatGPT, Gemini, and Claude**) and by **introducing a formal conceptual organization of the framework**.Experimental tasks included sentence reconstruction from disordered tokens, completion of phrases with missing elements, and integration of incoherent words. Results consistently showed that LLMs reorganize disordered inputs into coherent outputs and attempt to reconcile incoherent tokens within a logical structure. These findings suggest that beyond probabilistic token prediction, LLMs exhibit dynamics consistent with **inheritance of embedded linguistic rules** and **resurgence of latent logic**, enabling novel inferential processes. Together, this expanded analysis advances the understanding of Embedded Intelligence as a candidate explanatory model for emergent reasoning in artificial systems, bridging natural and artificial intelligence.

Disclosures: C.A. De la rosa: A. Employment/Salary (full or part-time); DE LA ROSA RESEARCH.

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West Virginia Foundation Distinguished Doctoral Scholarship Program Award
West Virginia University Center for Foundational Neuroscience Research and Education Award

West Virginia University Stroke and Alzheimer's Disease–Related Dementias (ADRD) T32 Program Award

Title: Embedding mapping of the equations of motion separately from the numerical integration enables forward dynamic simulations in neural networks

Authors: *S. BAHDASARIANTS[1], S. YAKOVENKO[2];
[1]Carnegie Mellon University, Pittsburgh, PA; [2]Human Performance, West Virginia University, Morgantown, WV

Abstract: Physics-aware control of prosthetics improves human-machine interfaces but is challenged by subject-specific morphological parameters. Neural networks, such as recurrent neural networks (RNNs), offer an opportunity to capture the transformation. Unlike the inverse simulations of limb dynamics, which compute joint torques from joint kinematics, the forward dynamics poses a problem with accuracy in the presence of mechanical perturbations and numerical noise. To solve this problem, we separated the trained models into a network representing the dynamic reference frames with the output processed by the conventional numerical integrator. We implemented this model using a shallow RNN (gated recurrent unit network; 16 hidden units) trained on simulated trajectories of a 2-DOF arm performing a vertical reaching task under gravity. After training on straight path movements between 20 radially placed targets, the model successfully generalized to 7 novel, held-out target locations. Crucially, the model demonstrated robustness to unseen torque perturbations, with its predictions closely matching the ground-truth physics engine (angle RMSEs: 0.71±1.04° shoulder, 2.8±3.98° elbow). These physics-aware computations reduced the errors in the mapping of state-dependent processing of shoulder and elbow torques by 20.26 and 4.51, respectively. These findings demonstrate the efficacy of using RNNs to represent the dedicated reference frames associated with the equations of motion. This solution provides the generalization of transformation and improved robustness, while enabling re-training to enhance individualized calibration of performance.

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Late-Breaking Poster

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Program #/Poster #: LBP022.20/LBP086

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

Support: NSF DOE CRCNS

Title: Factoring Multi-Channel LFPs into Interpretable Components using Locally-Competitive Sparse Coding

Authors: *N. G. BRUNS[1], G. T. KENYON[2];
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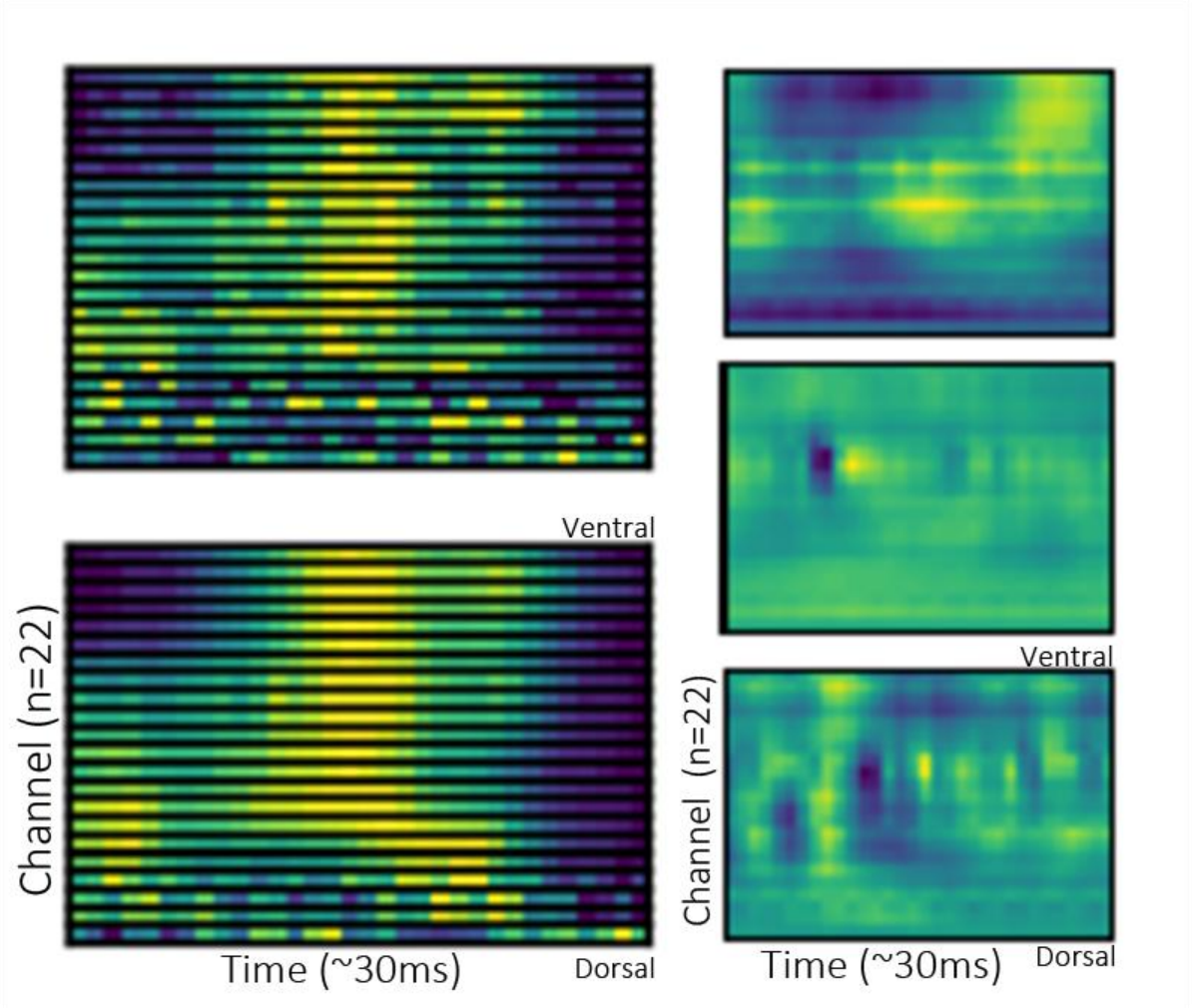
Abstract: Technology now exists to record local field potentials (LFPs) from multiple sites simultaneously across large areas of the brain. In order to interpret such recordings, it is necessary to first reduce their dimensionality. Typically, dimension reduction is accomplished via extensive spatial and/or temporal averaging but critical stimulus information encoded in the fine grained structure of LFP may be lost. Here, we present a technique based on sparse coding using the Locally Competitive Algorithm (LCA) for resolving multichannel LFP data into a tractable number (256) of generative components that retain non-trivial structure across spatiotemporal scales. To train our model, we use a 150min subset of the Allen Brain Observatory Neuropixels Visual Coding LFP dataset, segmented into ~160000, non-overlapping 33ms intervals sampled at 1250Hz (32 time steps) across 22 channels separated by 20μm within the mouse primary visual cortex (VISp). An LCA model with 256 nonconvolutional feature patches, each spanning the entire spatiotemporal LFP block (32 x 22), was then optimized for sparse reconstruction. A representative example of a sparse reconstruction of an LFP block exhibits substantial denoising (Fig 1, left), an inherent property of locally competitive sparse coding. Learned features moreover factor the LFP data into functional ensembles, several examples of which are shown (Fig 1, right). As is apparent from inspection, these learned features exhibit non-trivial spatiotemporal structure that may in turn encode non-trivial information about visual stimuli, a hypothesis we are currently investigating.Figure 1: An example of an input LFP block and its sparse reconstruction (left) and a subset (3) of the 256 learned features that factor the LFP data (right)[1] Rozell et al, Neural Comp., 20(10), 2526-2563, 2008.



Disclosures: N.G. Bruns: None. **G.T. Kenyon:** None.

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Program #/Poster #: LBP022.21/LBP087

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

Title: Convolutional kernel shaping: a framework for fine-grained analysis of functional brain networks

Authors: *A. MAHADEVAN[1,2], V. CALHOUN[3,1,2], J. LIU[1,2], B. T. BAKER[1,2];
[1]Georgia State Univ., Atlanta, GA; [2]Tri-Institutional Ctr. for Translational Res. in Neuroimaging and Data Sci. (TReNDS), Atlanta, GA; [3]Georgia Inst. of Technol., Decatur, GA

Abstract: Convolutional Neural Networks (CNNs) have become a cornerstone of medical image analysis, yet their performance is heavily influenced by architectural choices such as kernel initialization and dilation. In this work, we investigate the role of high-pass kernel initialization and varying dilation factors in enhancing 3D CNN-based feature extraction from resting-state functional magnetic resonance imaging (rs-fMRI). In particular, we leverage a hybrid approach to estimate multiple spatial brain networks and explore the ability of our proposed kernel shaping approach to capture features of particular interest, such as high spatial frequency changes in the spatial maps between a patient group (schizophrenia) and a control group. To do this, we implement a 3D CNN model with Laplacian-based initialization in the first convolutional layer and systematically compare it against standard random initialization across multiple dilation rates. To validate our method, we utilize rs-fMRI data from the Functional Biomedical Informatics Research Network (fBIRN) study, comprising 311 subjects- 160 healthy controls (HC) and 151 schizophrenia patients (SZ). Results demonstrate that high-pass initialization significantly improves the detection of fine-grained spatial features, while dilation enhances contextual representation. We also show that the resulting learned features are dramatically different depending on the initialization strategy and kernel dilation. Specifically, the baseline CNN model without dilation or high-pass initialization achieved 75% classification accuracy, whereas the proposed model with Laplacian-based initialization and a dilation rate of 3 achieved 93.75% accuracy. These findings highlight the importance of small-scale spatial differences in rs-fMRI networks and also of kernel shaping strategies for advancing deep learning methods in neuroimaging, particularly for distinguishing schizophrenia patients from healthy controls.

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MSCA-IF MoRPHEUS, Grant Agreement no. 101032054.

Title: Investigating multiscale changes in sleep-wake neural activity after a cortical lesion in vivo

Authors: *M. CHIAPPALONE[1], S. DEL CORSO[1], F. BARBAN[2], M. CARÈ[3], V. R. COTA, Sr.[4];
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Abstract: Stroke and traumatic brain injury are leading causes of adult-onset disability, with most survivors experiencing persistent motor dysfunction despite conventional rehabilitation.

While neuroprosthetic devices offer promising therapeutic potential, current approaches fail to harness the brain's intrinsic mechanisms for robust plasticity. The MoRPHEUS EU-funded project has the ultimate aim to develop a novel neuroprosthetic system that integrates sleep, a critical yet frequently neglected factor in neuroplasticity, into motor rehabilitation technology. Here we present the first results of this project, where we investigate the impact of a cortical ischemic lesion on sleep-related activity, in terms of both Local Field Potentials (LFPs) and spikes.Animals (Controls, N = 7; Lesions, N = 6; male Long Evans rats, 250-350 g) were subjected to surgical implantation of recording and stimulation electrodes (32-channel microwire arrays) in the primary somatosensory cortex (S1) and pre-motor cortex (RFA), and a focal infarct via Endothelin-1 microinjection in the primary motor cortex (Lesions group). This was followed by motor assessment through cylinder-mirror, grid walking and pasta matrix test The impact of the lesion was functionally assessed by the analysis of weekly 6 hours-long recordings of local-field potentials (LFPs) and multi-unit activity (MUA) one week after the lesion. Sleep Wake Cycle (SWC) was scored into hypnograms made of wakefulness (WK), slow wave sleep (SWS), and intermediate sleep (IS) via estimation of state-space maps based on LFP spectral ratios [Gervasoni et al., 2004].We found that Lesion animals have a shorter latency to SWS than Controls and show a significant correlation between behavioral-related indexes and clusters position in state maps. At the meso-level, the ischemia jeopardizes the temporal coordination between sleep spindles and slow oscillations. Time-frequency analysis via spectrograms-computed metrics of spindles [Sitnikova et al., 2014] reveals a different spectral content between groups, in S1 during IS and in how they differ between stages after lesion. Interestingly, micro-architecture (spikes) appears to be resilient to the lesion, as only inter-stage differences were found using widely adopted biomarkers [Averna et al., 2020]. Also, the units' firing properties present a similar balance between WK and SWS across groups. In the end, the coordination between spindles and MUA shows a possible trend in the difference of modulation across stages between groups, in S1 (second-level contrast).To conclude, SWC and macro-architecture of sleep-related cortical activity are altered following stroke.

Disclosures: M. Chiappalone: None. **S. Del Corso:** None. **F. Barban:** None. **M. Carè:** None. **V.R. Cota:** None.

Late-Breaking Poster

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Program #/Poster #: LBP022.23/LBP089

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

Title: Zero-transfer percept decoding from a contrastively pretrained fMRI transformer

Authors: *L. MAHLER[1], P. R. GRASSI[2,3,4], G. LOHMANN[3], K. SCHEFFLER[3,5];
[1]Max-Planck-Institute for Biological Cybernetics, Tübingen, Germany; [2]Vision and Cognition Lab, University of Tübingen, Tuebingen, Germany; [3]Max-Planck-Institute for Biological Cybernetics, Tuebingen, Germany; [4]Center for Integrative Neuroscience, Tuebingen, Germany;

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Abstract: Foundation models for human fMRI promise generalizable latent representations, but it remains unclear whether they support percept decoding without task-specific supervision. Most evaluations target coarse labels (e.g., task category) rather than internal perceptual states. A stronger test is when sensory input is fixed yet perception changes-as in binocular rivalry. We used a Face-House binocular rivalry paradigm with rivalry blocks (button-press labels) and replay blocks (non-rivalrous monocular presentations scheduled from each participant's rivalry durations).
We test whether SVMs trained on replay embeddings from a frozen, contrastively pretrained Swin4D Transformer (SWIFT) generalize zero-transfer to predict rivalry report labels from SWIFT embeddings, probing representation invariance under constant input.
Participants completed four runs (330 TR per run) on a Siemens Prisma 3T (TR = 1.75 s; 2.5 mm). Data were FSL-preprocessed and MNI registered. For each TR, we extracted embeddings from a contrastively pretrained SWIFT using a 20-TR window with 10-TR overlap; and Schaefer-200 parcel time series with 4-mm FWHM smoothing. Replay labels came from the stimulus schedule; rivalry labels came from button presses (Face/House/Mixed). Labels were smoothed, a minimum dwell time was enforced, and hemodynamic alignment was applied. A class-balanced linear SVM was trained only on replay and evaluated on rivalry. Performance was summarized with accuracy and macro-F1 and compared against label-shuffled permutation nulls. SWIFT embeddings yielded above-chance three-way decoding and outperformed the Schaefer-200 parcellation baseline in pooled zero-transfer evaluations; the same pattern held in within-subject analyses. Label-shuffled null models were near chance, and results were stable across reasonable choices of label smoothing and hemodynamic alignment. Confusions were concentrated around Face-House transition periods, with Mixed under-represented.
Without any rivalry supervision, embeddings from a contrastively pretrained SWIFT support above-chance three-way percept decoding under binocular rivalry and outperform a Schaefer-200 parcellation baseline, indicating that the learned latent space tracks perceptual state beyond motor or block idiosyncrasies. This replay-trained, rivalry-tested protocol offers a clean benchmark for representation invariance under constant sensory input. Together, these findings establish a practical zero-transfer benchmark for fMRI foundation models and show that SWIFT provides percept-sensitive embeddings that generalize across exogenous and endogenous alternations.

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Program #/Poster #: LBP022.24/LBP090

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

Support: Instructions on optical flow analysis from my mentor, Elisa Chinigo (Buzsáki Lab).

Title: A spatiotemporal optical-flow-based framework for cortex-wide characterization of UP/DOWN states and traveling waves

Authors: *Y. LI;
New York University, New York, NY

Abstract: Contemporary systems-consolidation models posit that newly encoded memory traces are reactivated during wake and then strengthened during sleep via a triple-nested loop linking neocortical slow oscillations, thalamocortical spindles, and hippocampal sharp-wave ripples (SWRs); notably, perturbing ripples degrades subsequent memory performance. Yet a quantitative mesoscale account of where cortical UP (spiking) and DOWN (silent) waves originate, how they propagate, and where they terminate has been lacking. To address this gap, we developed an end-to-end framework for wide-field calcium imaging in head-fixed mice that reconstructs movies (H×W×T) from masked pixel streams, denoises data via percentile-based cropping and variance filtering, and estimates optical flow using the Horn-Schunck algorithm. Divergence maps of the flow field detect cortical sources (positive divergence) and sinks (negative divergence), which are then linked into trajectories and registered to an atlas-based parcellation of 27 dorsal cortical regions. Spatiotemporal dynamics are quantified through density distributions, DBSCAN clustering, and trajectory statistics (duration, displacement, splitting/merging). Across regions, UP states consistently outlast DOWN states, and source/sink locations are spatially non-uniform: DOWN-state sources tend to initiate in motor cortex and dissipate in somatosensory areas, indicating a directional flow of cortical inactivity. Windowed conditional-probability matrices reveal structured inter-regional propagation tendencies among UP-sources, UP-sinks, DOWN-sources, and DOWN-sinks, while topological analysis of vector fields identifies canonical node-, saddle-, and focus-like behaviors. Raster analyses of binary UP/DOWN states further show cortex-wide fluctuations in the number of engaged regions, with peaks and troughs aligned to slow-wave events. The pipeline is applied uniformly across NREM sessions with fixed parameters, yielding reproducible flow fields, divergence maps, regional rasters, and trajectory-based statistics. Together, these results provide a cortex-wide, data-driven atlas of slow-wave generators, trajectories, and termination zones, and establish a scalable optical-flow-based framework for mesoscale brain dynamics. Ongoing work integrates simultaneously recorded hippocampal SWRs to test how ripple events perturb cortical UP/DOWN states and to delineate the pathways and consistency of hippocampo-cortical coupling—linking the observed mesoscale wave kinematics to the broader wake-to-sleep transfer of information posited by systems-consolidation theory.

Disclosures: Y. Li: None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.25/LBP091

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

Title: Discrimination of autism mice models via machine learning methods

Authors: *A. F. FRONTERA;
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Abstract: Autism Spectrum Disorder (ASD) affects millions worldwide, yet its neural underpinnings remain poorly understood. Understanding ASD's complex brain circuits requires powerful tools to analyze neural activity patterns. Machine learning, particularly deep learning architectures, offers unprecedented capabilities to understand complex systems such as the brain. In the present study, we employ a transformer-based machine learning approach to investigate how convergent neural phenotypes manifest in genetically modified mouse models with autism-like behavior. We analyze widefield calcium imaging data from mice with mutations in ASD-associated genes like GRIN2A, GRIN2B, and MECP2. We developed a Brain Vision Transformer (BrainViT) architecture that processes spatiotemporal brain activity. This can be used to discriminate between the neural dynamics of the genetic ASD mouse models and wild-type controls. Our preliminary data suggests that the transformer model differentiates between the neural activity patterns of mice with autism-associated mutations and wild-types, achieving classification accuracies substantially above chance. These findings indicate that mice with autism-associated mutations may have shared neural activity patterns, which differ from those of typical mice. These data suggest common circuit-level disruptions in ASD models despite different genetic alterations. This machine learning approach opens new avenues for understanding the neural basis of autism.

Disclosures: A.F. Frontera: None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.26/LBP092

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

Support: NIH Grant R01MH122258(DH)
NIH Grant R01EY035533(DH & KK)

Title: Integration of Electrical Stimulation and dMRI to estimate Axon Diameter Distributions in Human Brain

Authors: *S. ROMERO SANTIAGO[1], M. YÁÑEZ-RAMOS[1], J. BILDERBEEK[1], N. GREGG[2], M.-H. IN[3], E. GRAY[4], D. KANG[4], Y. SHU[4], G. A. WORRELL[2], C. MCINTYRE[5], K. J. MILLER[6], D. HERMES[1];
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Abstract: The information transmitted through white matter bundles such as the arcuate fasciculus (AF) and the uncinate fasciculus (UF) plays a crucial role in cognitive functions. The conduction velocity of signals along these fibers is mainly determined by neuroanatomical features such as axon diameter, following an approximate linear relationship: Velocity≈6*Axon Diameter (Equation 1). A few post-mortem studies in animals and humans have measured axon diameters, however, in vivo estimates of axon diameter and velocity distributions along different fasciculi in humans remain limited. In this work, we integrate diffusion MRI (dMRI) and stereo-electroencephalography (sEEG) to estimate conduction velocity of human AF and UF and predict axon diameter distributions in vivo. We used data from sixteen drug-resistant epilepsy patients that were implanted with sEEG electrodes for clinical monitoring. Before sEEG placement, dMRI data were acquired on a Compact 3.0 T MRI scanner with high-performance gradients using a double-encoding method to obtain two series, each containing two volumes at b=0 s/mm² and 48 directions at b=1000 s/mm². Whole-brain tractography was subsequently performed using constrained spherical deconvolution combined with probabilistic tracking, and the AF and UF for both hemispheres were segmented through streamline-based registration. Single-pulse electrical stimulation was applied to directly activate white matter fibers using biphasic pulses (100 μs per phase, 6 mA) to study effective connectivity. We calculate the reliability of the responses (coefficient of determination, CoD) using Canonical Response Parametrization (CRP) to identify significant responses. Latencies of the first peak were measured. Finally, we calculated the distance between the stimulation and the recording sites, along the streamlines. Velocities were then computed from distances and response latencies. The conduction velocities in the AF and UF both followed a right-skewed distribution. Axon diameters estimated based on a linear relationship with velocity (Equation 1) indicate that estimated axon diameters in the two major white matter bundles contain very few fast, thick fibers (>1 μm) and mostly contain slower, thinner fibers (<1 μm), consistent with histological evidence of axonal variability. These findings suggest that in vivo estimations of white matter conduction velocities, and, by extension, axon diameter, are feasible.

Disclosures: S. Romero Santiago: None. **M. Yáñez-Ramos:** None. **J. Bilderbeek:** None. **N. gregg:** None. **M. In:** None. **E. Gray:** None. **D. Kang:** None. **Y. Shu:** None. **G.A. Worrell:** None. **C. McIntyre:** None. **K.J. Miller:** None. **D. Hermes:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.27/LBP093

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

Support: NIH P50 HD105352

Title: A user-friendly centralized, API-driven acquisition system for scalable multi-camera video recording of animal behavior

Authors: *M. KISLIN;
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Abstract: High-throughput behavioral studies require reliable video systems that support precise experimental timing and integration with computer vision tools. Existing open-source platforms often lack scalability, intuitive graphical interfaces, robust data integrity features, or seamless multi-camera management without coding expertise.
This work presents RPi4Cam, a low-cost, scalable platform for controlling multiple Raspberry Pi cameras to capture time-locked videos in rodent behavioral studies. The system consists of a Tkinter-based GUI on a host machine and a Flask API service on each Raspberry Pi 4 or 5, enabling cluster management via a simple CSV configuration. Key functions include real-time monitoring of connectivity, disk space, and sub-millisecond clock synchronization via NTP-server; batch or individual control of recordings; on-demand live previews for framing and exposure; and support for configurable modes with resolutions and frame rates up to Picamera2 hardware limits.
To ensure reproducible data handling, RPi4Cam provides a remote file manager that lists completed sessions by name, animal ID, and date. Sessions can be transferred and backup with progress feedback and optional remote cleanup. The raw files are automatically segmented to minimize number of dropped frames, optionally converted with lossless compression, and logged in a session machine-readable manifest that records file sizes, checksums, active camera configurations, and the Git commit hash of the repositories for acquisition and analysis. A one-click clock auditing tool runs chronyc tracking on each Pi to report offsets in milliseconds, ensuring reliable alignment with external devices. GPIO integration allows logging of behavioral events such as trial starts, stimuli, and licks with 10-ms debounce and POSIX timestamps for sub-frame precision. In validation tests with up to 10 cameras, RPi4Cam achieved millisecond-accurate synchronization and robust event marking in head-fixed and freely moving behavior paradigms, with per-camera costs under $150.
By combining a user-friendly GUI, integrated data verification, and extensible APIs, RPi4Cam lowers barriers for high-throughput behavioral phenotyping, supports longitudinal and closed-loop experiments, and enables future extensions such as dual-color bundle-imaging fiber photometry and real-time tracking and posture detection using Raspberry Pi AI Camera or Pi HAT+ modules with onboard computer vision processing.

Disclosures: M. Kislin: None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.28/LBP094

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

Title: A Framework for Real-Time Laminar fMRI at 9.4 Tesla

Authors: *A. EROGLU[1], D. CHAIMOW[1,2], M. ANSARI[1,3], S. BISWAS[4], R. LORENZ[1,2]; [1]Max Planck Inst. for Biol. Cybernetics, Tuebingen, Germany; [2]Max Planck Inst. for Human Cognitive and Brain Sci., Leipzig, Germany; [3]Univ. of Tuebingen, Tuebingen, Germany; [4]Max Planck Sch. of Cognition, Hamburg, Germany

Abstract: Real-time fMRI enables closed-loop neuroscience, but until now relies on coarse regional or multivariate signals. Yet, the cortex is organized into layers that segregate feedforward and feedback processing, a core principle of cortical computation. Real-time access to laminar signals would provide mechanistic insights into cognitive computations and enable neurofeedback for clinical conditions characterized by laminar dysfunction. Achieving this requires submillimeter resolution at ultrahigh field, precise alignment and fast processing, which have so far limited real-time laminar readouts. Here, we address these challenges with a framework combining online performance and gold-standard offline-level precision.We designed a two-session protocol separating computationally intensive steps from real-time processing. In Session 1, anatomical scans (MP2RAGE), whole-brain and functionally localized slab fMRI (GE-BOLD, 0.8 mm iso, TR=2s) data are acquired at 9.4 Tesla. Anatomical scans are processed with a FreeSurfer-based pipeline to generate cortical surfaces, with optional manual refinement. Functional images are distortion-corrected with reverse-phase acquisitions and registered to the anatomical reference.In Session 2, a new slab is acquired, automatically matched to the Session 1 placement for consistent coverage. We apply distortion correction and perform a composite registration that aligns the slab via the whole-brain reference to the anatomy, merging all transformations into one interpolation to minimize blurring. In line with gold-standard practice, equivolume cortical layers are estimated in native space. During online runs, each slab volume is motion-corrected, layer-masked, and layer signals are extracted per TR. Multiprocessing enables parallel computations and a custom interface visualizes signals for quality control and neurofeedback applications.Here, we present the first open and adaptable framework for real-time laminar fMRI which lowers the barrier to laminar closed-loop studies with broad applicability for the field.

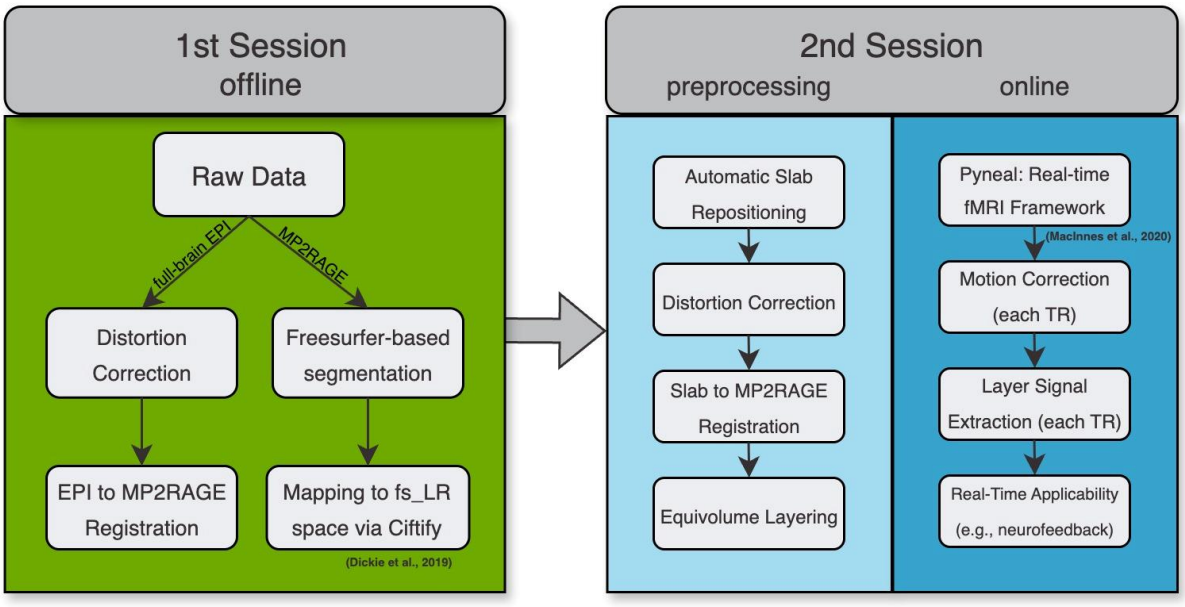

Figure 1. Two-session real-time laminar fMRI framework. Session 1 provides anatomical references and cortical surfaces. Session 2 includes automatic slab repositioning for consistent placement, streamlined preprocessing with distortion correction, registration, and equivolume layering, and online processing with motion correction and extraction of laminar signals.

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Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.29/LBP095

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

Support: ETRI Grant 25ZB1330

Title: Lightweight Embedded AI for Real-Time Neuro-Behavioral Classification in Freely Moving Mice

Authors: H. KIM[1], C. KIM[2], G. LEE[1,2], H. CHOE[2], S. Q. LEE[3], *H.-K. LEE[1];
[1]ETRI, Daejeon, Korea, Republic of; [2]Department of Brain and Cognitive Sciences, DGIST, Daegu, Korea, Republic of; [3]Dept. of Mechanical Engineering, San Diego State University, San Diego, CA

Abstract: Embedded artificial intelligence (AI) development enables real-time neuro-behavioral classification in freely moving animals, yet accurate classification on resource-constrained processors remains challenging. We present a lightweight AI framework optimized for

deployment on an ARM Cortex-M4 processor embedded within a wireless head stage, integrating multimodal neural and behavioral signals for edge computation. To balance classification accuracy and computational efficiency, we implemented a preprocessing pipeline combining raw electroencephalography with tri-axial accelerometer data, using Fast Fourier Transform (FFT)-based feature extraction. The neural network architecture comprises 36 input nodes, two hidden layers with 40 and 20 nodes respectively, and seven output nodes representing seven annotated behavioral states: inactive, waiting, moving, digging, rearing, scratching, and grooming. Data were collected from mice wearing wireless head stages during approximately 600 seconds of free exploration, synchronized to video sampling at 32-ms intervals. Training and testing datasets were constructed using a moving-window approach on 64-sample FFT segments. Supervised learning incorporated class-specific sample balancing to mitigate class imbalance. Our model demonstrated high classification accuracy for inactive, moving, rearing, grooming, and scratching behaviors despite limited training samples in some categories. Lower accuracy was observed for waiting and digging behaviors, likely due to overlapping signal features, indicating a need for refined feature extraction. Computational evaluations using the ARM math library revealed that inference required roughly 8,000 multiplications per cycle and completed in under 2 milliseconds, confirming the feasibility of compact neural network architectures for real-time applications on constrained hardware. This study validates the integration of a compact AI architecture on an ARM Cortex-M4 processor within a wireless head stage, enabling low-latency, multi-class behavioral classification in freely moving rodents. FFT-based preprocessing, optimized neural network design, and efficient math library utilization contributed to accurate classification with minimal computational overhead. Future work will focus on advanced feature-specific optimization and distributed processing to enhance classification accuracy in challenging behavioral categories, emphasizing the significant potential of edge AI to propel neural engineering by facilitating real-time brain-behavior interaction monitoring.

Disclosures: H. Kim: None. **C. Kim:** None. **G. Lee:** None. **H. Choe:** None. **S.Q. Lee:** None. **H. Lee:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

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Program #/Poster #: LBP022.30/LBP096

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

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Nell Hodgson Woodruff School of Nursing at Emory University

Title: Democratizing AI for neuroimaging via BrainChop: secure and accessible zero-footprint segmentation in browser and command-line

Authors: ***A. FANI**[1], M. DOAN[1], I. LE[1], A. FEDOROV[2], M. HOFFMANN[3], C. RORDEN[4], S. PLIS[1];
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Abstract: The immense potential of deep learning for neuroimaging is often bottlenecked by barriers that hinder widespread adoption: data privacy concerns, high computational demands, reliance on specialized hardware, and complex installation processes. We present BrainChop, a sustainable, "zero-footprint" platform that democratizes access to advanced AI models via a web browser interface (brainchop.org) and command-line package (brainchop-cli). The browser interface supports fast, client-side inference powered by WebGPU, offering a range of segmentation models with interactive visualization, result editing, and full data privacy. The command-line tool further enhances performance by supporting batch processing, customizable preprocessing options, and faster runtimes, all with one-click installation. As a compelling case study, we present the latest model added to our platform: MindGrab, a lightweight, omnimodal, fully convolutional network for robust skull stripping. Trained exclusively on synthetic data, it achieves a mean Dice score of 95.9 ± 1.6 on a retrospective dataset of 606 multimodal adult brain scans. It performs competitively with the state-of-the-art SynthStrip (96.5 ± 1.1), while boasting a 95% reduction in parameters (146,237 vs. 2,566,561). This efficiency translates to substantial performance gains, with 10-30x faster inference and up to 30x lower memory usage, making it a powerful model well-suited for deployment on BrainChop. Through this case study, we demonstrate the practical utility and broad accessibility of the BrainChop platform and its power to bridge the gap between innovation of deep learning models and their real-world implementation in the biomedical community.

Disclosures: A. Fani: None. **M. Doan:** None. **I. Le:** None. **A. Fedorov:** None. **M. Hoffmann:** None. **C. Rorden:** None. **S. Plis:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

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Program #/Poster #: LBP022.31/LBP097

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

Support: NIH Grant AA030585
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Title: Beyond the Open Field: A Deep Learning Approach for Decoding Latent Rodent Behaviors in Structured Reinforcement Tasks

Authors: B. MOON[1], Q. FLANAGAN-BURT[1,2], E. VAN DER RIJN[1,2], A. ECEVITOGLU[1,2], K. J. RESSLER[1,2], ***J. SUH**[1,2];
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Abstract: Understanding how animals adapt their behavior in structured, cognitively demanding environments remains a core challenge in systems neuroscience. Behavior is the observable output of neural activity, and quantitative analysis of rodent behavior offers critical insight into brain mechanisms underlying learning, sensory processing, and decision-making. While recent machine learning approaches have effectively classified rodent behavior in open field settings, they often fall short in reinforcement learning tasks, where actions are shaped by prior experience and anticipated outcomes. We processed 40 top-view videos (~30 min each) of mice performing operant behaviors in a chamber containing two nose-poke holes and a central reward port using DeepLabCut, a markerless pose estimation tool that extracts detailed body-part trajectories. Next, we evaluated two existing models: Deep Behavior Mapping (DBM), a supervised LSTM-based model, and Keypoint-MoSeq (KPMS), an unsupervised Hidden Markov Model-based method. DBM identified behavioral microstates (syllables) but was highly dependent on spatial location, lacked intuitive syllable visualization, and required extensive manual labeling. In contrast, KPMS discovered unsupervised motifs with visualization tools, but could not distinguish task-relevant actions (e.g., right nose poke vs. center reward retrieval) and assumed a stationary transition matrix, limiting its ability to capture evolving behavioral dynamics. To overcome these limitations, we developed a semi-supervised Bidirectional LSTM (Bi-LSTM) model. By incorporating both past and future time points, and integrating Med-PC-recorded behavioral events (e.g., nose pokes, the number of reward retrievals), the model learns a compact set of behavior categories while generalizing across time and context. Compared to DBM and KPMS, the Bi-LSTM achieved higher classification accuracy (0.86 ± 0.03), lower training loss (~0.02), and a mean F1 score of 0.81. Our efforts highlight the utility of expressive sequence modeling for capturing subtle, temporally structured, and context-sensitive rodent behaviors. This approach offers a powerful framework for linking behavioral microstates with neural activity, paving the way for deeper insights into brain-behavior dynamics in structured tasks.

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Title: Inpainting the Neural Picture: Inferring Unrecorded Brain Area Dynamics from Multi-Animal Datasets

Authors: *J. XIA[1], Y. ZHANG[1], S. WANG[2], G. ALLEN[3], L. PANINSKI[1], C. L. HURWITZ[1], K. D. MILLER[4];
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Abstract: Understanding how distributed brain circuits drive animal's behavior requires recording from cortical areas and interconnected subcortical areas. Neuropixels probes enable simultaneous sampling from multiple areas, yet no single experiment captures all areas of interest, and different neurons are sampled across sessions. This poses a central challenge: how can we integrate multi-animal datasets to study interactions across brain areas that are not recorded simultaneously in any single session?
We introduce *NeuroPaint*, a masked autoencoding approach for inferring the dynamics of unrecorded brain areas. By training across animals with overlapping subsets of recorded regions, *NeuroPaint* learns to reconstruct neural dynamics in missing areas using shared structure across individuals. We evaluate the method on synthetic data and two large multi-animal Neuropixels datasets: the International Brain Laboratory (IBL) dataset, and the Mesoscale Activity Map Project (MAP) dataset. Our results show that models trained across animals with partial observations can accurately predict single-trial neural population dynamics in unobserved areas, enabling multi-area analyses that transcend the limitations of individual experiments.
Our method is the first to infer area-specific single-trial dynamics across many sessions and animals for both recorded and unrecorded brain areas.

Disclosures: J. Xia: None. **Y. Zhang:** None. **S. Wang:** None. **G. Allen:** None. **L. Paninski:** None. **C.L. Hurwitz:** None. **K.D. Miller:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

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

Support: MSIT (Korea) Grant RS-2024-00431394
MSIT (Korea) Grant RS-2025-25443930
NRF (Korea) Grant 2021R1I1A3060828

Title: Improving N1 recall in automatic sleep staging with dual-modality features and BiLSTM sequential modeling

Authors: *H. OH[1], J. CHOI[2], C. HONG[1], M. AHN[1];
[1]Handong Global University, Pohang, Korea, Republic of; [2]Department of Anesthesia, Massachusetts General Hospital, Charlestown, MA

Abstract: Sleep is vital for cognitive, metabolic, and overall health, and automatic sleep staging is increasingly important for clinical assessment. Among the stages defined by the American Academy of Sleep Medicine (AASM), non-rapid eye movement stage 1 (NREM 1, or N1) marks the transition from wake to stable sleep and is clinically essential for evaluating sleep onset and fragmentation. Yet N1 remains the most challenging stage to classify due to subtle electroencephalography (EEG) signatures, similarity to adjacent stages, and class imbalance. To address this challenge, we evaluated spectral features, attention-based fusion, and sequential modeling using the Sleep-EDF-20 dataset (Fpz-Cz channel, 20-fold leave-one-subject-out validation). We also apply class-weighted loss with inverse frequency weights to mitigate imbalance. Raw EEG captured temporal patterns, while power spectral density (PSD) represented frequency characteristics. Results are reported as aggregate values across folds (outside parentheses) and mean ± standard deviation (SD) across 20 folds (in parentheses). A raw EEG baseline with multi-resolution CNN (MR-CNN) achieved 80.8% (80.6 ± 8.1) accuracy, macro-F1 of 74.0% (73.4 ± 6.1), and 37.7% (40.0 ± 16.3) N1 recall. Adding PSD (Raw+PSD) modestly improved N1 recall to 42.7% (43.8 ± 18.2) while maintaining similar accuracy and F1, underscoring its complementary role. Incorporating multi-head attention (MHA) to fuse dual-modality features (Raw+PSD+MHA) balanced performance, yielding 81.0% (81.0 ± 6.0) accuracy, 74.6% (73.8 ± 5.7) F1, and 42.4% (43.4 ± 15.9) N1 recall. Sequential modeling with bidirectional LSTM (BiLSTM) over stacked epochs drove a decisive improvement: Raw+PSD+BiLSTM achieved 81.9% (81.7 ± 7.5) accuracy, 76.9% (75.8 ± 7.6) F1, and 56.3% (56.3 ± 11.4) N1 recall with 5-epoch sequences, improving to 83.0% (83.0 ± 6.1) accuracy, 78.2% (76.9 ± 6.7) F1, and 56.7% (57.9 ± 14.1) N1 recall with 15-epoch sequences. The complete model (Raw+PSD+MHA+BiLSTM) delivered the most robust results: 83.6% (83.7 ± 5.2) accuracy, 79.1% (78.1 ± 5.7) F1, Cohen's kappa = 0.78, and 59.6% (59.7 ± 12.0) N1 recall with 15-epoch sequences. These findings demonstrate that PSD strengthens N1 detection by adding complementary spectral information, MHA balances performance and reduces inter-subject variability, with the associated reduction in SD highlighting its stabilizing effect, and BiLSTM—by modeling temporal transitions—drives the substantial N1 improvement. Notably, while sustaining state-of-the-art overall performance, our approach achieves a significant breakthrough in N1 classification relative to existing LOSO-based studies.

Disclosures: H. Oh: None. **J. Choi:** None. **C. Hong:** None. **M. Ahn:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.34/LBP100

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

Support: Clayton Foundation for Research

Title: Dynamic Inputs Enhance Robustness of Neuronal Parameter Estimation

Authors: *S. EPSTEIN[1,2], D. PAYDARFAR[2,1], J. CHANG[2,1];
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Abstract: Precise estimation of ionic channel parameters is essential for translating experimental understanding of neuronal excitability into predictive computational models. Traditional approaches provide a detailed characterization of individual channel properties but require technically demanding protocols and cellular manipulations that may alter native channel behavior. Moreover, conventional fitting methods yield only point estimates without quantifying parameter uncertainty—a critical limitation for model reliability and experimental design. We introduce a scalable Bayesian framework that combines Hamiltonian Monte Carlo with gradient-based solvers to infer full posterior distributions over Hodgkin-Huxley parameters in multi-compartment cable models. Our approach explicitly quantifies uncertainty while accommodating realistic noise and limited prior knowledge. We systematically evaluated the framework across >100 parameter configurations spanning physiologically realistic ranges from giant squid axon, mammalian cortical neurons, and peripheral fiber models. Current clamp recordings were simulated with three stimulus protocols—step currents, sinusoidal waveforms, and frequency-chirped inputs—under varying noise levels (signal-to-noise ratio of 8-10 dB) matching typical laboratory conditions. Stimulation protocol emerged as the dominant factor governing identifiability. Dynamic sine and chirping protocols maintained >90% coverage (i.e. how frequently the method's estimated confidence intervals contain the true values of the parameters) and mean systematic errors deviating less than <20% from true values for recovering all conductance and reversal potential parameters even under wide prior uncertainty (>2 standard deviations). Meanwhile, step current protocols quickly lost their ability to separate the true parameters: small increases in uncertainty caused large error jumps, making inferences unreliable. Posterior analysis showed that time-varying inputs mitigated confounding between conductances and reversal potentials, enabling robust recovery under weak prior knowledge. Validation across parameter configurations demonstrated 89% coverage with 9.3% mean systematic error at realistic noise levels. This framework establishes a reproducible, uncertainty-aware pipeline for fitting conductance-based models directly to electrophysiological data, enabling parameter estimation and providing insight into experimental design.

Disclosures: S. Epstein: None. **D. Paydarfar:** None. **J. Chang:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.35/LBP101

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

Title: Temperature Induced Codimension-One and Codimension-Two Bifurcations in Hodgkin-Huxley Neurons

Authors: *B. HAN[1], A. DAOU[2];
[1]Stanford University, Stanford, CA; [2]Biomedical Engineering, American University of Beirut, Beirut, Lebanon

Abstract: Temperature fluctuations can have detrimental effects on the firing pattern and electrical activity of biological neurons, eliciting diverse responses depending on the neuronal cell types and the underlying ion channels exhibited. Using the classical Hodgkin-Huxley (HH) model, we performed a comprehensive dynamical systems analysis to determine how temperature fluctuations alter neuronal excitability, spike morphology, and bifurcation structure. We first relied on experimentally-derived temperature coefficients, or Q10 values, associated with gating kinetics and conductances, and examined codimension-1 and codimension-2 bifurcations across a range of temperatures and standard HH parameters governing the intrinsic properties (firing frequency, spike amplitude, spike width, afterhyperpolarization (AHP), time-to-peak AHP, etc...) of the model HH neuron. Our analysis revealed that increasing temperature accelerates gating dynamics, leading to narrower and higher-frequency spikes but reduced amplitudes, and ultimately to a loss of sustained firing via temperature-induced depolarization block. We identified generalized Hopf (Bautin) bifurcations as critical boundaries beyond which the system becomes strictly monostable. Extending the model to independently scale sodium activation, sodium inactivation, and potassium activation kinetics showed that excitability is particularly sensitive to potassium gating dynamics. Our findings provide a quantitative framework for understanding temperature modulations of neuronal activity, highlighting how temperature reshapes the excitability landscape, unveiling the intricate interplays between the activation/inactivation kinetics of ion channels, and identifying key parameters governing temperature robustness in neuronal models.

Disclosures: B. Han: None. **A. Daou:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.36/LBP102

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

Title: Pattern recognition for exact synchronization in the brain applied to MEG recordings

Authors: *A. KATZ;
Bar Ilan University, Ramat Gan, Israel

Abstract: Identifying thoughts from different brain activities is a difficult challenge faced by many researchers in many labs around the world. Successes have been reported in identifying whether a person is thinking about one object (for example, an elephant) or another object (like a

car). In this paper, we present a technology for the first time to identify which of the numbers 1,2,3,4, or 5 a person is thinking of. We used brain recording via MEG (Magnetoencephalography). We developed a methodology and algorithms for characterizing properties of brain activity related to different numbers (e.g., number 2 and number 3) and distinguished between brain activity during different visual stimuli of the same number(e.g. the figure 3 or three circles). Guessing which one-digit number a person is thinking of was done via MEG recording. 100 percent accuracy can be reached after 45 seconds (on average) of trials, and for many cases after 15 seconds. This is the most refined thought identification that has been achieved so far. The newly developed methods include geometric characteristics-based encoding of MEG recordings and a multidimensional distance function that measures virtual distance among matrices with numerical entries. Later developments ensure a higher accuracy and evidence for neuro-synchronization.

Disclosures: A. Katz: None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.37/LBP103

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

Support: NIH grant 1R01MH135293-01

Title: One-size-fits-all pipeline for EEG Source Localization? Impact of data quality, head model, forward and inverse solution algorithms on EEG reconstruction precision

Authors: *M. SHAMAS[1], T. VALLES[1], J. CORLIER[2], A. LEUCHTER[2];
[1]UCLA, Los Angeles, CA; [2]University of California Los Angeles, Los Angeles, CA

Abstract: EEG source localization is highly sensitive to head model selection, forward/inverse algorithms, and signal quality but few studies have systematically evaluated how these parameters interact to influence localization accuracy. To address this gap, we examined the impact of these algorithmic choices on the spatial, temporal and spectral accuracy of source reconstruction using realistic, simulated EEG signals.
We simulated a 70Hz amplitude modulated EEG signals (10Hz modulator) with 3 different signal-to-noise-ratios (SNR) and forward-projected to the scalp using 4 head models (A: head template, B: head template with digitized individual electrode position, C: a warped version fitted to digitized positions, and D: subject-specific MRI anatomy). We then used these data to reconstruct the sources using 11 different Minimum Norm Estimate (MNE) and Beamformer (BF) based inverse methods. We assessed head model accuracy by comparing electrode positions and gain matrices to those derived from an MRI-based model. To assess the reconstruction accuracy of different algorithms, we calculated the time-series correlation between recovered signals and original simulated signals at each brain region of the Destrieux atlas and corrected

for multiple comparisons ($p < 4.17\times10^{-3}$). For spectral accuracy we calculated the dispersion in the spectrogram of the modulated and modulating recovered signals. Gain matrix differences were lowest between head models B and C (mean = 2.14±0.33), followed by A vs. B (3.52±1.60), and highest when MRI was involved (12.48±2.45 and 11.07±2.57 for default-MRI and projection-MRI, respectively). Surprisingly, MRI-based models showed slightly worse temporal correlation than other models, with a median-based Cohen's d = 0.5747. However, MRI-based models consistently outperformed all other models in spectral recovery. MNE-based inverse methods achieved higher temporal accuracy compared to Beamformer-based methods (MNE mean correlation = 0.29±0.2 vs. BF 0.09±0.1; Cohen's d = 1.24). Accuracy for modulated signal remained high across all SNRs (mean = 0.87±0.1), but accuracy of the modulating signal sidebands was SNR-dependent, where beamformer methods outperformed MNE-based methods in low SNR environments. Algorithm decisions should be tailored to address the specific scientific question. MRI-based models should be prioritized in clinical or surgical contexts where spatial accuracy is essential, while template projection models may suffice for cognitive or group-level studies. MNE-based methods are more suitable for time-domain metrics, whereas Beamformers better capture spectral features, particularly in noisy data.

Disclosures: M. Shamas: None. **T. Valles:** None. **J. Corlier:** None. **A. Leuchter:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.38/LBP104

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

Title: Cross-Modality Translation Between MRI and Functional Connectivity to Address Missing Data in Alzheimer's Disease

Authors: *R. HASSANZADEH[1], V. CALHOUN[2];
[1]Georgia Institute of Technology, Atlanta, GA; [2]Georgia Institute of Technology, Decatur, GA

Abstract: Multimodal neuroimaging holds promise for uncovering the interplay between brain structure and function, but many large-scale studies contain incomplete data, with only a subset of participants having both structural and functional scans. This missingness reduces the power of multimodal analyses and limits opportunities for biomarker discovery. To address this challenge, we developed a generative modeling framework for cross-modality translation between T1-weighted MRI and functional network connectivity (FNC) derived from resting-state fMRI. Unlike traditional imputation or subsampling strategies, which discard data or oversimplify missing information, our framework synthesizes absent modalities using a GAN-guided diffusion approach that integrates conditional diffusion modeling, adversarial training, and cycle-consistency learning. This hybrid design allows the model to leverage both paired and unpaired data, a critical advantage in neuroimaging studies where missing modalities are common.

We evaluated our approach on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), which includes more than 8,000 imaging sessions from over 1,700 participants. fMRI data were processed with the NeuroMark ICA framework to extract reproducible functional components, and FNC maps were derived from correlations among 53 networks spanning seven brain domains. Generated data were benchmarked against real samples, achieving high fidelity (PSNR = 24.95, SSIM = 0.86 for T1 synthesis; Pearson correlation = 0.65 for FNC). Importantly, the model captured subject-level variability and preserved disease-related contrasts across controls, mild cognitive impairment, and Alzheimer's disease, despite not being trained with diagnostic labels.
Comparisons with baseline models, including conditional DDPMs and CycleGANs, showed that our framework achieved superior image fidelity, preserved functional connectivity structure, and reproduced clinically relevant group differences. Beyond individual reconstructions, group-level analyses demonstrated that generated modalities replicated distributions of mean and variance across subjects, and highlighted atrophy and connectivity disruptions consistent with Alzheimer's disease pathology. Together, these results show that generative cross-modality translation can mitigate the impact of missing data, enable fuller use of longitudinal cohorts, and accelerate biomarker discovery in Alzheimer's disease and related neurodegenerative conditions.

Disclosures: R. Hassanzadeh: None. **V. Calhoun:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.39/LBP105

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

Support: NSF Grant DMS-2436216

Title: Hybrid CNN-RNN Conditional VAE with RS-fMRI for ASD Severity and Comorbidity Analysis

Authors: Z. MALIK, ***C. PARK**;
Biomedical Engineering, George Washington University, Washington, DC

Abstract: Objective: Resting-state fMRI connectivity varies across autism spectrum disorder (ASD) subtypes and comorbidity. We want to know whether a hybrid CNN-RNN Conditional VAE (CVAE) improves reconstruction reliability while exposing network deviations tied to severity of comorbidity clusters.
Methods:Multisite ABIDE resting state-fMRI were parcellated with Schaefer's and Harvard-Oxford atlas to ROIXROI connectivity as well as 200x200 normalized matrices. We trained CNN-VAE, RNN-VAE, and hybrid CNN-RNN CVAE with conditioning vectors (inject_dim) and held-out validation. We computed cluster-mean matrices and per edge Δ-connectivity to summarize these deviations within canonical networks (DMN, salience, executive,

sensorimotor). Rigor: de-identified public data; multi-site cohort; sex-recorded and used in conditioning (ABIDE is male-skewed); stratified splits; fixed seeds; metrics reported on held-out data; sample size for current connectivity clustering N=36 processed scans.
Results:The hybrid CVAE achieved the lowest reconstruction loss and highest validation cosine similarity (~0.97) versus single-stream CNN- or RNN-VAEs. Latent embeddings separated ASD vs. TD and ASD subtypes; single-stream baselines underperformed (e.g., CNN latent accuracy ~0.51; RNN: ~0.68). Example subject-level reconstructions show markedly lower MSE and higher SSIM for CNN-VAE than RNN-VAE, while the hybrid balances spatial and temporal fidelity. In connectivity analyses, cluster contrasts emphasized DMN and salience: severe/comorbid clusters showed increased salience coupling and reduced DMN integration, with subject-level Δ-connectivity maps pinpointing the strongest edges.
Conclusions: A spatio-temporal CVAE conditioned on subject variables yields high-fidelity reconstructions and network-specific deviations aligned with ASD severity/comorbidity, supporting individualized Δ-connectivity profiling and providing a principle for multimodal fusion (e.g., EEG/speech assessments) and downstream prognostic/optimization models.

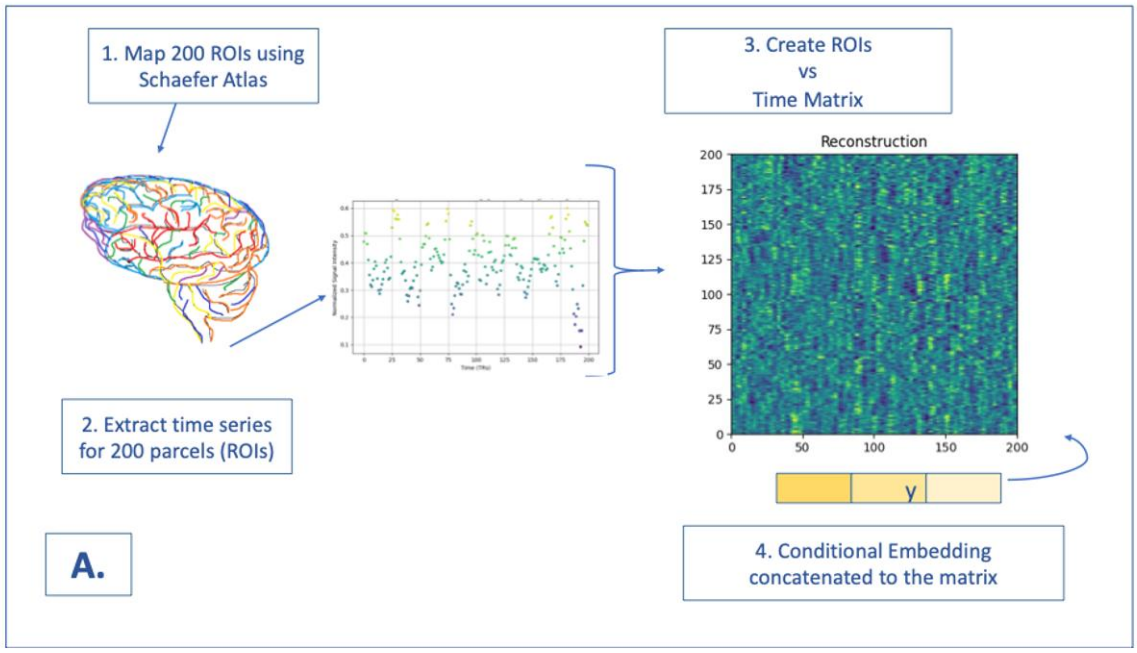

Figure 1. Overview.

Disclosures: Z. Malik: None. **C. Park:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.40/LBP106

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

Support: EU Horizon 2020 No. 945539 (Human Brain Project SGA3 and Partnering Project (AstroNeuronNets))
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HiRSE PS
Research Council of Finland, Nos. 297893, 318879, 326494, 326495, 345280, and 355256
BMBF No. 01UK2104 (KHK c:o/re)

Title: Scalable Simulation of Neuron-Astrocyte Networks in NEST with Astrocyte-Mediated Synaptic Currents

Authors: *T. MANNINEN[1], H.-J. JIANG[2], J. ACIMOVIC[1], I. AHOKAINEN[1], J. STAPMANNS[2], M. LEHTIMÄKI[1], M. DIESMANN[2], S. J. VAN ALBADA[2], H. E. PLESSER[3], M.-L. LINNE[1];
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Abstract: Astrocytes play a fundamental role in shaping synaptic activity, network dynamics, and behavior through their complex interactions with neurons and other glial cells. Yet, large-scale computational models that incorporate neuron-astrocyte interactions remain limited (Manninen et al., 2023). In this study, we introduce an advanced simulation framework in the NEST environment (Graber et al., 2024) to model tripartite connectivity, where astrocytes form connections with both presynaptic and postsynaptic neurons, extending conventional binary synaptic architectures (Jiang et al., 2025). The framework integrates astrocytic calcium dynamics and astrocyte-induced synaptic currents (SICs), enabling dynamic modulation of neuronal activity and providing a mechanistic representation of proposed astrocyte-neuron interactions. In silico experiments demonstrate that astrocytes influence neuronal population activity by modulating network states and enhancing coordination across local circuits. By tuning astrocytic parameters, the model captures transitions between asynchronous and synchronized regimes, offering insights into how astrocytes regulate network behavior. Benchmarking experiments further establish the scalability and efficiency of the implementation. Strong scaling benchmarks show that increased computational resources reduce network connection and state propagation times, while weak scaling benchmarks reveal only moderate increases in communication costs such as spike and SIC delivery. The framework robustly supports simulations of networks with up to one million cells, validating its applicability for large-scale studies of neuron-glia interactions. This work provides a computationally accessible and reproducible tool for studying the dynamic interplay between neurons and astrocytes. By advancing the integration of tripartite connectivity into large-scale network models, the framework creates new opportunities to investigate glial contributions to synaptic modulation, neural computation, and the pathophysiology of brain disorders such as epilepsy and neurodegenerative diseases.
Acknowledgements: JA is currently AstraZeneca employee, but here presented research was conducted during her previous employment at Tampere University and is unrelated to her current employment.

Disclosures: T. Manninen: None. **H. Jiang:** None. **J. Acimovic:** None. **I. Ahokainen:** None. **J. Stapmanns:** None. **M. Lehtimäki:** None. **M. Diesmann:** None. **S.J. Van Albada:** None. **H.E. Plesser:** None. **M. Linne:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.41/LBP107

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

Title: Leveraging self-supervised electroencephalography representation learning to improve schizophrenia diagnosis using deep learning

Authors: *D. GENARO[1], S. CHATTERJEE[1], D. MACCRIMMON[2], S. COLIC[1];
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Abstract: Despite decades of study, schizophrenia lacks reliable biomarkers, making diagnosis largely reliant on clinical interviews. Electroencephalography (EEG) provides a means to study real time brain activity in an affordable, non-invasive manner. EEG data tends to be high-dimensional and difficult to analyze; however, advances in deep learning techniques can be used to extract meaningful patterns in these signals. In this study, we first trained a convolutional neural network (CNN) on EEG spectrograms to classify clozapine-treated patients from healthy controls. Clozapine, a drug prescribed exclusively for treatment-resistant cases, served as a reliable proxy for schizophrenia in this population. The initial CNN showed a bias toward the clozapine class and required extensive training times; but it reached 78% accuracy and a receiver operating characteristic-area under the curve (ROC-AUC) of 76%. In pursuit of improvement, we trained a convolutional auto-encoder on over 34,000 EEG recordings, several of which were unlabelled, giving the model an opportunity to learn compact, general features from the EEG spectrogram. By then freezing the encoder and inserting a lightweight CNN classifier, model performance improved to 85% accuracy and ROC-AUC of 92%, whilst simultaneously reducing training time eightfold. This coupling of encoder and CNN also required less EEG data during training, further enhancing model effectiveness. Notably, this work motivates the possibility of an EEG foundation model: a model that could leverage large-scale unlabelled data to not only improve schizophrenia diagnosis, but extend to other psychiatric disorders where sufficient data may not be readily available.

Disclosures: D. Genaro: None. **S. Chatterjee:** None. **D. Maccrimmon:** None. **S. Colic:** None.

Late-Breaking Poster

LBP022: J.06. Computation, Modeling, and Simulation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP022.42/LBP108

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

Support: Research supported by Università Vita Salute San Raffaele through seed funding of the MINE Lab
Bertarelli Foundation

Title: Combined neuroelectric-musculoskeletal modeling of single-finger movements evoked by peripheral nerve stimulation

Authors: *N. GIANNOTTO[1,2], C. VERARDO[3,2], E. LOSANNO[3], F. AGNESI[4], S. SHOKUR[5], S. MICERA[5], S. ROMENI[4];
[1]Scuola Superiore Sant'Anna in Pisa, Pordenone, Italy; [2]Equally contribution, Pisa, Italy; [3]Scuola Superiore Sant'Anna, Pisa, Italy; [4]Modular Implantable Neuroprostheses (MINE) Laboratory, Univ. Vita-Salute San Raffaele & Scuola Superiore Sant'Anna, Milan, Italy, Milano, Italy; [5]EPFL, Geneva, Switzerland

Abstract: Our group recently reported the results of a first-in-human trial to restore independent finger movements in chronic tetraplegia using intraneural stimulation of the median and radial nerves. Here, we present a hybrid computational framework supporting two key related applications: (1) pre-operative planning, predicting which movements and grasps are achievable by stimulating specific nerves robustly to anatomical variability; (2) interpretable performance assessment, shifting implant evaluation from traditional neurophysiological metrics to biomechanical endpoints (e.g., percentage of the range of motion). To this end, our computational framework couples detailed neuroelectrical modeling of peripheral nerve stimulation with musculoskeletal forward dynamics to predict evoked functional hand dynamics. The neuroelectric component predicts recruitment patterns of motor and sensory fibers upon injection of electric currents from the implant active sites. Specifically, induced electric potential fields are simulated through finite-element modeling in COMSOL Multiphysics and then input to machine learning-based predictors of fiber activation trained to reproduce the behavior of multicompartmental axon models implemented in NEURON. The musculoskeletal component maps motor fiber recruitment into muscle activations, which are used to predict the hand joint dynamics via forward dynamics in MyoSuite's MyoHand. We have applied our framework to the setup of intraneural stimulation performed by our team in our clinical trial, studying the performance of a transverse intrafascicular multichannel electrode (TIME) implanted in the anterior and posterior interosseous nerves, branches of the median and radial nerves responsible for the innervation of multiple extrinsic hand muscles. The selectivity of evoked finger movements is evaluated across several TIME insertions and plausible internal topographies of the targeted nerves. Simulations revealed that even minimal neural recruitment can elicit full-range finger motion, highlighting the importance of assessing implant performance in the

kinematic domain for fine-movement restoration applications. Looking forward, our framework may be extended to different nerve structures, implant designs, and optimization routines to enhance functional selectivity. Furthermore, the framework may be tailored to patient-specific anatomy to support personalized surgical planning and neuroprosthetic operation, thereby accelerating the adoption of peripheral nerve stimulation as a clinically effective motor restoration technique.

Disclosures: N. Giannotto: None. **C. Verardo:** None. **E. Losanno:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Action Potential Neurotechnology Srl. **F. Agnesi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Action Potential Neurotechnology Srl. **S. Shokur:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Action Potential Neurotechnology Srl. **S. Micera:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); WO2024095142A2, Action Potential Neurotechnology Srl. **S. Romeni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); WO2024095142A2.

Late-Breaking Poster

LBP023: J.07. Data Analysis and Statistics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP023.01/LBP109

Topic: J.07. Data Analysis and Statistics

Support: Polish National Science Centre (SHENG 02.SS.113)
Polish National Agency for Academic Exchange (BPN/BEK/2023/1/00204/DEC/01)

Title: Neural Mechanisms of Compulsive Sexual Behavior Disorder: Insights from Large-Scale fMRI and EEG Studies

Authors: *M. GOLA[1], I. SZUMSKA[2], C. LACADIE[3], A. STANISZEWSKA[4], D. STELMASZYNSKA[2], M. N. POTENZA[5];
[1]UCSD / Polish Academy of Sciences, San Diego / Warsaw, CA; [2]Institute of Psychology, Polish Academy of Sciences, Warszawa, Poland; [3]Yale University, Department of Diagnostic Radiology, New Haven, CT; [4]Institute of Psychology, Polish Academy of Sciences, Warsaw, Poland; [5]Dept Psychiat, Yale Univ Sch Med, New Haven, CT

Abstract: Compulsive Sexual Behavior Disorder (CSBD) was recently included in the 11th edition of the International Classification of Diseases (ICD-11; WHO, 2022), reflecting growing recognition of its clinical relevance. Individuals with CSBD report impaired control over sexual

behavior (e.g., excessive pornography use, paid or risky sex, chemsex) and their negative life consequences. While clinical descriptions are well established, the underlying neurocognitive mechanisms remain insufficiently understood; this is what we aim to change with advanced computational modeling and neuroimaging.
We applied connectome-based predictive modeling (CPM) to fMRI data from an Incentive Delay Task (IDT; Gola et al., 2017) with erotic and monetary trials in 190 men (116 treatment-seekers, 74 controls). Functional connectivity across 268 nodes was modeled to predict CSBD severity ($r = 0.1698$, $p = 0.019$, 10,000 permutations). The positive network linked stronger salience-medial frontal-frontoparietal coupling with higher severity, whereas the negative network linked weaker salience-sensorimotor connectivity with greater symptoms. Overlap analyses highlighted the central role of salience, medial frontal-sensorimotor coupling, and cerebellar hubs.
To extend these findings, we adapted the IDT for EEG and tested 66 participants (33 CSBD, 33 controls). Reward prediction error signals, reflected in Feedback-Related Negativity (FRN) and P300, interacted with reward type: significant effects emerged in erotic but not monetary conditions. This indicates context-dependent alterations in reward learning, with erotic stimuli driving distinct neural responses.
Together, our results show that distributed connectivity patterns activating within specific contexts, rather than isolated regions and general alteration of reward processing, predict CSBD symptoms. CPM provides the first large-sample, data-driven model of CSBD, identifying targets for future EEG studies. Crucially, CPM facilitates translation of fMRI-derived markers into EEG, and EEG enables cost-effective, non-invasive, multi-site and longitudinal studies as well as treatment evaluation in CSBD.

Disclosures: **M. Gola:** A. Employment/Salary (full or part-time); Institute of Psychology, Polish Academy of Sciences, Institute for Neural Computations, University of California San Diego. 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.; Polish National Science Centre (SHENG 02.SS.113) Towards an integrative model of reward prediction error in compulsive sexual behavior, substance and behavioral addictions: ERP study., Polish National Agency for Academic Exchange (BPN/BEK/2023/1/00204/DEC/01). **I. Szumska:** None. **C. Lacadie:** None. **A. Staniszewska:** None. **D. Stelmaszynska:** None. **M.N. Potenza:** None.

Late-Breaking Poster

LBP023: J.07. Data Analysis and Statistics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP023.02/LBP110

Topic: J.07. Data Analysis and Statistics

Title: Inter-brain Complexity Synchronization as a novel approach to understand human teaming

Authors: J. C. BRADFORD[1], ***S. SULLIVAN**[2], J. SCHLEGEL[3], B. STORY[1], T. JACKSON[3], K. MAHMOODI[1], D. L. BOOTHE[1], S. KERICK[1];

[1]US Army DEVCOM, US Army Research Laboratory, Aberdeen, MD; [2]Army Research Laboratory, Aberdeen, MD; [3]United States Military Academy, Cornwall, NY

Abstract: Complexity Synchronization (CS) captures coordination and information flow between systems by tracking how their complexity co-varies over time. While CS has been observed within individuals across organ networks, it has not been applied between people. We introduce a novel use of CS to capture inter-brain dynamics during teaming. Unlike hyperscanning metrics influenced by shared stimuli or stationarity assumptions, CS analyzes signal complexity and detects coordinated fluctuations in scale-free dynamics. We measured the neural activity of Soldier teams performing a complex, real world task. We hypothesized that inter-brain CS emerges during teaming. Fourteen healthy subjects paired in dyads completed a resting baseline and six rhythmic tasks: two clapping tasks (clapping to music, leader/follower), three instrumental tasks (playing familiar, unfamiliar, and improvised pieces), and a listening task. We recorded 64-channel EEG synchronized with the audio recording of each musician. Inter-brain CS was computed by correlating (ρ) partners' scaling-index trajectories δ(t) derived via Modified Diffusion Entropy Analysis (MDEA). Questionnaires assessed individual experience, partnership history, and familiarity with paired partner; trial-level errors were scored. Preliminary results shown in Figure 1.

A

CS (ρ) with annotated significance per condition per dyad							
Trial	*Dyad01*	*Dyad02*	*Dyad03*	*Dyad04*	*Dyad05*	*Dyad06*	*Dyad07*
Resting Baseline	-0.1071	0.0798	0.0741	0.0528	0.0682	0.0639	0.0368
Clapping	**0.3148*** **	**0.4112*** **	0.0804	**0.2997*** **	0.2008	-0.0544	**0.2295***
Leader-follower clapping	0.1112	0.0660	0.0180	-0.0196	-0.0871	-0.1127	-0.0756
Familiar Music	**0.2739** **	-0.1920	0.1479	-0.0428	**0.4134*** **	**0.2240***	0.0200
Unfamiliar Music	0.0394	0.1307	0.0103	**0.3425*** **	**0.2469***	0.0328	0.0258
Improvisation	**0.4160*** **	**-0.2821*** **	**0.2635*** **	**0.2284** **	**0.2377** **	**-0.2429** **	-0.0706
Active Listening	0.1705	-0.0598	-0.0776	0.0557	0.0989	-0.0376	0.0128

B

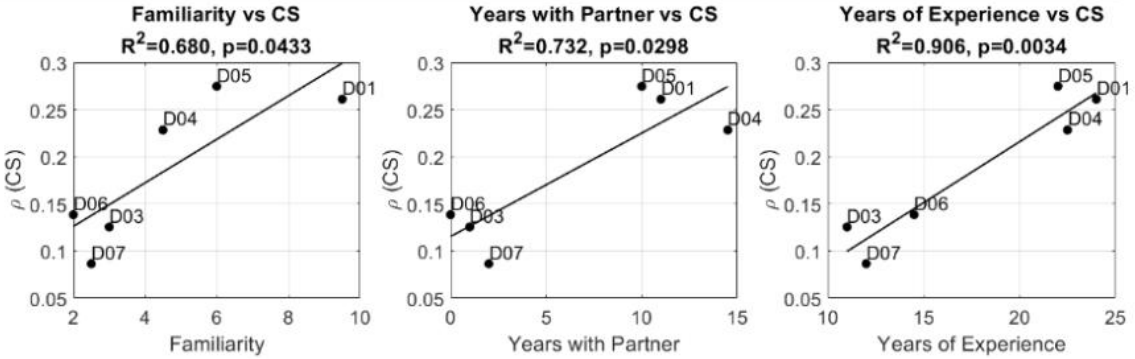

Figure 1. Preliminary results **A.** Correlation between partners' channel-averaged MDEA δ trajectories; * p < .05, ** p<0.01, ***p<0.001; underlined denotes close to significance. **B.** Scatter-plots show dyad-level synchrony strength (|ρ|, averaged across dynamic trials) versus averaged partner familiarity, years of partner experience, and individual musical experience; lines depict linear fits with R^2 and p-values shown on each panel.

This study introduces the first use of CS to track teaming via neural signals. Significant inter-brain CS emerged during interactive tasks like improvisation and synchronized playing, but not during passive conditions such as listening or rest. This shows CS is sensitive to active coordination rather than shared stimuli. Familiarity, experience, and partnership were also positively associated with CS, suggesting that prior relational history contributes to neural coupling. Together, these findings establish CS as a robust technique for measuring real-time coordination in teams.

Disclosures: J.C. Bradford: None. **S. Sullivan:** None. **J. Schlegel:** None. **B. Story:** None. **T. Jackson:** None. **K. Mahmoodi:** None. **D.L. Boothe:** None. **S. Kerick:** None.

Late-Breaking Poster

LBP023: J.07. Data Analysis and Statistics

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP023.03/LBP111

Topic: J.07. Data Analysis and Statistics

Title: Detecting large-scale neuronal activity changes in astronauts aboard the ISS using EEG microstate analysis

Authors: *K. ARMONAITE[1,2,3], L. CONTI[2,3,4], P. CROCE[5], L. NARICI[6,3], M. PIANA[7], S. SOMMARIVA[7], F. ZAPPASODI[5], F. TECCHIO[8,2];
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Abstract: Crewed spacecraft missions in near-Earth orbit rely heavily on the well-being of astronauts, who are exposed to microgravity, high radiation doses, demanding tasks, and other harsh environmental conditions. In this context, our study contributes to a better understanding of astronauts’ brain activity by investigating the emergence of large-scale neuronal networks. In this study, we analyzed electroencephalography (EEG) data from astronauts who participated in the ALTEA (Anomalous Long-Term Effects in Astronauts) experiment aboard the International Space Station (ISS). After investigation of oscillatory activity in the resting wakefulness state using power spectrum analysis, we found that in space the delta frequency band was greater than the alpha band (in contrast to the ground control group, $p = 0.01$). However, the frequencies of the alpha peak maximum and width remained comparable to those observed on ground. We then examined the emergence of large-scale neuronal networks through microstate analysis. Microstates are recurrent topological configurations of electrical activity, each characterized by a specific duration and reoccurrence pattern. In our study, five microstates consistently emerged across all astronauts and recording sessions, showing topographies comparable to the canonical

ones (A, B, C, D, and E) observed on the ground. Each of these microstates exhibited a similar duration in space and on ground ($p = 0.1$). Interestingly, microstate B, often associated with the visual system, explained less global variance (GEV) in astronauts than in the control group ($p = 0.03$). In space, the GEV of microstate B was positively correlated with delta power ($p = 0.03$) and negatively correlated with alpha power ($p = 0.02$). These patterns were not observed on ground control group. The results of our spectral and microstate analyses indicate differences of resting state wakefulness neurodynamics in space and on the ground, suggesting that the ISS environment induces measurable changes in ongoing neuronal electrical activity.

Disclosures: K. Armonaite: None. **L. Conti:** None. **P. Croce:** None. **L. Narici:** None. **M. Piana:** None. **S. Sommariva:** None. **F. Zappasodi:** None. **F. Tecchio:** None.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP023.04/LBP112

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant 1R01AR083626-01
NIH Grant R01DK121724

Title: Independent component analysis identifies functional subregions of the human thalamus and their cortical networks

Authors: *J. CHERIN[1], M. HEINDEL[2], J. J. KUTCH[1];
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Abstract: The thalamus serves as both a sensory relay and a regulator of affective processing, making it a critical hub in pain-related brain circuits. Emerging evidence suggests that differences in thalamocortical dynamics may underlie distinct patterns of pain distribution in chronic pain populations. However, most prior work has defined thalamic subregions using anatomical atlases, an approach that risks obscuring functionally distinct subcircuits. The aim of this study was to functionally parcellate the thalamus using group independent component analysis (ICA) and examine the cortical connectivity of the emergent components, providing a functionally grounded framework for future investigations of thalamocortical dysfunction in chronic pain. Resting-state fMRI data from 52 healthy participants (31 males and 21 females; mean age: 28.37±7.48) were analyzed using a thalamus-restricted group ICA. The resulting independent components were then used as seeds in a seed-to-voxel functional connectivity analysis to characterize their distinct cortical networks. Multiple ICAs were run with a varying number of independent components. A four-component solution provided the cleanest separation of the thalamus at the lowest model order, revealing reproducible posterolateral and anteromedial divisions. The functional connectivity analysis demonstrated strong coupling between the

posterolateral component and the occipital, sensorimotor and posterior insular cortices, while the anteromedial component showed strong connectivity with frontal, prefrontal and cingulate regions. These findings demonstrate that group ICA can isolate temporally distinct thalamic subregions whose connectivity profiles align with established sensory and affective thalamocortical circuits. This approach provides a robust foundation for future work investigating how disruptions in specific thalamocortical pathways may contribute to the neural mechanisms underlying chronic pain subtypes.

Disclosures: J. Cherin: None. **M. Heindel:** None. **J.J. Kutch:** None.

Late-Breaking Poster

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Program #/Poster #: LBP023.05/LBP113

Topic: J.07. Data Analysis and Statistics

Title: Neurovlm: A neuroscience vision-language model

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Abstract: Over the past decades, tens of thousands of neuroimaging studies have created an extensive corpus pairing natural language descriptions with brain activation coordinates, forming a rich multimodal dataset. Recent advances in generative and predictive models now enable leveraging this vast knowledge base to fill scientific gaps and accelerate scientific discovery. However, most state-of-the-art vision-language models require billions of parameters and / or extensive computational resources, limiting their accessibility and practicality. In this work, we introduce Neurovlm, a vision-language model that aligns neuroscientific text with coordinate-based brain activation maps. The model supports natural language queries, retrieves literature, and generates predicted activation patterns, thereby unifying text, brain representations, and large-scale scientific knowledge within a single architecture. We trained Neurovlm on a novel dataset of 30,000 fMRI-based text-neuroimage pairs extracted from the literature, alongside 200,000 published papers without coordinates (meaning text-only). We evaluated Neurovlm across three complementary tasks using 10-fold cross-validation. For brain reconstruction, the autoencoder within Neurovlm outperformed atlas-based representations (DiFuMo) across mean squared error, structural similarity index, and Dice coefficient. In the literature ranking and retrieval task, Neurovlm achieved a recall@200 of 0.576±0.009 using SPECTER 2 (a 110M-parameter text encoder), closely matching NeuroConText (0.583±0.014) which used the nearly two orders of magnitude larger, 7B-parameter Mistral LLM. Moreover, for text-neuroimage decoding, Neurovlm surpassed NeuroQuery on the same evaluation metrics used for brain reconstruction. Together, these results demonstrate that while vision-language models for neuroscience benefit from large-scale datasets, they can achieve strong performance with smaller

architectures. Neurovlm, which is openly available, matches or surpasses state-of-the-art systems despite using far fewer parameters. To support further progress, we also release the largest text-neuroimage dataset to date, to encourage benchmarking and foster broader adoption of vision-language approaches in neuroscience.

Disclosures: J. Aguirre-Chavez: None. **R. Hammonds:** None. **B. Voytek:** None.

Late-Breaking Poster

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Topic: J.07. Data Analysis and Statistics

Support: RS-2022-NR069934
RS-2022-NR070502

Title: A preliminary study on cognitive task-induced ERD/ERS assessment with in-ear EEG

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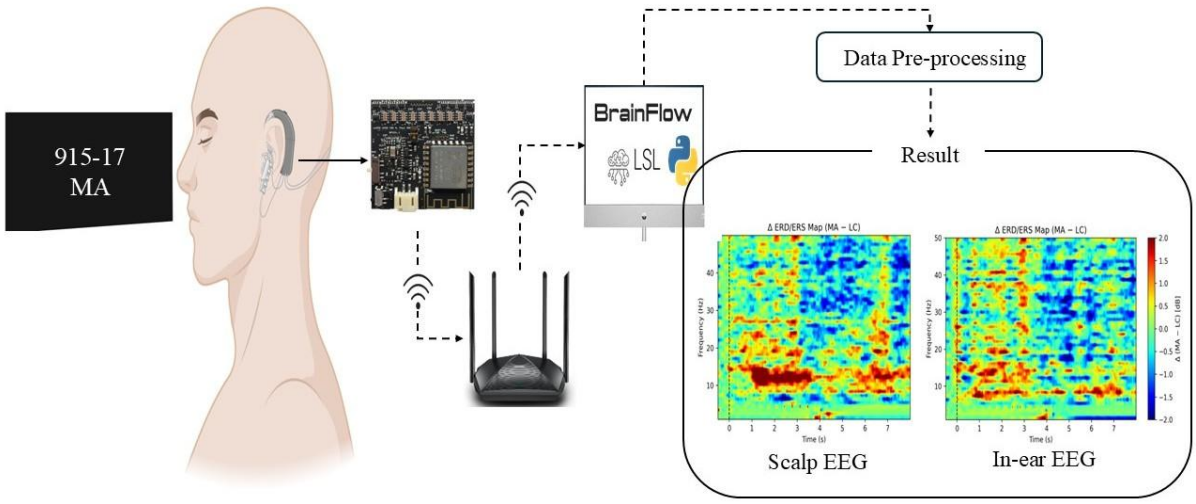
Abstract: EEG-based brain-computer interfaces (BCIs) measure brain responses from external stimuli or intrinsic cognitive states, generating command signals to control external devices. They enable communication and assistive control for patients with neuromuscular impairments (e.g., Motor Neuron Disease, MND), improving quality of life. However, conventional EEG requires expert electrode placement, bulky equipment, and is conspicuous, limiting daily use. To overcome these issues, in-ear EEG has been proposed, placing electrodes in the ear canal to allow self-application and invisibility. Yet anatomical variations often required custom earpieces, complicated fabrication and still relying on large equipment. Also, most in-ear EEG studies have focused on stimulus-induced paradigms, while research on intrinsic paradigms remains scarce despite their potential for daily-life applications. In this study, we developed electrodes using generic earpieces to simplify fabrication and designed a miniaturized wireless PCB board for data acquisition. EEG signals were simultaneously recorded at 1000 Hz from the scalp (2 occipital channels) and ear canals (2 channels) of three participants during mental arithmetic and light cognitive tasks and analyzed using ERD/ERS methods. Results showed that during mental arithmetic, in-ear EEG exhibited alpha-band ERS patterns similar to those observed in occipital scalp EEG, indicating that suppression of visual processing under cognitive load can also be observed with in-ear EEG. In contrast, no significant ERD/ERS patterns appeared during the light cognitive task, suggesting the absence of substantial cognitive load. These findings demonstrate that the proposed electrodes and wireless system can reliably capture subtle EEG

signals and show the potential of in-ear EEG for BCI applications based on endogenous paradigms suitable for daily-life environments.



Disclosures: H. Son: None. **H. Baek:** None.

Late-Breaking Poster

LBP023: J.07. Data Analysis and Statistics

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Program #/Poster #: LBP023.07/LBP115

Topic: J.07. Data Analysis and Statistics

Support: NIMH Grant MH122023

Title: Predicting nicotine dependence from multimodal MRI data

Authors: *P. LASARTE[1], V. OMELYUSIK[1], S. UPTON[2], N. HENIGMAN[2], B. FROELIGER[2], S. S. NAIR[1];
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Abstract: Nicotine addiction is a serious public health issue that affects millions and leads to long-term adverse health risks. It is associated with major changes in brain circuitry, detectable in both anatomical and functional imaging data. Traditional methods for analyzing these changes focus on statistical comparison of pairwise signal-based connectivity, often using generalized linear modeling (GLM). However, the complex brain-wide nature of this condition poses the question of whether more advanced non-linear analysis techniques, such as those used in machine learning (ML) applications, can reveal additional neural signatures underlying nicotine addiction.

We analyzed anatomical and resting-state MRI recordings from 101 subjects across two nicotine dependence studies. For each subject and region of interest (ROI; 68 total, DK atlas), we computed anatomical (surface area, gray matter volume, etc., 8 total) and functional (average BOLD signal per ROI) characteristics and estimated correlation-based between-ROI similarity for each modality. We then investigated whether these data could predict the total self-reported nicotine dependence score (i.e., FTND). We considered the characteristics data and the similarity data separately and compared the performance of four models: a baseline chance predictor, a traditional GLM, and two popular ML classifiers, support vector machine with a Gaussian kernel (SVM) and random forest (RF). Additionally, we explored which modality (anatomical-only, functional-only, and their combination) yielded the highest accuracy.
We found that for both the characteristics and similarity datasets, the two ML models predicted FTND with test accuracy significantly above chance (highest accuracy was achieved by SVM, 0.232 vs 0.09, $p < 0.001$, paired t-test) and GLM ($p < 0.001$ in all cases, paired t-test), which performed at chance level. Moreover, SVM's test accuracy significantly differed based on data modality in the characteristics dataset (0.232 vs 0.173 vs 0.204, $p < 0.01$, paired t-test). Findings will be presented in the context of how these analytic approaches may be applied in experimental studies with humans.

Disclosures: P. Lasarte: None. **V. Omelyusik:** None. **S. Upton:** None. **N. Henigman:** None. **B. Froeliger:** None. **S.S. Nair:** None.

Late-Breaking Poster

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Title: Zero-Training Motor-Imagery BCI with Minimal Channels via a Spatio-Temporal Transformer

Authors: *D. GWON[1], M. AHN[2];
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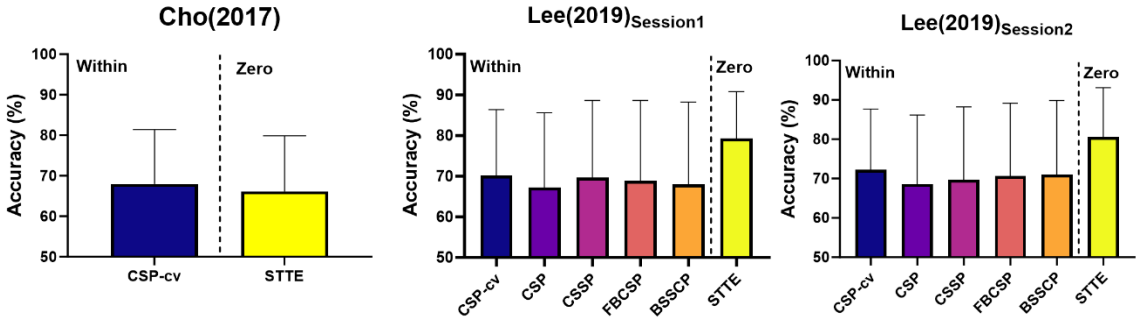
Abstract: Multi-channel electroencephalography (EEG) has been demonstrated to enhance spatial resolution; however, its practical implementation as a brain-computer interface (BCI) is hindered by the complexity of the setup process and the associated computational demands. The proposed method is a calibration-free MI-BCI that effectively learns brain signal dynamics with

a Spatio-Temporal Transformer for EEG (STTE). Two public MI datasets were used (Cho 2017: n=52; Lee 2019: n=54). We used four sensorimotor electrodes (C3, C4, CP5, CP6); signals were band-decomposed from 4-84 Hz in 4-Hz steps. The STTE embeds per-channel time samples into 32-D vectors and adds fixed sinusoidal positional encodings. A spatial transformer (multi-head self-attention with channel attention and residuals) models inter-channel structure. A temporal block applies depthwise-separable convolutions for efficient compression, then a transformer encoder with learnable positional encodings and a class token aggregates trial-level information; a linear head performs classification. Models were optimized with Adam (lr = 2×10^{-4}); early stopping on validation loss controlled overfitting. The model is trained on all other subjects only, ensuring no target-subject leakage. We compare to within-subject baselines—Common Spatial Pattern (CSP), Common Spatio-Spectral Pattern (CSSP), Filter Bank CSP (FBCSP), and Bayesian Spatio-Spectral Filter Optimization (BSSFO)—under their standard preprocessing. On Lee (2019), STTE achieves 79.31% (session 1) and 80.27% (session 2), exceeding within-subject baselines (e.g., CSP-cv 70.16%/72.26%) with paired t-tests, p<0.01. On Cho (2017), STTE (67.15%) is statistically comparable to CSP-cv (68.58%, p<0.01) [Figure 1]. These results indicate that spatial-temporal attention can remove per-user calibration while matching or surpassing strong within-subject pipelines, enabling lightweight MI-BCIs.



Disclosures: D. Gwon: None. **M. Ahn:** None.

Late-Breaking Poster

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CureSHANK
CURE Epilepsy

Title: Toothy: a graphical user interface for dentate spike detection and curation

Authors: *K. N. ESFAHANY[1,2,3], A. L. SCHOTT[2,3], J. M. GROCOTT[2,3], J. S. FARRELL[2,3,4]; [1]Neurobiology, Harvard University, Boston, MA; [2]F.M. Kirby Neurobiology Center, Boston Children's Hospital, Boston, MA; [3]Rosamund Stone Zander Translational Neuroscience Center, Boston Children's Hospital, Boston, MA; [4]Department of Neurology, Harvard Medical School, Boston, MA

Abstract: Although seldom studied, dentate spikes (DSs) - recorded as a positive voltage peak in the local field potential of the dentate gyrus hilus - are the largest physiological brain pattern and are thought to subserve unique hippocampal computations. Despite growing interest in their functional relevance, no standardized framework exists for detecting, analyzing, or classifying DSs in large-scale electrophysiological recordings. We present Toothy, an open-source graphical user interface for comprehensive DS detection, curation, and classification. Toothy provides a modular, interactive workflow encompassing five key steps: (1) configuration of global parameters and probe geometry, (2) raw data ingestion and preprocessing, (3) detection of hippocampal events, (4) channel selection and manual event curation, and (5) classification of DS subtypes (DS1 and DS2) using current source density (CSD) estimation and principal components analysis. The software supports multiple recording file formats, facilitates waveform review, and allows event labeling based on laminar CSD features. Together, these tools enable robust identification and comparison of DS1 and DS2 events, offering a standardized pipeline for DS research and supporting broader efforts to characterize hippocampal circuit dynamics across species and conditions.

Disclosures: K.N. Esfahany: None. **A.L. Schott:** None. **J.M. Grocott:** None. **J.S. Farrell:** None.

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Whitehall Foundation Grant 2022-08-051
NARSAD Young investigator Grant 31308

Title: A comparison between machine-learning and user-driven approaches to morphometric analyses of microglia

Authors: *J. SHEHU[1], F. MROUE RUIZ[2], K. GROVE[2], J. L. BOLTON[3];
[1]Neuroscience Institute, Georgia State University, Atlanta, GA; [2]Georgia State University Neuroscience Institute, Atlanta, GA; [3]Neuroscience Institute, Georgia State University Neuroscience Institute, Atlanta, GA

Abstract: Microglia, the resident macrophages of the central nervous system, are essential for neural circuit development, neuroprotection, neuroinflammation, and phagocytosis. They exist in diverse morphological states, likely reflecting distinct functional roles. Given their dynamic nature, precise morphometric analysis is crucial for understanding microglial function across physiological and pathological conditions. Imaris software (Oxford Instruments) is widely used for quantifying microglial volume and morphology through 3D-reconstructions. In our previous work, we compared the effects of constitutive CX3CR1-Cre expression on microglial morphology between Cre (+/-) and (-/-) animals using user-driven classification methods that required manual parameter adjustments, such as threshold intensity and background subtraction. However, because samples vary in fluorescence intensity, manual adjustments introduced subjectivity into the analyses. With the integration of a native machine-learning (ML) tool in Imaris v10.1.0, we reanalyzed our data using the AI Trainable Segmentation method. Instead of manual tuning, we trained the algorithm to recognize microglial structures across multiple tissue samples stained with the same marker, despite staining variability. By classifying morphology based on pixel intensity, continuity, and shape, this model reduces human bias and increases reproducibility. When comparing manual- and ML-directed analyses, both approaches produced consistent results with no significant differences in overall morphology. However, the ML approach enabled us to isolate soma and segment volume from total microglial volume, pinpointing where differences originated and providing a more comprehensive morphological profile. This method also allows for accurate quantification of soma volume, segment volume, total volume, process thickness, and improved Sholl intersection analyses in microglia. Overall, the integration of machine learning provides a powerful advance for studying microglial morphology in a high-throughput manner, underscoring the importance of continuously improving and adopting these technologies in neuroscience research.

Disclosures: J. Shehu: None. **F. Mroue Ruiz:** None. **K. Grove:** None. **J.L. Bolton:** None.

Late-Breaking Poster

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Program #/Poster #: LBP023.11/LBP119

Topic: J.07. Data Analysis and Statistics

Support: ERC-2021-STG 101042309
AGYR2021
AARG-22-974392

Title: Brain-wide differences in immediate early genes in (fear) learning

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IPMC, CNRS, Valbonne, France

Abstract: The comprehensive mapping of neural circuits is essential for understanding brain function. Recent advances in histological and imaging techniques have enabled the acquisition of large datasets that scale up to the entire brain and to large experimental groups. However, efficient and accurate quantitative analysis of whole-brain histological datasets still poses significant challenges. To address this, we developed an integrated software suite that enables unbiased whole-brain analysis from 2D histological sections. The suite includes **Aligning Big Brains and Atlases (ABBA)**, a novel tool for the automated registration of 2D brain sections onto 3D reference atlases, and **BraiAn**, a pipeline for multi-channel segmentation, statistical analysis, and interactive visualization. Together, these tools provide a scalable and efficient solution for whole-brain cytoarchitectural mapping. Combining these tools, we performed a comprehensive comparative study of the whole-brain expression of three of the most widely used immediate early genes (IEGs). We systematically compared the brain-wide expression of cFos, Arc and NPAS4, three abundantly used IEGs, across three different behavioral conditions related to memory. Our results highlight major differences in both their distribution and induction patterns, indicating that they do not represent equivalent markers across brain areas or activity states, but can provide instead complementary information. This work highlights the power of our mapping suite for uncovering complex neural activation signatures underlying behavior and opens the door for systematic exploration of brain-wide circuit mechanisms of cognitive functions.

Disclosures: B.A. Silva: None.

Late-Breaking Poster

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Program #/Poster #: LBP023.12/LBP120

Topic: J.07. Data Analysis and Statistics

Title: Auxiliary device for precise stereotaxic placement of deep electrodes in animal models

Authors: *C. ROMÁN[1], R. BELTRAN-RAMIREZ[2], J. MARTINEZ-MENDOZA[3], X. M. BECERRA-GONZÁLEZ[4], J. A. DOMINGUEZ-RAMIREZ[5], A. PADILLA[4], A. CARDENAS[6], I. ROJAS[4], J. VALENZUELA LÓPEZ[4], E. BECERRA LÓPEZ[7], M. IBARRA[7];
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Abstract: The accurate placement of deep electrodes is essential in experimental neuroscience, but conventional stereotaxic procedures may risk cranial damage and increase invasiveness when electrode support structures require additional perforations. To address this limitation, we developed a patented auxiliary device that facilitates the safe and precise insertion of deep electrodes in animal models for laboratory research. The device is designed to be mounted on stereotaxic frames using adjustable clamps, ensuring stability during procedures. It consists of a fixation plate with cavities, an electrode plate equipped with securing elements, and an oval opening that allows direct access to the skull. Additional perforations accommodate the animal's ears, ensuring correct positioning and minimizing movement. A sliding electrode frame with a translucent interchangeable sheet provides accurate guidance for electrode placement, reducing the likelihood of tissue damage. The device also integrates an ejection system that allows rapid replacement of electrode frames, thereby supporting multiple insertions in a reproducible manner. Proof-of-concept demonstrations in small animal models confirmed that the device simplifies electrode placement, ensures skull immobilization, and provides secure and repeatable trajectories for deep brain access. By reducing unnecessary perforations and mechanical stress, the system enhances animal welfare and improves experimental reliability. This auxiliary stereotaxic device represents a novel approach for electrode implantation in preclinical neuroscience. Its patented design emphasizes precision, safety, and reproducibility, making it a valuable addition to the methodological toolbox for neurophysiology, deep brain stimulation studies, and experimental neurobiology.

Disclosures: C. Román: None. **R. Beltran-Ramirez:** None. **J. Martinez-Mendoza:** None. **X.M. Becerra-González:** None. **J.A. Dominguez-Ramirez:** None. **A. Padilla:** None. **A. Cardenas:** None. **I. Rojas:** None. **J. Valenzuela López:** None. **E. Becerra López:** None. **M. Ibarra:** None.

Late-Breaking Poster

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Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP023.13/LBP121

Topic: J.07. Data Analysis and Statistics

Title: Differential blood immune cell signatures in alzheimer's disease.

Authors: *Y. CHEN[1], X. ZHOU[2];
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Abstract: **Introduction:** Alzheimer's disease (AD) is a progressive neurodegenerative disorder where mounting evidence implicates systemic immune and inflammatory pathways in its pathogenesis. However, the current understanding of AD biomarkers remains predominantly centered on central nervous system-derived molecules, with a critical gap in the characterization of accessible peripheral blood-based signatures that reflect disease progression.

Method: Leveraging high-throughput proteomic (ADNI-SomaScan; N=739) and transcriptomic (ADNI-Blood Transcriptome; N=736) data from the Alzheimer's Disease Neuroimaging Initiative (ADNI), we sought to identify these replicable peripheral biomarkers and elucidate their interaction with genetic risk. We employed the xCell Analysis from xCell library to deconvolute both datasets into enriched immune and stromal cell type scores, which were then integrated with clinical phenotyping from ADNIMERGE, which is the phenotype table of ADNI. Multivariate logistic regression analyses, adjusted for patients' sex, race, and age for every visit, were used to identify cell-type signatures associated with diagnostic status across the AD continuum (CN, MCI, AD).
Results: Our analysis revealed significant alterations in peripheral immune cell composition, one being the increase of Erythrocyte levels ($p = 2.40$ E-02) with AD in the proteome result. The most notably variations were of neutrophils and B cells apparent in both results (Proteome- neutrophil $p = 8.36$E-03 & B-cells $p = 4.20$E-02; Transcriptome- neutrophil $p = 6.98$E-03 & B-cells $p = 4.50$E-02), however, results conflict on whether the correlations are positive or negative, making it worth of further investigation. Parallel analysis identified specific dysregulated transcriptomes (e.g., HOMER1, PPIL1) and proteins (e.g., MMP10, YWHAG).
Discussion: Critically, we were able to lock on key proteomic and transcriptomic features that variate in levels as AD Dementia progresses, which could be used to further pin and investigate the specific biological processes that affect AD. These findings illuminate a dynamic peripheral immune response throughout AD progression, highlighting the potential of blood-based immune signatures as accessible biomarkers for disease tracking and patient stratification.

Disclosures: Y. Chen: None. **X. Zhou:** None.

Late-Breaking Poster

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Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP023.14/LBP122

Topic: J.07. Data Analysis and Statistics

Title: Smart Insole-measured Foot Tapping Movements Can Monitor Parkinson’s Disease Symptoms and Progression

Authors: *R. HUA[1], I. ALMUTEB[2], H. LIU[2], Y. WANG[2];
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Abstract: Parkinson’s disease (PD) presents complex motor symptoms that are often difficult to monitor accurately in the community. Wearable technologies offer a promising solution by enabling continuous, objective, and real-time tracking of PD symptoms in daily life, thus bridging the gap between clinical observation and actual patient experience. Unlike other wearable devices, smart insoles offer the ability to measure whole-body movements, such as walking, as well as fine-grained movements, like foot tapping. We have developed five versions of accelerometer-based smart insoles and tested them with patients of Parkinson’s disease and

age-matched healthy controls in the community. Compared to gait assessments, fine-grained foot movements of PD patients, such as heel-to-toe tapping, are under investigated in terms of how they can indicate PD symptoms and progression. To fill in the gap, we have developed and tested accelerometer-based smart insoles to measure heel and toe tapping movements in 27 patients with Parkinson's disease and 12 age-matched healthy controls. Referencing test items in MDS-UPDRS, participants were instructed to perform toe tapping and heel tapping: 1) in a continuous manner with their comfortable paces for 10 seconds on the left and right sides, and 2) following light switches to perform in-phase and anti-phase tapping to incorporate the factor of coordination in game settings. Acceleration and timing features were extracted to quantify these continuous movements, including amplitude and rhythmicity. Differences were found between age-matched healthy controls and patients with early-stage and mid-to-late-stage PD in both toe and heel tapping ($p < 0.05$) in all settings. In addition, through the toe and heel tapping motion data, the smart insoles captured individual cases of foot tremors, foot drop, motor function differences between medication ON and OFF status, and motor function changes before and after deep brain stimulation, as well as during stimulation parameter tuning. These preliminary data indicate that the smart Insole-measured foot tapping movements can identify the PD symptoms, differences before and after intervention, and progression between different PD stages. These results suggest that smart insole-measured foot tapping movements may be used as wearable-derived biomarkers to monitor PD symptoms and progression in daily life through simple game settings. Our work on smart insoles and foot tapping motion analysis could be a novel assistive tool to assist clinicians in decision-making and support patients and caregivers to manage PD symptoms and treatments in daily life.

Disclosures: R. Hua: None. **I. Almuteb:** None. **H. Liu:** None. **Y. Wang:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.01/LBP123

Topic: J.08. Methods to Modulate Neural Activity

Support: Wu Tsai Neurosciences (Big Ideas in Neuroscience)
Stanford Wearable Electronics Initiative (eWEAR) seed funding
the Stanford Nano Shared Facilities (SNSF) and Stanford Nanofabrication (SNF)
Schmidt Sciences and Rhodes Trust

Title: Spiral NeuroString: A platform solution for stable, high resolution neural interfacing with soft, elastomeric polymers

Authors: *M. J. WURDACK, M. KHATIB, E. T. ZHAO, S. WEI, K. CHEN, T. ZALUSKA, Z. BAO;
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Abstract: Our understanding of the intricate neural dynamics underlying perception, cognition, memory, learning and behavior are hindered by current methods struggling to capture and induce single neuron resolved brain activity over extended periods in humans. Intracranial neural interfaces provide valuable insights at highest spatiotemporal resolutions; however, they are highly invasive and often induce neuroinflammation, drift and degrade over time; non-invasive methods lack the resolution needed for single-neuron measurements. Advanced silicon manufacturing has enabled neural probes with the largest electrode densities and count, which enabled large scale brain recordings at single-cell resolution, i.e., most notably with the introduction of Neuropixels probes. However, their long-term applications in large animal models and humans are still to be determined. For neuromodulation, traditional metal electrodes exhibit limited lifetimes and stability when exposed to the harsh environment in our brains. Neural implants based on soft materials have shown enhanced biocompatibility and stability. However, reaching with soft materials the required electrode density and count for large scale recording and modulation at single neuron level is an unsolved challenge.
Here we present our innovation, Spiral NeuroString [1], for overcoming the challenge of making soft high-density neural probes, which harnesses 2D high-resolution patterning of soft, low impedance, and electrically conductive elastomers and 3D packing of functional components, i.e., rolling up of the photopatterned 2D sheets into fiber structures. By using our unique fabrication, bonding and crosstalk suppression strategies we can reach electrode density, count, and electrical performance previously only attained with silicon manufacturing. With a Young's modulus of up to 10^6 less compared to silicon, our probes are mechanically compliant in the brain tissue and maintain performance, enabling stable neural recordings and maintained relationships between electrodes and neurons over multiple months.
Ultimately, our probes will help advancing our knowledge in systems neuroscience and connectomics by facilitating chronically stable bi-directional interfacing with brain wide activity at high spatiotemporal resolutions. Our research will provide essential tools for understanding the relationships between microscopic neural dynamics and macroscopic behavior, paving the way for both high-resolution research and targeted therapeutic applications in behaving non-human primates and humans.
[1] M. Khatib et al., bioRxiv (2023), in press at *Nature*.

Disclosures: M.J. Wurdack: None. **M. Khatib:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Filed patent application related to this technology (63/528846). **E.T. Zhao:** None. **S. Wei:** None. **K. Chen:** None. **T. Zaluska:** None. **Z. Bao:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Filed patent application related to this technology (63/528846).

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

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Program #/Poster #: LBP024.02/LBP124

Topic: J.08. Methods to Modulate Neural Activity

Title: Preserving stimulation-evoked iEEG dynamics through targeted artifact removal

Authors: *M. TOUFANI[1], G. ACHARYA[2], E. NOZARI[3];
[1]Neuroscience, University of California Riverside, Riverside, CA; [2]University of California, Riverside, Riverside, CA; [3]Mechanical Engineering, Univ of California, Riverside, Riverside, CA

Abstract: The most valuable milliseconds in neuromodulation are the ones we routinely throw away. In particular, stimulation-site channels are routinely discarded because short-latency, high-amplitude artifacts obscure the true response. Standard approaches—band-limited filtering, interpolation, or template subtraction—introduce systematic distortions and fail to preserve underlying neural dynamics. We present and preliminarily validate an event-locked preprocessing pipeline that removes near-site stimulation artifacts while preserving evoked iEEG activity.In the proposed artifact removal algorithm, corresponding to each biphasic stimulation pulse a strict 9 ms window centered on the detected peak response (−2ms to +6ms) was excised and reconstructed via cubic-spline interpolation followed by smoothing only at interpolated samples using an 11ms, third-order Savitzky-Golay filter. To avoid filter-induced ringing and remove high-frequency artifacts, a 95 Hz low-pass and 60 Hz notch were applied after reconstruction. The proposed approach was tested on multichannel iEEG data from a single patient with drug-resistant epilepsy undergoing clinical monitoring (1,000 Hz sampling; 92 channels), made publicly available as part of the Restoring Active Memory (RAM) Parameter Search (PS2) dataset. A total of 276 stimulation events, each lasting 500 ms, were analyzed under 10, 25, and 50 Hz stimulation, with artifacts time-locked to onset and offset of each pulse train. Performance was quantified by comparing the correlation between the processed signal and subsequent artifact-free, length-matched segments and similar baseline correlations from unprocessed data. These differences were calculated per window, summarized by channel and stimulation frequency, and aggregated across all channels. The proposed pipeline achieved the strongest preservation of evoked dynamics (overall difference in correlation: +0.147; 10 Hz: +0.151; 25 Hz: +0.146; 50 Hz: +0.146), outperforming filter-only processing (+0.043), multiple template-subtraction variants (mean-scalar plus intercept: +0.013; weighted-scalar: +0.013; median-scalar: +0.007), and PCA projection-based approaches (rank-1: −0.069; rank-2: −0.141). By recovering stimulation-site data often discarded, our pipeline expands the usable fraction of stimulation-evoked iEEG for neuromodulation research. Statistical rigor, spectral validation, and direct comparisons with alternative methods set a new standard for artifact removal, enabling more accurate insight into how electrical stimulation modulates brain activity.

Disclosures: M. Toufani: None. **G. Acharya:** None. **E. Nozari:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.03/LBP125

Topic: J.08. Methods to Modulate Neural Activity

Title: Modulation of c. elegans neural excitability via non-invasive electrical stimulation

Authors: *V. L. KAMARA, D. R. ALBRECHT;
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Abstract: Electrical stimulation can improve the symptoms of psychiatric and neurodegenerative disorders, such as Parkinson's disease, depression, and epilepsy, by modulating neural pathways and restoring chemical balance. How optimal stimulation parameters (magnitude, polarity, frequency, and localization) vary among patients, disorders, and medication states remains an active research area, yet can be difficult to study systematically in humans. Here, we leveraged optogenetics, microfluidics, and a programmable electrical stimulator to examine the impact of unbalanced unipolar and charge-balanced bipolar stimulation waveforms on neural excitability. We chose the C. elegans nematode for its compact nervous system, shared neurochemical and genetic homology with humans, and the tools available for neural imaging and genetic manipulation.

Young adult NZ1091 animals co-expressing Chrimson, a red-light excitable cation channel, and a GCaMP fluorescent calcium sensor in AWA neurons were loaded into dual-channel, serpentine microfluidic devices filled with S. Basal buffer solution and paralyzed with tetramisole for imaging. Each experiment consisted of 20 one-minute trials with 10s optogenetic activation. Control animals only received optical stimulation, while the experimental group additionally experienced current-controlled electrical stimulation every other trial.

Unipolar stimulation was orientation-dependent: at 1.6mA or greater, head-positive animals were directly activated by electrical stimulation and showed over 3-fold increased excitability to optical stimulation, while head-negative animals showed direct hyperpolarization and no response to red light. Post-stimulation, the orientation-dependent modulation was reversed, suggesting a temporary, compensatory change to neural excitability. Responses were consistent across consecutive trials. Bipolar electrical stimulation caused an increase in excitability for both orientations, followed by a decrease in excitability after removal.

These results indicate the importance of stimulation parameters on neural modulation and demonstrate the applicability of this platform for systematically determining parameter effects. In particular, orientation-independent biphasic pulses are useful for behavioral studies with freely navigating animals, for example, to restore motor function in C. elegans Parkinson's model. Understanding the link between electrical stimulation and neurobehavioral outcomes will help guide clinicians to better manage patient-specific outcomes.

Disclosures: V.L. Kamara: None. **D.R. Albrecht:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.04/LBP126

Topic: J.08. Methods to Modulate Neural Activity

Title: Non-volitional swallowing induced via surface stimulation of the superior laryngeal nerve: foundation for targeted neuroplastic dysphagia rehabilitation

Authors: S. SCHAEFFER[1], E. MYERS[2], A. SCHROEDER[3], ***T. E. LEVER**[1], M. AWADALA[1];
[1]Univ. of Missouri, Columbia, MO; [2]Univ. Hosp., Columbia, MO; [3]Univ. of Missouri Syst., Columbia, MO

Abstract: Neurological disorders, neck surgery, and head and neck cancers commonly cause swallowing impairment (dysphagia), resulting in diminished quality of life and increased morbidity/mortality from aspiration pneumonia. This risk stems from degeneration or injury of superior laryngeal nerve (SLN) afferents innervating the upper airway, which disrupt sensory input to the brainstem central pattern generator for swallowing (CPGsw), impairing initiation and coordination of the motor swallowing response. Existing therapies are primarily palliative or nonspecific, rarely address underlying neural pathology. The SLN's superficial location within the carotid triangle of the anterior neck suggests it may be amenable to noninvasive surface electrical stimulation to restore lost sensory signaling, re-engage damaged pathways, and induce neuroplastic changes in the CPGsw. Over the past decade, we used invasive surgical approaches in rodents to identify electrical stimulation parameters that activate SLN afferents and robustly evoke rhythmic swallowing, demonstrating direct recruitment of central swallowing networks. Here, we translate these findings into humans using noninvasive transcutaneous electrical nerve stimulation targeting the SLN (TENS-SLN). Ten healthy adults (5 males, 5 females, age 20-40) were enrolled in this pilot study. SLN localization within the carotid triangle was achieved via surface anatomy palpation and ultrasound when needed. Proprietary TENS-SLN stimulation parameters were delivered via surface electrodes positioned over the presumed SLN location in the carotid triangle. Non-prandial (non-feeding) swallows were confirmed using laryngeal EMG, detection of brief apnea in the respiratory trace, and visual observation via webcam or laryngoscopy. Vital signs were continuously monitored for safety. Preliminary results show TENS-SLN reliably evoked 3-4 rhythmic swallows per 20-second stimulus train in 9/10 participants, reproducible over three 5-minute blocks without evidence of fatigue or significant changes in vital signs. These findings support the safety and effectiveness of TENS-SLN to directly engage sensory and central neural pathways essential for swallowing, mechanistically lowering the threshold for involuntary swallowing reflex activation and promoting neuroplasticity within the CPGsw. Additional subjects are being recruited to strengthen statistical validity. This TENS-SLN approach represents a promising foundation for restoring swallowing and reducing aspiration risk by addressing the neural basis of dysphagia.

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Late-Breaking Poster

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Program #/Poster #: LBP024.05/LBP127

Topic: J.08. Methods to Modulate Neural Activity

Support: ERC Adv grant Holovis 885090
NIH grant RF1NS128772
Sorbonne Univ. Emergence grant - PARSEC
NIH grant NS136027

Title: Expanding the limits of two-photon holographic optogenetics through pulse-peak intensity optimization

Authors: *D. TANESE[1], C. CHAN[1], D. DE DIETRICH[1], C. GRIMM[1], B. FORGET[1], Y. ZAOUTER[2], E. PAPAGIAKOUMOU[1], V. EMILIANI[1];
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Abstract: Two-photon (2P) holographic illumination enables multi-target optogenetic stimulation with single-cell and millisecond precision in vivo. With recent advances in high-power laser technology, the number of achievable targets is now limited primarily by tissue heating rather than available power. Low-repetition-rate sources improve efficiency by exploiting the inverse dependence of 2P absorption on repetition rate, thereby reducing the average power, and are currently the most widely used sources for multitarget 2P optogenetics. Here, we show that their efficiency can be further enhanced by combining low repetition rates with a pulse compressor stage to shorten their pulses. In this case, however, a trade-off must be found between increased peak power and the nonlinear photodamage threshold. We present a holographic system driven by a high energy fiber laser incorporating a nonlinear compression stage delivering up to 35 µJ pulse energy at 0.5 MHz (17.5 W average power) at 1030 nm with excellent beam quality (M^2 <1.2). The compression stage produces 50-70 fs pulses at the sample plane, yielding a 5-7-fold increase in peak intensity compared to the uncompressed source and ~200-fold compared to a conventional 80 MHz, 120 fs Ti:Sapphire oscillator. *In-vitro* experiments in neurons expressing ChroME and GCaMP7 enabled robust multi-cell optogenetic activation at reduced average power, below the nonlinear photodamage threshold.By concentrating excitation into fewer and shorter high-energy pulses, this strategy minimizes tissue heating while expanding the number of simultaneously addressable targets. Combined with large field holographic light-patterning, it offers a scalable route to mesoscale, single-cell-precise optogenetic control in the mammalian brain.

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Late-Breaking Poster

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Program #/Poster #: LBP024.06/LBP128

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant UF1NS116241
NIH Grant R01NS118188
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NSF Grant 1926668

Title: All optical neural recording and cell-specific patterned optogenetic stimulation in a freely moving mouse using a MEMS based two-photon miniscope (Opto2P-FCM)

Authors: G. L. FUTIA[1], M. ZOHRABI[2], C. M. MCCULLOUGH[3], A. TEEL[1], F. M. SIMOES DE SOUZA[4], R. OROKE[5], B. N. OZBAY[6], K. KILBORN[7], V. M. BRIGHT[5], D. RESTREPO[8], J. T. GOPINATH[5], ***E. A. GIBSON**[1];
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Abstract: Multiphoton microscopy combined with optogenetic photostimulation is a powerful technique in neuroscience enabling precise control of cellular activity to determine the neural basis of behavior in a live animal. Two-photon photostimulation has taken this further by allowing interrogation at the individual neuron level. However, it remains a challenge to implement imaging of neural activity with cell-specific patterned two-photon photostimulation in a freely moving mouse. We developed a miniature microscope for high resolution two-photon fluorescence imaging with spatially patterned two-photon optogenetic stimulation. The design incorporates a MEMS scanner for two-photon imaging and a second beam path for patterned two-photon excitation in a compact and lightweight design that can be head-attached to a freely moving animal. We demonstrate spatially localized optogenetics and high resolution MEMS based two-photon imaging in a freely moving mouse. The new capabilities of this miniature microscope design can enable cell-specific studies of behavior that can only be done in freely moving animals.

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Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP024.07/LBP129

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH R01 NS092882
Birdel Fund Mayo Clinic Philanthropy

Title: GPCR-based optogenetic inhibition suppresses pathological and physiological network activity in an acute porcine MTLE model

Authors: F. MIVALT[1], *Y. ELDAR[2];
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Abstract: GPCR-BASED OPTOGENETIC INHIBITION SUPPRESSES PATHOLOGICAL AND PHYSIOLOGICAL NETWORK ACTIVITY IN A ACUTE PORCINE MTLE EPILEPSY MODELF. Mivalt[1*], Daniela Maltais[1*], Karni Lev Bar-Or[2], Yoav Kfir[2], Jiwon Kim[1], Inyong Kim[1], Matan Hershko[2], Ofir Levi[2], Ofer Yizhar[3], Yotam Eldar[2+], Su-Youne Chang[1+], G. Worrell[1+]
[1] Department of Neurology, Mayo Clinic, Rochester, MN, USA[2] Modulight Bio, Boston, MA, USA[3] Department of Brain Sciences, Weizmann Institute of Science, Rehovot, Israel
Abstract: Rationale: Translating optogenetic therapies for drug-resistant epilepsy faces significant challenges in large, gyrencephalic brains due to limitations in light delivery and opsin sensitivity. We evaluated eOPN3, a highly sensitive, red-shifted, inhibitory G-protein coupled receptor (GPCR) opsin, for its potential to modulate seizure networks in a translational porcine model. **Methods:** Using MRI-guided surgery, an optogenetic vector expressing eOPN3 under the excitatory neuron-specific CaMKIIa promoter was injected into the hippocampus (HPC) of Göttingen minipigs (n=3). After a ~3-month expression period, an acute terminal experiment assessed the effects of green light illumination on physiological and pathological hippocampal activity. **Results:** The eOPN3 expression was demonstrated in-vivo HPC using fiber photometry and ex-vivo tissue microscopy. Optogenetic activation of eOPN3 potently suppressed functional connectivity between the anterior nucleus of the thalamus (ANT) and the HPC, reducing brain stimulation-evoked potential (BSEP) amplitude by an average up to 43.9% (95% CI [-52.8%, -34.9%], $p<0.001$). Illumination also broadly suppressed spontaneous local field potential (LFP) power across all frequency bands, with the most pronounced reductions in the alpha (-39.7%, 95 % CI [-53.73, -25.75], $p<0.001$) and beta (-52.1%, 95% CI [-66.70, -37.53], $p<0.001$) bands. Critically, optogenetic inhibition significantly suppressed seizures induced by kainic acid (KA). In two of three subjects, the initial light application terminated early-stage epileptiform activity ($p<0.01$). However, this efficacy was diminished in later, more established seizure states. **Conclusion:** Our findings demonstrate that eOPN3-mediated inhibition can robustly modulate both physiological and pathological ANT-HPC network activity in a large animal model, and supports the therapeutic potential of GPCR-based optogenetics for treating focal epilepsy.

Disclosures: **F. Mivalt:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH R01 NS092882, Birdel Fund Mayo Clinic Philanthropy. **Y. Eldar:** A. Employment/Salary (full or part-time); Modulight Bio.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

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Topic: J.08. Methods to Modulate Neural Activity

Support: NIH RF1NS131069
NIH R01NS124564

Title: High-Pressure Transcranial Focused Ultrasound Stimulation Induces Parameter-Dependent Cell-Type Specific Effects

Authors: S. RAMACHANDRAN[1], ***H. GAO**[1], P. ZOLOTAVIN[2,3], K. LEE[1], C.-Y. YEH[1], M. KIM[1], S. WANG[4], L. LUAN[2,3,5], C. XIE[2,3,5], K. YU[1], B. HE[1,6];
[1]Carnegie Mellon University, Pittsburgh, PA; [2]Department of Electrical and Computer Engineering, Rice University, Houston, TX; [3]NeuroEngineering Initiative, Rice University, Houston, TX; [4]Applied Physics, Rice University, Houston, TX; [5]Department of Bioengineering, Rice University, Houston, TX; [6]Neuroscience Institute, Carnegie Mellon University, Pittsburgh, PA

Abstract: Transcranial focused ultrasound (tFUS) is a promising technique that has been shown to have high spatial precision, deep brain penetration, as well as cell-type specificity in modulating neural circuits. Intracranial electrophysiological recordings can measure neuronal responses to tFUS with high spatial and temporal resolution (Yu et al., 2021), but conventional silicon-based multi-electrode arrays cause artifacts due to electrode vibrations induced by higher-pressure tFUS (Kim et al., 2021). In this study, we establish the capability to perform intracranial electrophysiological recordings during high-pressure tFUS with the aid of recently developed nanoelectric thread (NET) electrodes. We applied the 128-element random array ultrasound transducer H276 (fundamental frequency: 1.5MHz) to stimulate the somatosensory cortex (S1) of anesthetized wild-type rats (n=10) and tested the use of NET probes for recording neuronal activities across a range of ultrasound pressures from 100 kPa to 1300 kPa, as well as ultrasound pulse repetition frequency (PRF) from 30 Hz to 4,500 Hz, and duty cycle (DC) from 0.6% to 60%. We found that the flexible nature of the NET probes mitigates the vibration effect, eliminating resulting artifacts even when pressure levels exceed the typical vibration threshold, at as high as 1300 kPa. We tested a range of ultrasound pressures and found that tFUS responses increase nonlinearly with pressure, providing further evidence for acoustic radiation force as a key mechanism of tFUS neuromodulation. Testing a range of DCs at different pressure levels,

we found that the response curve varies at higher pressure levels, with highest responses coming from the DC being 60% rather than 30%. Testing a range of PRFs, we demonstrated that PRF alone with DC held constant is a significant factor. Both DC and PRF tests showed much higher neuronal responses at all parameters using a high pressure, showing that even parameters which yield no response at low pressure levels can elicit responses using a higher pressure. These findings advance the mechanistic understanding of tFUS and inform optimized stimulation strategies for future translational applications. References:Kim MG, Yu K, Niu X, He B (2021) Investigation of Displacement of Intracranial Electrode Induced by Focused Ultrasound Stimulation. IEEE Trans Instrum Meas, vol. 70, 2021, doi: 10.1109/TIM.2021.3125978. Yu K, Niu X, Krook-Magnuson E, He B (2021) Intrinsic functional neuron-type selectivity of transcranial focused ultrasound neuromodulation. Nat Commun 12:2519 Available at: https://doi.org/10.1038/s41467-021-22743-7.

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Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

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Program #/Poster #: LBP024.09/LBP131

Topic: J.08. Methods to Modulate Neural Activity

Support: Naval Information Warfare Center (NIWC) and the Defense Advanced Research Projects Agency (DARPA) Contract N65236-19-C-8013

Title: Neurodegeneration associated with repeated high-frequency transcranial focused ultrasound

Authors: *A. P. BRNA[1], O. V. FAVOROV[2], T. CHALLENER[3], A. BILIROGLU[4], F. Y. YAMANER[4], R. KEMAL[4], M. ANNAYEV[4], O. ORALKAN[4], D. M. EIDUM[1], S. SIMONS[1], M. P. WEISEND[1], P. M. CONNOLLY[1];
[1]Intelligent Systems Laboratory, Teledyne Scientific Company, Research Triangle Park, NC; [2]Lampe Joint Department of Biomedical Engineering, University of North Carolina, Chapel Hill, NC; [3]Neurology Department, University of North Carolina, Chapel Hill, NC; [4]Department of Electrical and Computer Engineering, North Carolina State University, Raleigh, NC

Abstract: Transcranial Focused Ultrasound (tFUS) is a popular tool for non-invasive neuromodulation which prior testing paradigms have suggested is benign. However, emerging use cases such as clinical therapies and brain-machine interfaces will likely require repeated or long-duration exposures with novel combinations of stimulus parameters (e.g., frequency, focal volume), and the safety of these conditions have not yet been rigorously validated. Therefore, as an initial study we delivered 1.8 MHz tFUS stimulation to the cortex of 4 non-human primates in

4 sessions each of approximately 90 min over 2 weeks. Motor skills were measured daily with a food pellet picking task. Animals were euthanized and the brain sections were processed for histological markers of neurodegeneration (Fluoro-Jade C). While the animals did not show disruption on the behavioral task, there was clear evidence of neurodegeneration in regions associated with short, intermediate, and extended-duration stimulation, but not with unstimulated control tissues in deeper brain areas. Additional neurodegeneration was observed at locations distant from but functionally connected to stimulated regions, consistent with retrograde damage propagated from neuron processes. We discuss alternative causes for the neurodegeneration, and we recommend the use of additional animal studies to understand this phenomenon, especially for novel stimulation paradigms or parameters and applications where extended or repeated exposures are planned. This work was supported by the Naval Information Warfare Center (NIWC) and the Defense Advanced Research Projects Agency (DARPA) under Contract No. N65236-19-C-8013. The views, opinions, and/or findings contained in this abstract are those of the authors and should not be interpreted as representing the official views or policies, either expressed or implied, of the NIWC Atlantic, DARPA, or the Department of Defense. Distribution Statement "A" (Approved for Public Release, Distribution Unlimited)

Disclosures: **A.P. Brna:** A. Employment/Salary (full or part-time); Teledyne Scientific Company. 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.; Naval Information Warfare Center, Defense Advanced Research Projects Agency. **O.V. Favorov:** A. Employment/Salary (full or part-time); University of North Carolina. 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.; Defense Advanced Research Projects Agency. **T. Challener:** A. Employment/Salary (full or part-time); University of North Carolina. **A. Biliroglu:** A. Employment/Salary (full or part-time); North Carolina State University. **F.Y. Yamaner:** A. Employment/Salary (full or part-time); North Carolina State University. **R. Kemal:** A. Employment/Salary (full or part-time); North Carolina State University. **M. Annayev:** A. Employment/Salary (full or part-time); North Carolina State University. **O. Oralkan:** A. Employment/Salary (full or part-time); North Carolina State University. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Defense Advanced Research Projects Agency. **D.M. Eidum:** A. Employment/Salary (full or part-time); Teledyne Scientific Company. 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.; Naval Information Warfare Center, Defense Advanced Research Projects Agency. **S. Simons:** A. Employment/Salary (full or part-time); Teledyne Scientific Company. 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.; Naval Information Warfare Center, Defense Advanced Research Projects Agency. **M.P. Weisend:** A. Employment/Salary (full or part-time); Teledyne Scientific Company. 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.; Naval Information Warfare Center, Defense Advanced Research Projects Agency. **P.M. Connolly:** A. Employment/Salary (full or part-time); Teledyne Scientific Company. 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.; Naval Information Warfare Center, Defense Advanced Research Projects Agency.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.10/LBP132

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH NS123066
Neurelis Inc.
Cadence Neuroscience Inc

Title: QUANTIFYING THE THERAPEUTIC EFFECTS OF INTRANASAL DIAZEPAM ON NEURAL BIOMARKERS IN A CHRONIC PORCINE MODEL OF EPILEPSY

Authors: *F. MIVALT[1], V. SLADKY[1], S.-Y. CHANG[2], I. KIM[1], D. MALTAIS[1], J. KIM[3], V. KREMEN[3], G. A. WORRELL[1], B. BRINKMANN[1];
[1]Mayo Clinic, Rochester, MN; [2]Neurologic Surgery, Mayo Clinic, Rochester, MN; [3]Neurology, Mayo Clinic, Rochester, MN

Abstract: Intro: Implantable neural recording devices enable the development of biomarker-driven therapies for epilepsy. These systems can evaluate physiological biomarkers to guide multi-stage interventions, such as combining neuromodulation with fast-acting pharmaceuticals. The goal of this study was to characterize the core electrophysiological effects of intranasal diazepam and to demonstrate that these neural signatures can be reliably captured by a continuous monitoring system in a large animal model of mesial temporal lobe epilepsy (mTLE). **Methods:** A chronic Kainic Acid-induced porcine mTLE model was implanted with Cadence Alera, the implantable neural stimulating and recording (INSR) device, with an electrode placed in the lesioned hippocampus. Following a weight adjusted intranasal administration of Valtoco® diazepam (2.6 mg/kg), local field potentials (LFPs) were monitored for a 36-hour period and compared against baseline control periods. **Results:** Administration of intranasal diazepam produced distinct and quantifiable effects on neural biomarkers. First, LFP beta band power showed a strong, dose-dependent reactivity to the drug, with a significant positive correlation between its elevation and blood diazepam concentration (Pearson's $r = 0.654$, $p<0.001$). Second, the medication demonstrated clear anticonvulsant activity, significantly decreasing interictal epileptiform discharge (IED) rates by 53.5% (95% CI [29.8 %, 72.6 %) compared to control days ($p<0.001$). **Conclussion:** These results characterize a robust electrophysiological signature of diazepam's therapeutic action in the epileptic brain. The findings demonstrate that key

biomarkers—beta power for target engagement and IED rate for anticonvulsant efficacy—can be effectively quantified with continuous electrophysiological monitoring. This approach validates a method for assessing pharmacodynamic effects in preclinical studies and suggests that these identified biomarkers could serve as reliable endpoints for various neural recording platforms, paving the way for data-driven, closed-loop systems that integrate both neuromodulation and pharmacological interventions.

Disclosures: **F. Mivalt:** A. Employment/Salary (full or part-time); Cadence Neuroscience Inc. **V. Sladky:** None. **S. Chang:** None. **I. Kim:** None. **D. Maltais:** None. **J. Kim:** None. **V. Kremen:** None. **G.A. Worrell:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cadence Neuroscience Inc. **B. Brinkmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cadence Neuroscience Inc..

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.11/LBP133

Topic: J.08. Methods to Modulate Neural Activity

Support: NNSFC Grant 32200916

Title: Patterned odor delivery enables neural population manipulation with single-neuron precision

Authors: *Z. RENCHANG[1], G. SI[2];
[1]Institute of Biophysics, Chinese Academy of Sciences, Beijing, China; [2]Institute of Biophysics, Chinese Academy of Scienc, Beijing, China

Abstract: Abstract: Olfactory systems employ combinatorial receptor codes to represent odors. Systematically probing the combinatorial possibilities of such codes presents unique challenges, creating a bottleneck in understanding olfactory information processing in the central brain. Here, we present a method that mixes a set of primary odorants on demand to activate arbitrary combinations of olfactory receptors, thereby generating diverse and controllable olfactory patterns. We further combine this odor delivery system with customized real-time neural activity analysis software, enabling adaptive generation of odor stimulus sequences for efficient circuit interrogation. The approach is implemented using microfluidics and demonstrated in *Drosophila* larvae. We identified primary odorants for 19 of the 21 larval olfactory receptor neurons (ORNs). Each primary odorant is carefully selected to specifically activate a single type of ORN at an optimal concentration. Using this setup and set of odors, we revealed diverse odor-evoked responses in local interneurons (LNs) of the larval antennal lobe, the first olfactory neuropil: one type of LN exhibited spatially distributed odor representations in its dendrites, while another

displayed distinct odor preference emerging from a large search space of combinations. In the downstream mushroom body, we characterized heterogeneous receptive fields across Kenyon cell populations. The precision and flexibility of this olfactory pattern generator, capable of probing odor space efficiently and at high throughput, provide a powerful tool for systematic studies of how olfactory codes are processed and transformed across neural circuits.

Disclosures: Z. renchang: None. **G. Si:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.12/LBP134

Topic: J.08. Methods to Modulate Neural Activity

Support: Rosetrees Trust and the John Black Charitable Trust Grant ID2021\100054
Medical Research Council MR/X006417/1

Title: Suppression of pathological oscillations with transcranial focused ultrasound

Authors: *J. ERAIFEJ[1], J. TOTH[1], S. HE[1], C. BUTLER[2], A. L. GREEN[1];
[1]University of Oxford, Oxford, United Kingdom; [2]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, United Kingdom

Abstract: Transcranial ultrasound stimulation (TUS) is an emerging method for non-invasive neuromodulation of deep brain structures. However, to date, there is no evidence that TUS can directly modulate disease-related pathological oscillations in the same direction as known therapies. Inspired by clinical deep brain stimulation, in this randomised controlled cross-over study we probed the effects of pallidal TUS pulsed at 130Hz on subthalamic beta-band activity, a biomarker in Parkinson's Disease (PD). Beta-band power reduced in the ipsilateral subthalamic nucleus (STN) by 10.34% (95% CI:3.81% to 16.87%, $p<0.05$, false discovery rate (FDR) adjusted). Beta power reduction was correlated between the ipsilateral (R^2=0.980, $p<0.05$, FDR adjusted), but not contralateral, STN and primary motor cortex. Bradykinesia, as measured by change in reaction time, was also reduced by 17.70% (95% CI:8.95% to 26.41%, $p<0.05$, FDR adjusted). For the first time, we have demonstrated that TUS can suppress pathological oscillations, potentially opening the door for therapeutic TUS.

Figure 2: A) Normalised power spectral density (PSD) in the subthalamic nucleus (STN) for each participant and condition. B) Normalised mean beta power difference in the STN: Group mean beta power difference (GPI-TUS – Ventricle-TUS) in the left and right STN. **C) Normalised mean beta power difference in the primary motor cortex (M1):** Group mean beta power difference between GPI-TUS and Ventricle-TUS in the left and right M1 region. **D) Electrode reconstruction:** Electrode reconstruction of all four participants in MNI space[22]. Electrode numbering convention is shown for reference. *Blue = STN* **E) Network-level**

reduction in beta power during to GPi-TUS: Correlation between M1 beta power reduction and STN beta power reduction in the ipsilateral (left) hemisphere (left panel) and the contralateral (right) hemisphere (right panel). **F) Change in reaction time:** Difference in reaction time relative reduction compared to sham (GPI-TUS – Ventricle-TUS) during the random dot-motion task. **G) Normalised abbreviated Unified Parkinson's Disease Rating Scale part III (UPDRS-III) difference:** Difference presented (GPi-TUS – Ventricle-TUS). *Horizontal lines represent the mean. Each active TUS block was normalised to the*
Suppression of Pathological Oscillations with Transcranial Focused Ultrasound*respective sham block data on that day. GPi=Globus pallidus internus. Vent=frontal horn left lateral ventricle. STN=Subthalamic nucleus, M1=primary motor cortex, LEFT=left hemisphere, RIGHT=right hemisphere, n.s.=non-significant*
Suppression of Pathological Oscillations with Transcranial Focused Ultrasound

Disclosures: J. Eraifej: None. **J. Toth:** None. **S. He:** None. **C. Butler:** None. **A.L. Green:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.13/LBP135

Topic: J.08. Methods to Modulate Neural Activity

Support: NSF grant #2304513
NSF grant ,#2349694
State of Virginia grant, #CCF22-0084-HE

Title: Anatomical TMS phantoms for the investigation of hybrid TMS/DBS treatment protocols using a wearable magnetic shielding cap

Authors: *W. H. LOHR, R. HADIMANI;
Virginia Commonwealth University, Richmond, VA

Abstract: Evidence suggests combining deep brain stimulation (DBS) and transcranial magnetic stimulation (TMS) is not safe for all DBS probe placements, and TMS target locations, though TMS can alleviate several DBS-resistant Parkinson’s disease (PD) symptoms such as dysphagia. Addressing this issue, head phantoms designed for TMS with embedded electric fields (E-fields) probes are used to explore a wearable magnetic shielding cap that can protect implants from periphery E-fields and focalize magnetic fields. Through segmentation of MRI files, 3D printing, and injection molding of clinically significant conductive composites, anatomical head phantoms are created. Brain tissue conductivity remains debated, but reported values lie within a clinically relevant range. Simulations indicate that TMS-induced E-field profiles are largely unaffected by conductivity differences within this range. Anchoring triaxial dipole probes to regions in the brain (M1, DLPFC, ACC, etc.) creates a precise coordinate system for mapping E-fields.

Preliminary E-field measurements in phantoms were cross-validated with Sim4Life simulations, showing less than 5% error. High-permeability composites attenuated up to 30% of low TMS fields (Cohen's *d* effect size) before saturation; when combined with highly conductive layers for eddy-current shielding, saturation dropped markedly and shielding effectiveness increased substantially. Preliminary Ansys Maxwell simulations of shield apertures for focal stimulation (Fig. A) suggest the potential to attenuate over 70% of peripheral E-fields at the cost of *E*-max, while tailored aperture geometries can redirect peripheral magnetic flux toward the focal point (Fig. D). These findings demonstrate the feasibility of creating a multimodal TMS/ DBS treatment, without risking patient safety or device performance, reliant on an effective balance between attenuation and stimulation.

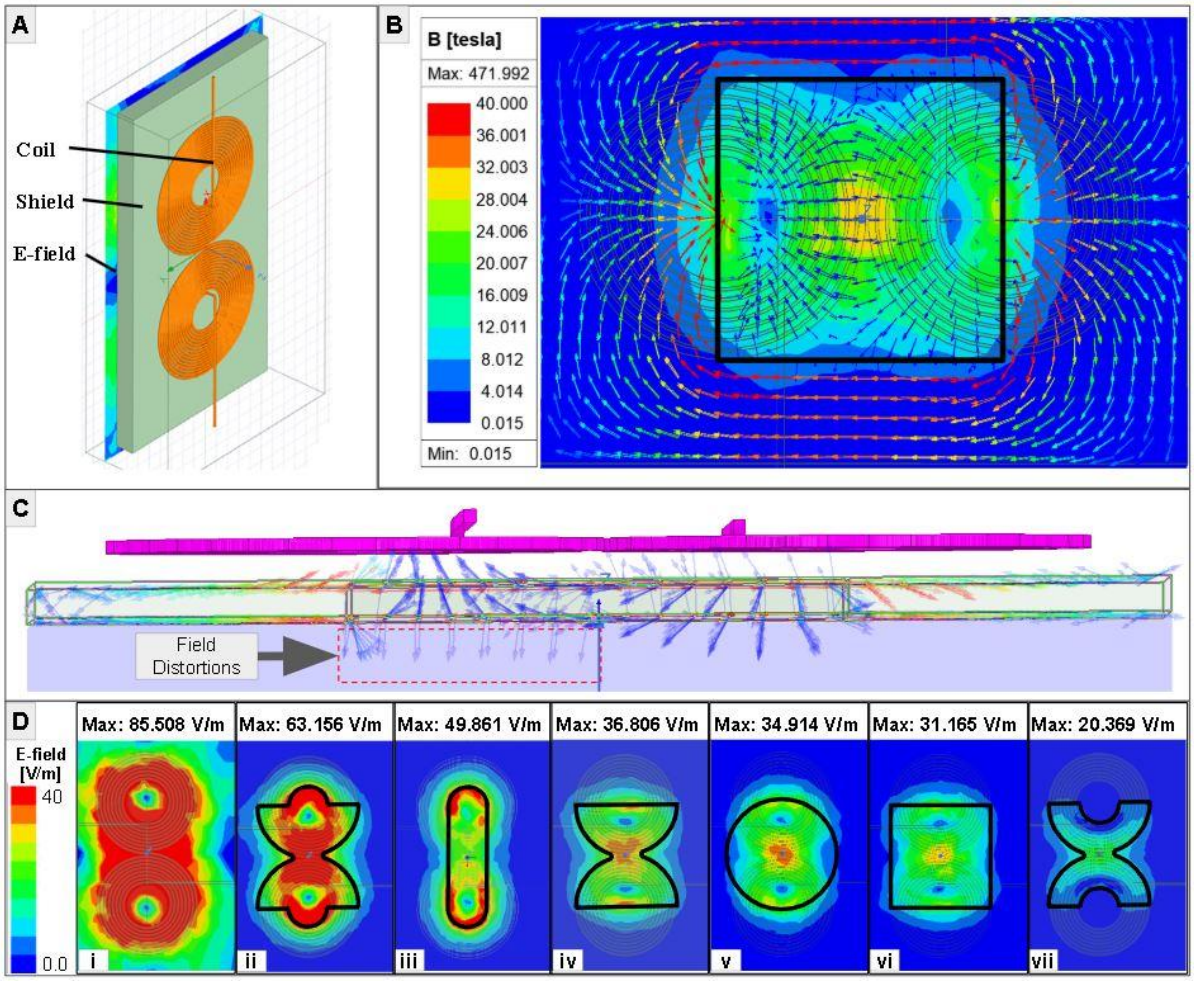

Fig Title. (A) Simulation setup. (B) Top view of magnetic field in shield with square aperture. (C) Side view of the same. (D) Aperture iterations, all set to the same scale.

Disclosures: W.H. Lohr: Other; The PI has created a spinoff company with an exclusive option to license the TMS phantom. So far this phantom is not a commercially available product, nor is it commercially viable. **R. Hadimani:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds);

Hadimani is listed on three patents related to the work. The university is the patent holder for all three..

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.14/LBP136

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant K00NS118719

Title: Long-term sensorimotor cortex sensing using implanted subgaleal leads during deep brain stimulation

Authors: *S. SANDOVAL-PISTORIUS[1], **S. LIU**[2], S. CERNERA[3], P. MCMILLAN VILLALOBOS[2], R. FERNANDEZ-GAJARDO[2], S. S. WANG[4], D. D. WANG[2], S. LITTLE[2], P. A. STARR[2];
[1]UC San Francisco, San Francisco, CA; [2]University of California, San Francisco, San Francisco, CA; [3]Neurological Surgery, University of California, San Fransisco, San Francisco, CA; [4]Neurology, University of California, San Francisco, San Francisco, CA

Abstract: Pathological oscillatory activity in cortico-basal ganglia circuits (BG) is linked to motor symptoms in Parkinson's disease (PD). Sensing-enabled deep brain stimulation (DBS) devices connected to subdural electrocorticography (ECoG) leads over sensorimotor cortex show that changes in oscillatory activity across the cortex-BG motor network correlate with motor signs and therapeutic response. Advances in adaptive DBS (aDBS), which adjusts stimulation based on neural signals, requires identification of neurophysiological biomarkers that correlate with various motor symptoms. Cortical biomarkers are promising feedback signals for aDBS, but limited studies exist due to the invasiveness of subdural ECoG paddles. Using less invasive permanent leads to record cortical activity would reduce risks associated with placing electrodes directly on the brain's surface. This study aims to establish the feasibility of long-term subgaleal (under the scalp) cortical sensing.
Three individuals with PD were implanted with bilateral sensing-enabled DBS devices, each connected to a directional lead targeting the subthalamic nucleus (STN) and a cortical lead placed in the subgaleal space over sensorimotor cortex. For cortical sensing, a cylindrical segmented DBS lead was implanted over one side and a paddle type lead over the other. In clinic, we recorded local field potentials (LFPs) from the STN cortical leads while the study participant was at rest, during movement tasks, and during stimulation amplitude titrations. We also chronically tracked alpha-theta, beta, and gamma LFP power outside of the clinic.
We found that both subgaleal leads were able to detect beta band oscillatory activity at rest. During stimulation amplitude titrations, both subgaleal leads could detect stimulation-entrained finely tuned cortical gamma at half the stimulation frequency. Both leads could detect cortical movement-task-related beta desynchronization. Additionally, both subgaleal leads were able to

detect circadian rhythmicity in chronically tracked frequencies.
These findings suggest that subgaleal cortical recordings can detect sensorimotor activity in physiologically relevant frequency bands.

Disclosures: S. Sandoval-Pistorius: None. **S. Liu:** None. **S. Cernera:** None. **P. McMillan Villalobos:** None. **R. Fernandez-Gajardo:** None. **S.S. Wang:** None. **D.D. Wang:** None. **S. Little:** None. **P.A. Starr:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.15/LBP137

Topic: J.08. Methods to Modulate Neural Activity

Support: New and Emerging Children's Mental Health Researchers Initiative, NECMHR01

Title: Investigating a truncated version of aiTBS in treatment-naive adolescents with depression: an open-label acceptability trial

Authors: *E. LEMKE[1], J. MOSAHEB[1], T. HA[2], K. JAKIMIER[1], A. HERRMANN[1], J. LAGRONE[1], S. O'SULLIVAN[1];
[1]Psychiatry and Behavioral Sciences, Dell Medical School, University of Texas at Austin, Austin, TX; [2]Northwestern University, Evanston, IL

Abstract: Developing novel, safe treatments for adolescent depression is imperative, as depression rates rise and conventional pharmacotherapies exhibit modest efficacy and considerable side effects. Accelerated intermittent theta burst stimulation (aiTBS), a rapid-acting, precision-targeted form of transcranial magnetic stimulation, is cleared by the Food and Drug Administration for treatment-resistant depression in adults but remains understudied in adolescents. This pilot study investigates whether aiTBS can address this urgent need by evaluating its safety, tolerability, and efficacy in treatment-naive adolescents experiencing their first depressive episode. We aim to provide evidence for aiTBS as a first-line treatment. Our two armed study investigates a full-dose and half-dose aiTBS protocol based on prior studies demonstrating rapid remission halfway through the full-dose protocol. We hypothesize half-dose aiTBS will yield comparable antidepressant effects with greater acceptability due to convenience. Both arms will recruit 20 participants each to receive full-dose or half-dose aiTBS in a single-blind open-label design. The primary outcome is change in Children's Depression Rating Scale-Revised (CDRS-R) scores one month post-treatment. Pre- and post-treatment adolescent and parent interviews measure preference, convenience, and satisfaction. Participants undergo brain resting-state functional magnetic resonance imaging before treatment to identify individualized treatment targets and at follow-up visits to assess functional connectivity changes. Participants remain antidepressant and psychotherapy-free for one month post-treatment, then resume standard psychiatric care. The six-month follow-up assesses treatment durability. Three

participants have completed treatment, and no adverse events have been reported. Participant 1 received full-dose aiTBS, while Participants 2 and 3 received half-dose aiTBS. All three achieved remission at one week post-treatment with further decreases in depressive symptoms one month post-treatment. CDRS-R scores fell from 60 to 22, 36 to 17, and 49 to 21 in Participants 1, 2, and 3 from baseline to one month post-treatment, respectively, averaging a 58% reduction in symptoms. Participants 1 and 2 completed the three-month follow-up and remain in remission. These preliminary findings suggest aiTBS is safe and likely efficacious for treatment-naive adolescents with depression. Ongoing enrollment will determine replicability and the feasibility of using aiTBS as a first-line treatment for adolescent depression.

Disclosures: E. Lemke: None. **J. Mosaheb:** None. **T. Ha:** None. **K. Jakimier:** None. **A. Herrmann:** None. **J. LaGrone:** None. **S. O'Sullivan:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.16/LBP138

Topic: J.08. Methods to Modulate Neural Activity

Support: Canon Medical

Title: EEG Decoding Reveals Distinct Temporal Dynamics of Neural Activity Evoked by Transcranial Focused Ultrasound in Humans

Authors: L. KRISST[1], D. A. WAGENAAR[1], *M. H. SHEHATA[2,3], S. SHIMOJO[1];
[1]Biology and Biological Engineering, California Institute of Technology, Pasadena, CA; [2]California Institute of Technology, Pasadena, CA; [3]Toyohashi University of Technology, Toyohashi, Japan

Abstract: Introduction: Transcranial focused ultrasound (tFUS) is a promising noninvasive neuromodulation method with millimeter-scale precision. Previous studies have shown that tFUS alters electroencephalography (EEG) signals, including modulation of spectral power (Kim et al., 2022), early evoked responses resembling somatosensory evoked potentials (SEPs; Legon et al., 2015; Kim et al., 2023), and modulation of visual evoked potentials (VEPs; Nandi et al., 2023). These reports suggest that tFUS can engage neural circuits at relatively early latencies (<500 ms). However, whether trial-by-trial decoding of stimulation versus sham is possible, and whether unique temporal signatures emerge beyond those previously described, remain open questions. **Methods:** Participants viewed a blank OLED screen while receiving randomized trials of tFUS or sham. Stimulation was delivered with a single-element transducer (265 kHz, 64 mm aperture, 51.74 mm focal depth; 1 kHz pulse repetition frequency; 50% duty cycle; 150-300 ms train durations). After 3 s, participants reported whether they perceived any visual experience. Concurrently, EEG was recorded and multivariate pattern analysis (MVPA) was applied to decode stimulation versus sham conditions across time. **Results:** Decoding analysis revealed a

small but significant increase in classification accuracy at ~1200 ms after tFUS onset. Our results demonstrate a delayed neural signature that has not been reported before and suggest a distinct temporal profile of cortical engagement. **Conclusion:** EEG decoding can reliably differentiate tFUS from sham at the single-trial level, revealing a late-onset neural signature not reported in earlier EEG-tFUS studies. This distinct temporal dynamic highlights the feasibility of EEG decoding for real-time monitoring of tFUS effects and provides new insights into how ultrasound influences cortical processing over extended timescales.

Disclosures: L. Krisst: None. **D.A. Wagenaar:** None. **M.H. Shehata:** None. **S. Shimojo:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.17/LBP139

Topic: J.08. Methods to Modulate Neural Activity

Title: Pseudorandom Number Driven Methods for Real Time Biosensing and Neuromodulation

Authors: *E. GRAPSIA[1], P. ANDREADAKIS[2];
[1]Education and Psychology, NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS, Athens, Greece; [2]STATISTICS, ATHENS UNIVERSITY OF ECONOMICS AND BUSINESS, Athens, Greece

Abstract: Randomness-based interventions are emerging as a novel and versatile approach to modulate human physiological and cognitive states with high precision. We introduce two original methods: Random Intensity Training (RIT) and Random Breath Technique (RBT). These methods form the basis of Quantum Rep and Quantum Breath, respectively, which both use a pseudorandom number generator (PRNG) certified for global compliance by Gaming Laboratories International (GLI 11, GLI 19), to introduce high-quality unpredictability. Quantum Rep delivers randomized motor control cues including initiation, cessation, directional modulation and velocity scaling of movement. These unpredictable perturbations in contraction dynamics prevent the neuromuscular system from stabilizing into a fixed rhythm. This increases localized mechanical strain, enhances hypertrophic signaling, stimulates strength adaptations, and makes resistance training more efficient in a shorter duration. Quantum Breath applies a similar principle to respiration, delivering randomized sequences across inspiratory phase, respiratory apnea and expiratory phase. This stochastic modulation disrupts fixed respiratory patterns, promoting adaptive autonomic regulation. Continuous monitoring via heart rate variability (HRV) allows real-time assessment of autonomic responsiveness, leading to reduced sympathetic arousal, increased parasympathetic activity and restoration of physiological balance. In preliminary trials with 12 healthy adults (ages 22-35, 6 females), Quantum Rep reduced high-intensity resistance training sessions to approximately 15 ± 2 minutes compared to 60-120 minutes in conventional protocols, while increasing neuromuscular engagement by 15% ± 4%.

Quantum Breath detected autonomic changes with 18% ± 6% improved sensitivity over baseline and participants reported heightened engagement, adaptability and perceptual awareness. All protocols were carefully controlled, systematically logged and replicated to ensure reproducibility. These findings demonstrate that pseudorandom input can reliably modulate both physiological and behavioral parameters, providing a scalable framework for adaptive, personalized interventions. Our results highlight the feasibility and translational potential of PRNG-driven neuromodulation through RIT and RBT, providing a novel platform for exploring human physiological and cognitive plasticity and serving as a foundation for next-generation neuroadaptive interventions beyond traditional deterministic paradigms.

Disclosures: E. Grapsia: Other; Potential future commercialization of research findings presented in this abstract. **P. Andreadakis:** Other; Potential future commercialization of research findings presented in this abstract.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.18/LBP140

Topic: J.08. Methods to Modulate Neural Activity

Support: National Natural Science Foundation of China (No. 12204322)
Natural Science Foundation of Guangdong Province (Nos. 2023A1515010649)

Title: Distinctive and state-dependent effects of ultrasound on astrocytic and neuronal calcium dynamics in mouse cortex

Authors: *F. LI[1], Y. YONG[2];
[1]Shenzhen Bay Laboratory, Shenzhen, China; [2]Gladstone Institute, San Francisco, CA

Abstract: Astrocytes are abundant in the brain and their calcium signaling is reported to have an important effect on neuronal activity in both physiological and pathological conditions. Low-frequency focused ultrasound (FUS) has recently emerged as a powerful noninvasive neuromodulation approach, yet its impact on astrocyte calcium dynamics in different brain states *in vivo* is poorly understood. Here we combined a customized 0.521MHz FUS transducer with two-photon microscopy, allowing simultaneous single-cell resolution imaging and FUS stimulation at intensities of 0.91 or 1.5 W/cm^2 to examine astrocyte and neuronal calcium responses in somatosensory cortex of both awake and lightly anesthetized mice. In awake mice, FUS significantly enhanced the amplitude, frequency, and temporal integral of astrocyte calcium transients, while suppressing neuronal calcium activity and reducing the proportion of activated neuronal subpopulations. In contrast, lightly anesthetized mice displayed a blunted yet increased astrocyte response and negligible neuronal modulation under FUS, suggesting that baseline suppression from anesthesia partially masks FUS effects. Our study demonstrates that FUS elicits distinctive, state-dependent effects on cortical astrocytes and neurons, highlighting

astrocytes as previously underappreciated targets of ultrasound neuromodulation. These findings will pave the way for FUS-based therapies targeting astrocyte-neuron interactions in conditions involving abnormal brain excitability.

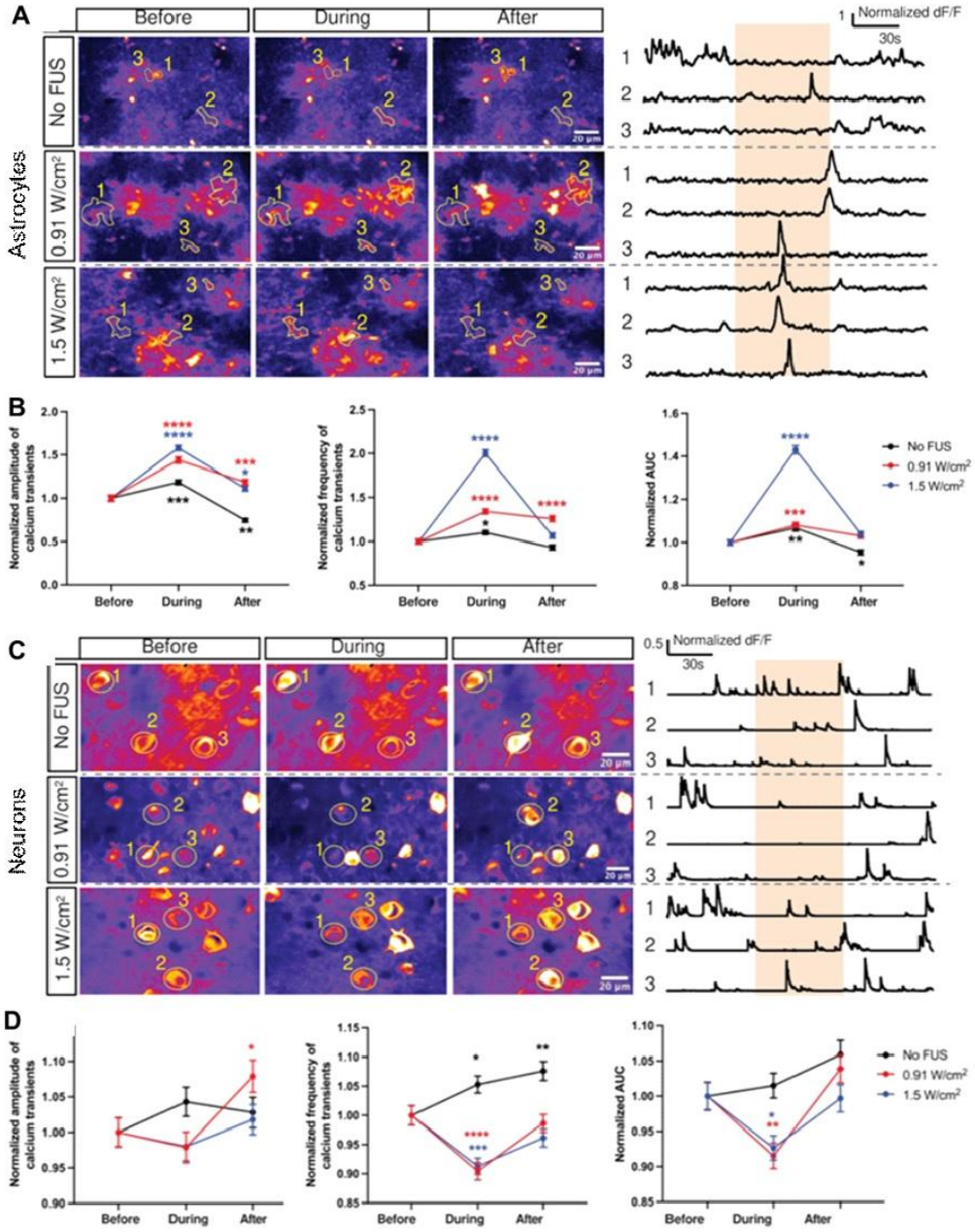

Figure 1: *in vivo* 2-photon (2P) imaging of astrocytic (A-B) and neuronal calcium dynamics (C-D) in response to focused ultrasound in awake mice. AUC: normalized area under the curve. Data are presented as mean ± SEM. n = 1567 (No FUS), 1377 (0.91 W/cm^2) and 1636 (1.5 W/cm^2) astrocyte responsive events from 7 awake mice. n = 1671 (No FUS), 1650 (0.91 W/cm^2) and 1611 (1.5 W/cm^2) neurons from 10 mice.. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001. Significant differences were determined by two-way ANOVA with Tukey's and Dunnett's multiple comparisons tests.

Disclosures: F. Li: None. **Y. Yong:** None.

Late-Breaking Poster

LBP024: J.08. Methods to Modulate Neural Activity

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP024.19/LBP141

Topic: I.09. Spatial Navigation

Support: NIH Grant NS120594
NIH Grant EB036591

Title: Optical Glutamate Imaging Reveals Cortical Activation Induced by Ultra-Short Micro-Magnetic Stimulation

Authors: L. GOMEZ CID[1], F. MARTURANO[1], X. YU[2], J. DENG[3], ***G. BONMASSAR**[1]; [1]Harvard Medical School, Charlestown, MA; [2]Radiology, Massachusetts General Hospital, Charlestown, MA; [3]Harvard University, Charlestown, MA

Abstract: Micro-magnetic stimulation (μMS) has the potential to become an implantable tool for focal circuit manipulation, yet coil design, stimulation parameters, and in vivo efficacy remain to be defined. Here, we designed and tested a μMS device in the rat somatosensory cortex. Long Evans rats were injected with 900 nl of viral vector 98929-AAV9 (Addgene) to express an optical glutamate sensor in hSyn+ cells (S1Tr, 3.0 ML, -2.5 AP, -0.4 DV). After three weeks, animals were anesthetized (2% isoflurane), and a craniotomy exposed the target site. A custom-fabricated μMS device (200 × 400 × 7 μm^3; coil, via, and lead layers) was produced on silicon using advanced microfabrication (maskless lithography, electroplating, parylene coating, ICP-RIE). The stimulator was mounted with an optical fiber and a Local Field Potential (LFP) electrode on the cortical surface. Glutamate release was measured with a custom fiber photometry system. Stimulation was delivered at 1 Hz (5 s on/15 s off, 20 μs pulse, 10 A) using a class D amplifier and pulse generator. LFPs, glutamate signals, and stimulation triggers were acquired with BIOPAC. Control recordings were performed post-euthanasia with the fiber, electrode, and coil in the same position. μMS elicited significant glutamate increases in the local region. While LFP traces contained stimulation artifacts, also observed post-euthanasia, optical recordings provided reliable readouts of neuronal activity. Stimulus-locked glutamate elevations were present in vivo but absent after euthanasia, confirming biological origin. Quantitative analyses showed significant increases in glutamate signal peak amplitude, pulse response, and area under the curve (AUC) during stimulation intervals compared with baseline (N=3 rats, Student's t-test). These findings demonstrate that μMS can drive localized glutamate release in vivo and establish optical photometry as a robust method for assessing neuronal activation. Future work will optimize coil geometry and field orientation to refine spatiotemporal control of cortical activity.

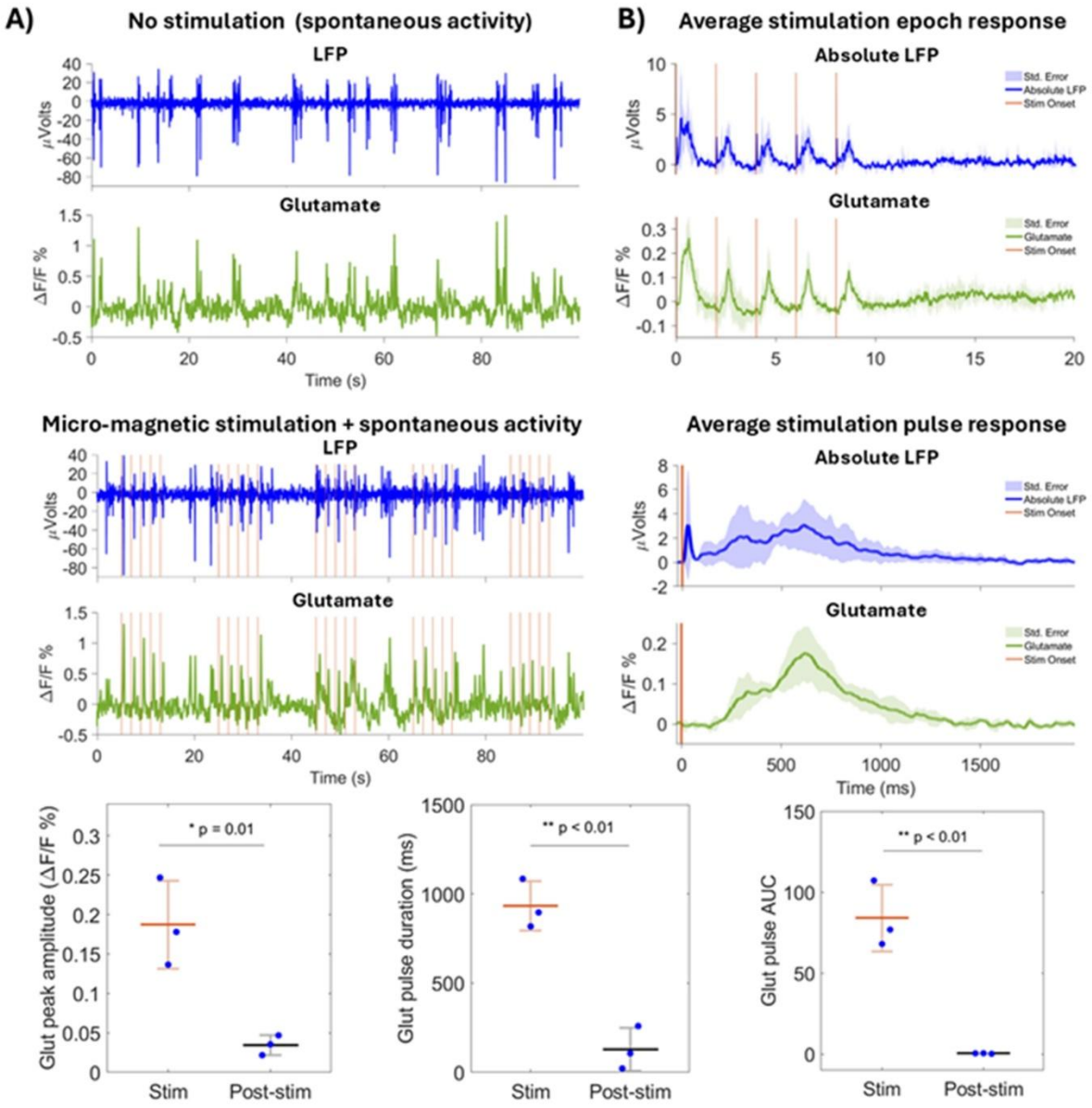

Figure. ***(a)*** *Example of Local Field Potential (LFP) and glutamate recordings using fiber photometry in resting state pre-stimulation and after applying the micro-magnetic stimulation.* ***(b)*** *Average stimulation epoch and pulse response (N=3 rats)* ***(c)*** *Average glutamate signal peak amplitude, pulse duration and area under the curve for stimulation intervals and post-stimulation intervals. p-values obtained using Student's T-test.*

Disclosures: L. Gomez Cid: None. **F. Marturano:** None. **X. Yu:** None. **J. Deng:** None. **G. Bonmassar:** None.

Late-Breaking Poster

LBP025: I.01. Attention

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP025.01/Web Only

Topic: I.01. Attention

Support: Healthy Brains, Healthy Lives - Cognitive Neuroscience kNowledge Exchange for Clinical Translation (CONNECT) initiative, McGill University

Title: Your mind and brain on poetry: neural correlates of a deep attentional state

Authors: *L. K. CHIU[1], L. KHAYYAT[2], I. HOLMES[3], M. HICKMAN[3], J. RISTIC[2]; [1]Faculty of Medicine and Health Sciences, McGill University, Montréal, QC, Canada; [2]Psychology, McGill University, Montreal, QC, Canada; [3]English, McGill University, Montreal, QC, Canada

Abstract: While "deep attention" has been discussed conceptually in psychology (James, 1890), media theory (Hayles, 2007), and literary studies (Alford, 2020), it has never been empirically characterized. Here we present the first multimodal study investigating the behavioural, cognitive, and neural correlates of 'deep attention,' which we define as a sustained, absorptive attentional state, proposed to be elicited by engagement with poetry and other adjacent aesthetic forms of experience. Participants (n=45) read 4 poems and 4 prose pieces and rated each for likeness, interest, and engagement. We used eye tracking glasses to monitor their eye movements and a 32-channel EEG to monitor their brain activity during the entire session. Overall, participants subjectively ranked poems significantly higher than prose on all metrics ($p<.05$). Participants also looked longer at poems compared to prose ($p=0.054$). Brain activity was analyzed in terms of a wavelet-based power spectral density, which revealed lower Alpha (8-12Hz), Beta (13-20), and Theta (4-8Hz) power during poetry reading compared to prose. Specifically, while Alpha power was numerically lower during poetry reading ($p=0.098$), statistically significant differences between poetry and prose reading were found in beta ($p=0.028$) and theta power ($p=0.0005$). Channel-wise paired t-tests confirmed these findings. During poetry reading, lower Alpha and Beta power were found across frontal and occipital channels, whereas lower Theta power was found across multiple channels across the brain (p-FDR$<.05$). Together, these results show broad differences in brain activity associated with attentional states during poetry reading and converging results in eye tracking and behavioural responses. As such, this work provides a pioneering insight into how aesthetic forms such as poetry shape brain states, opening new interdisciplinary directions for cognitive neuroscience and literary arts.

Disclosures: L.K. Chiu: None. **L. Khayyat:** None. **I. Holmes:** None. **M. Hickman:** None. **J. Ristic:** None.

Late-Breaking Poster

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Program #/Poster #: LBP025.02/LBP001

Topic: I.01. Attention

Support: the National Science and Technology Innovation 2030 Major Program of China (2022ZD0204802)
the National Natural Science Foundation of China (31930053)

Title: Causal contribution of the right superior parietal lobule to mental effort in shaping multiple object tracking performance

Authors: K. BI, ***X.-Y. YANG**, F. FANG;
Peking University, Beijing, China

Abstract: The dorsal attention network (DAN) is consistently engaged by multiple object tracking (MOT), yet the functions—and causal roles—of its subregions remain unclear. To this end, we conducted an exploratory, two-experiment study combining functional MRI (fMRI), pupillometry, and high-definition transcranial direct current stimulation (HD-tDCS). In Experiment 1, healthy adults (n=15; 21.6±2.75 years; 7 female; sex differences unassessed) performed fixated MOT at three loads (0/2/4 items; randomized across trials) during fMRI with eye tracking. Blood-oxygen-level-dependent (BOLD) signals and pupil size were modeled using orthogonalized linear and quadratic load regressors (general linear model), followed by mediation testing with load as X, BOLD signal as M, and pupil size as Y. Both pupil size and BOLD signals in bilateral superior parietal lobule (SPL) showed significant positive linear trends and significant quadratic (inverted-U) components; critically, right SPL (rSPL) BOLD signals significantly mediated load's effect on pupil size, which indexes mental effort. In Experiment 2, participants (n=54; 20.45±1.93 years; 30 female) were evenly assigned to sham, anodal, or cathodal HD-tDCS targeted to rSPL and completed MOT at load=4 before and after stimulation. Mixed-effects Group×Session analyses indicated greater post-stimulation increases in both tracking accuracy and pupil size for the anodal group versus the sham group, with no greater change for cathodal versus sham; pupil size further mediated the effect of anodal stimulation on tracking accuracy. These converging results identify a causal contribution of rSPL within the DAN to mental effort, which in turn influences tracking performance. Our findings suggest a mechanistic entry point for enhancing attention-demanding visuospatial behavior and validate pupil size as an effort-indexed biomarker sensitive to parietal excitability.

Disclosures: K. Bi: None. **X. Yang:** None. **F. Fang:** None.

Late-Breaking Poster

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Program #/Poster #: LBP025.03/LBP002

Topic: I.01. Attention

Support: UO1 NS128921

Title: Neural dynamics supporting goal-directed visual attention

Authors: *M. J. MCCARTY[1], O. WOOLNOUGH[2], K. SNYDER[3], E. MURPHY[4], N. TANDON[5];
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Abstract: Contemporary theories of flexible attention suggest that the frontoparietal network (FPN) supports the dynamic selection of sensory information. Direct evidence of how and where this flexibility is indexed, and how the FPN interacts with task-relevant sensory regions has yet to be unveiled. We examined data from large-scale multifocal intracranial recordings in 31 epilepsy patients performing a target detection task in which the relevance of visual objects to behavioral goals varied. We first derived a comprehensive map of object-selectivity in ventral occipitotemporal cortex (vOTC) and then investigated how interactions between category-selective vOTC and the FPN evolve with each object's relevance to shifting task demands. We discovered evidence of adaptive coding within the FPN comprised of the frontal operculum, inferior frontal cortex, and intraparietal sulcus. Local activity and inter-areal communication between these regions was significantly elevated across task conditions, with increased top-down signaling from FPN to vOTC when objects became task-relevant. These findings provide evidence that category selectivity emerges from the integration of bottom-up visual features and top-down attentional modulation, enabling the rapid identification of relevant stimuli. Collectively, these findings reveal flexible FPN to higher-order sensory cortical dynamics are what enable the selection and identification of behaviorally relevant information.

Disclosures: M.J. McCarty: None. **O. Woolnough:** None. **K. Snyder:** None. **E. Murphy:** None. **N. Tandon:** None.

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Topic: I.01. Attention

Support: China, National Science and Technology Innovation 2030 Major Program (2022ZD0204802)

Title: Attention multiplexing: neural mechanism underlying rhythmic sampling of multiple-locations attention

Authors: *C. ZHUANG[1], H. ZHANG[2], Y. SONG[1], X. GONG[1], F. FANG[1];
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Abstract: Recent studies revealed that attention is not a static process but samples the visual environment rhythmically. During single-location monitoring, behavioral performance correlates with the phase of 8Hz neural oscillation, whereas it alternates rhythmically at 4 Hz between two simultaneously attended locations. From these observations, researchers have proposed a "general 8 Hz sampling mechanism"—positing that in multi-location attention, the single-location sampling rhythm is divided by the number of attended locations. However, direct neural evidence supporting this hypothesis remains scarce.To address this gap, the present study aimed to unravel the process of attentional allocation during multi-location attention and clarify the neural mechanism underlying attentional multiplexing. Using magnetoencephalography (MEG), we recorded high-temporal-resolution neural activity while participants performed a multi-location attention task, and applied a decoding method to predict attentional states at each task time point. Three experiments were conducted: attention to left-right locations (Exp. 1), up-down locations (Exp. 2), and three locations (Exp. 3).Results from the three experiments demonstrated that attention samples each location sequentially, with a basic sampling unit of ~60ms, which results in a θ-rhythm sampling cycles (4-10 Hz), depending on the sampling order and the number of attended locations. Additionally, we found that the attentional sampling process exhibited two stages with distinct profiles: an early stage (<~300ms) that is more sensory-driven with a faster sampling rate (~6-8 Hz); and a late stage (>~300ms) with a lower rate (~3-4 Hz), the phase of which predicts behavioral performance and is modulated by top-down θ power from the frontal lobe. Overall, the entire attentional sampling process is modulated by the phase of low θ rhythms (2-4 Hz), and behavioral results corroborated these neural findings. This study challenges the general 8 Hz sampling hypothesis and instead we propose a general sampling mechanism-the “theta/gamma phase code” of attentional multiplexing in visual-spatial attention.

Disclosures: C. Zhuang: None. **H. Zhang:** None. **Y. Song:** None. **X. Gong:** None. **F. Fang:** None.

Late-Breaking Poster

LBP026: I.02. Perception and Imagery

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Program #/Poster #: LBP026.02/Web Only

Topic: I.02. Perception and Imagery

Title: Investigation of threat temporal distance on the specificity of episodic future thinking

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Abstract: Episodic Future Thinking (EFT) is the ability to pre-experience or imagine a specific future event. The study aimed to investigate how the perceived temporal proximity of threat word cues (near versus distant) influences the specificity and phenomenological characteristics of EFT. Since the near-future events form a more concrete representation than distant future events. Therefore, we hypothesized that EFT for Near-threat cues would have high phenomenological ratings as compared to Distant-threat cues. We employed a two-phase design of the EFT task using PsychoPy. Day 1 comprised 15 participants *(M= 26.09, S.D. 2.43)* rating a list of 55 words taken from ANEW database on valence, arousal, dominance, and threat perceived proximity on a 5-point Likert scale. Then, 15 words (5- Near, distant threats, and neutral) were selected based on Day 1 ratings and used as a cue for EFT task on Day 2. After giving brief instructions, an example, and a trial session took place. Then participants verbally responded to a personally relevant future event based on the cue presented, followed by subjective ratings like Clarity, Detail, Valence, Vividness, Perspective, Emotion intensity, and Importance of the imagined event, on a 7-point Likert scale. The word cues were pseudo-randomised, and all ethical considerations were met. Audio-based EFT responses were transcribed, and each response was rated on specificity on a 6-point Likert scale. Quantitatively, results showed no significant differences in episodic specificity scoring between near-threat, distant-threat, and neutral cues. However, phenomenological differences in clarity, valence, detail, intensity of emotion, and the importance of imagined future events were observed. Qualitatively, participants' responses were vague and hypothetical, showing participants avoided responding in detail to the threatening cue irrespective of their temporal proximity. The results showed differences in the experimenter's episodic specificity scoring and participants' subjective ratings. This challenges the Construal Level Theory (CLT) and explains that individuals may use emotional regulation strategies when faced with threatening stimuli, and with avoidance, they limit vivid and detailed future imagination for that stimulus. Hence, this shows that emotional avoidance and reappraisal for threat cues can minimise the effect of temporal proximity on episodic specificity. This gives an implication to include specific temporal and contextual factors in guidelines, an objective scoring method, and using physiological measures for a better understanding of the mechanism underlying the above findings.

Disclosures: S. Mishra: None. **M.K. Asthana:** None.

Late-Breaking Poster

LBP026: I.02. Perception and Imagery

Location: SDCC Hall B

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Program #/Poster #: LBP026.03/LBP004

Topic: I.02. Perception and Imagery

Title: Frequency specific EEG microstates are distinct between music sensitive and low sensitive individuals during emotional music experiences

Authors: *M. IWASHITA[1], M. GOTO[2], I. CHANPORNPAKDI[3], M. ISHIKAWA[4], K. ISHIDA[5], T. TANAKA[6];
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Abstract: Music is prominently observed in humans and several bird species. The neural basis of music perception is thought to be shaped by species' ecological or behavioral demands. In humans, emotional music is thought to have a profound impact on social emotions and memory consolidation by altering neural connectivity in the medial prefrontal cortex, insula, and hippocampus. However, the brain states representing strong musical emotions—chill, goosebump, or awe—are unclear. Moreover, whether these brain states differ depending on individual sensitivity to music has not been studied. To address these gaps, we analyzed EEG microstates while subjects were listening to emotional or neutral music. We collected 160 subjects who completed the Barcelona Music Reward Questionnaire (BMRQ). 17 subjects scoring ≥0.5 SD above the BMRQ mean were classified as high-sensitive, and 18 scoring ≤0.5 SD below were classified as low-sensitive. The 64-ch EEG data from these 35 subjects were acquired during emotional and neutral music, bandpass-filtered into four bands (theta, low alpha, high alpha, and beta), and followed by microstate analysis. Microstates are quasi-stable topographical patterns of the electrical potential lasting over 30 ms. To investigate the randomness of microstate sequences, Shannon entropy was calculated for four specific microstate topographies. In the theta band, high-sensitive subjects showed lower entropy during intense emotional experiences than neutral ones. In contrast, low-sensitive subjects showed no significant changes. In the theta band in music-sensitive subjects, the Class D microstate, associated with the frontoparietal network, showed increased prevalence during strong emotional experiences, while other microstate classes decreased. These results suggest that the emergence of a dominant microstate in the theta band may represent the music-induced emotional states in the highly sensitive individuals. Also, our results indicated that even among noisy representation, careful grouping (ex., high- vs. low-sensitive) in the subjects can reveal detectable signals in the

brain microstates. Thus, our results hint at an alternative approach for the heterogeneity of musical reward processing.

Disclosures: **M. Iwashita:** A. Employment/Salary (full or part-time); DENSO CORPORATION. **M. Goto:** None. **I. Chanpornpakdi:** None. **M. Ishikawa:** A. Employment/Salary (full or part-time); DENSO CORPORATION. **K. Ishida:** A. Employment/Salary (full or part-time); DENSO CORPORATION. **T. Tanaka:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); DENSO CORPORATION.

Late-Breaking Poster

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Program #/Poster #: LBP026.04/LBP005

Topic: I.02. Perception and Imagery

Support: NIA R03AG087366
Alzheimer's Association AARF-22-926755

Title: The effects of aphantasia on visuospatial task performance

Authors: ***S. SUTHERLAND**[1], I. BRENES[2], A. D. EKSTROM[1], P. F. HILL[3];
[1]Psychology, University of Arizona, Tucson, AZ; [2]University of Arizona, New York, NY;
[3]Department of Psychology, University of Arizona, Tucson, AZ

Abstract: Aphantasia, the inability to generate vivid visual mental imagery, is an uncommon neurocognitive trait. Although increasingly recognized, its role in memory retrieval remains poorly understood. In the present study, we examined whether the absence of vivid mental imagery in aphantasia affects the ability to retrieve precise, high-fidelity details from memory. Three young adults with self-reported aphantasia (AP; determined via Vividness of Visual Imagery Questionnaire using a threshold score of ≤ 23) and 72 age-matched healthy controls (HC) completed three episodic memory tasks that demand precise retrieval but differ in their perceptual and spatial requirements. Participants performed two versions of the Mnemonic Similarity Task (MST): the Item MST, requiring discrimination between old items and perceptually similar lures, and the Location MST, requiring discrimination between a studied location and spatially similar lure locations. They also completed a continuous report item-location associative memory task, in which participants studied trial-unique objects placed along the perimeter of an invisible circle and later recalled their locations using a continuous response dial. Retrieval fidelity was indexed by the angular distance between studied and remembered locations, and probabilistic mixture modeling estimated retrieval success (probability of non-guessing) and precision (dispersion of errors on successful trials). AP participants additionally completed a brief standardized cognitive battery assessing verbal and visuospatial memory, visuospatial ability, and executive function. For each memory task, HC reference values (mean ±

95% CI) were derived, and each AP score was compared to this benchmark. APs performed within the HC range on both spatial memory tasks (Location MST and item-location task), suggesting intact retrieval of precise spatial details despite the absence of visual imagery. Each AP performed reliably above the HC benchmark on the Item MST, indicating enhanced discrimination of old items from perceptually similar lures. This advantage may reflect reduced perceptual interference in aphantasia, consistent with the idea that the absence of vivid imagery could lessen overlap between internally generated representations and externally presented stimuli. These results converge with prior neuroimaging findings to suggest that vivid mental imagery and mnemonic precision are dissociable components of memory retrieval. They also underscore the need for expanded tools to operationalize and diagnose aphantasia, as current measures may not fully capture the cognitive profile demonstrated by behavioral testing.

Disclosures: S. Sutherland: None. **I. Brenes:** None. **A.D. Ekstrom:** None. **P.F. Hill:** None.

Late-Breaking Poster

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Topic: I.02. Perception and Imagery

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Title: Recent decisions override older history in serial dependence

Authors: *J. LIM, S.-H. LEE;
Seoul Natl. Univ., Seoul, Korea, Republic of

Abstract: Visual perception is systematically biased toward recently encountered stimuli and decisions, a phenomenon known as *serial dependence*. In the continuity-field framework, perceptual and decisional outcomes attract spatiotemporally proximate future perception, with this attraction decaying as spatial or temporal distance increases. This temporal decay is often described in trial-based terms, with serial dependence decreasing as more trials intervene. However, the decay may arise from two distinct mechanisms. First, past perceptual traces may simply degrade with elapsed time, as supported by inter-trial interval manipulations in previous studies. Second, new perceptual decisions may actively suppress the influence of older information on subsequent perception, such that more recent experiences override earlier ones. Despite its importance, the second mechanism has received little investigation to our knowledge.To investigate this, we conducted an orientation reproduction experiment (N = 17). On each trial, participants reproduced the orientation of a white grating (target) while ignoring a green grating (non-target) across consecutive trials. Non-target trials provided comparable visual input and motor responses but required no orientation decision. We quantified the influence of 2-back target orientations on current responses, separately for conditions where the intervening (1-

back) trial contained a target versus a non-target. Attraction to 2-back orientations was significantly reduced when the intervening trial required an attended decision (target), compared to when only a non-target intervened. These results cannot be explained by intervening visual stimulation or key presses alone, but rather implicate a decisional updating process that down-weights older information once a new decision is formed.Our findings support an information-updating account of serial dependence: recent perceptual decisions override older ones, rather than simply accumulating with time-weighted decay. Such an overriding process may provide a more efficient basis for real-world inference, where future states depend primarily on the immediately preceding state, and older information is discarded once new state information becomes available.

Disclosures: J. Lim: None. **S. Lee:** None.

Late-Breaking Poster

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Program #/Poster #: LBP026.06/LBP007

Topic: I.02. Perception and Imagery

Title: Blindness reorganizes the cortical network for lexical tone perception

Authors: *Q. YUE[1], L. ZHANG[2];
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Abstract: Previous research has shown that the loss of one sensory modality (e.g., blindness) often alters information processing in another. However, the neural mechanisms underlying such cross-modal reorganization are not fully understood. Using functional magnetic resonance imaging, this study investigated the neural substrates of Mandarin lexical tone perception in sighted controls (SC, n=25) and congenitally blind (CB, n=34) adults. Participants performed a tone categorization task in which they identified which of the four lexical tones a given sound represented by making a corresponding manual response during brain scanning. Behaviorally, both groups performed the task with high and comparable accuracy. However, the CB group responded significantly faster (by approximately 200 ms) than the SC group and exhibited a distinct pattern of response times across the four tone conditions. Neuroimaging results indicated that the SC group engaged a typical network for lexical tone perception, including bilateral superior temporal cortices, the left inferior frontal gyrus (IFG), the left inferior frontal junction (IFJ), and motor areas. The CB group also activated bilateral superior temporal regions, but time-resolved activation analyses revealed a distinct neural activation profile characterized by shorter response durations in these cortices, paralleling their faster behavioral responses. Notably, the CB group did not recruit the IFG; instead, they exhibited activation in visual areas, including left V5. Multivoxel pattern analysis demonstrated that while bilateral superior temporal cortices discriminated tone categories in both groups, left V5 discriminated tones exclusively in the CB group. Representational similarity analysis further indicated that left V5 encoded pitch height in

the CB group. Furthermore, functional connectivity analysis revealed stronger temporal-frontal coupling in the SC group, whereas the CB group exhibited enhanced connectivity between temporal areas and left V5. These findings suggest that congenital blindness leads to a systemic functional reorganization, with visual areas (e.g., left V5) becoming engaged in auditory feature representation during lexical tone perception in blind individuals.

Disclosures: Q. Yue: None. **L. Zhang:** None.

Late-Breaking Poster

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151490/EXCELLENCE_24 grants of the National Research, Development and Innovation Office, Hungary

Title: Decoding the impact of face familiarity on EEG time-frequency representations of gender perception

Authors: *S. SÁRINGER, A. BENYHE, A. BERENYI, P. KAPOSVÁRI;
University of Szeged, Szeged, Hungary

Abstract: Processing the facial gender has been studied extensively using multivariate pattern analysis (MVPA) of single-channel event-related potentials (ERP). Differences between male and female faces emerge with a short latency (less than 100 ms after stimulus presentation) and are maintained for approximately 500 ms, depending on the level of familiarity with the face. These decoding algorithms, however, can also handle higher-dimensional, complex data, thus potentially increasing information extraction regarding facial gender. In this study, we analyzed the EEG recordings of two face presentation paradigms, where we decoded both ERP and the Fourier spectrum, to observe whether decoding of the time-frequency representation (TFR) provides further information about face processing. To probe the role of familiarity, in Experiment 1, a small set of faces was repeated frequently (high familiarity), while in Experiment 2, a larger set was presented less often (low familiarity). In each experiment, 25 healthy volunteers were presented with faces (600 trials) during EEG recording. We used MVPA on the ERP data, subsequently, on the complex Fourier spectrum along the channels to compare the neural patterns of male and female faces. We also extracted the scalp distribution of the activity by decoding the data along the time dimension, in discrete windows. All decoding values were compared against chance (0.5), and significant windows were determined using threshold-free cluster enhancement. In Experiment 1, a 500-ms long time window emerged at the

beginning of the stimulus presentation in the 2-17 Hz frequency range when comparing female and male faces. Less familiar faces, in Experiment 2, showed similar, but more restricted time-frequency windows spanning from 6-20 Hz in the first 300 ms of stimulus presentation. ERP decoding revealed the same time windows in both experiments. Spatial analysis showed that faces with higher familiarity elicited both occipital and frontal activity, while low-familiarity-related activity was restricted to the occipital area. TFR decoding revealed that processing the gender of unfamiliar faces elicits shorter time windows and a narrower frequency band, while it is also confined to the occipital region. Processing more familiar faces is maintained longer in the cortex and evokes lower frequency activity. The higher familiarity also engages the frontal areas alongside he occipital regions. Our results show that decoding the TFR can provide the same temporal results as ERP decoding, while also adding crucial frequency information and spatial distribution of the different frequency bands.

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Late-Breaking Poster

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NSF BCS-1945230
McDonnell Center for Systems Neuroscience
Brain and Behavior Research Foundation

Title: Enhanced spike-field coherence for face familiarity in human amygdala and hippocampus neurons

Authors: Y. LI, J. ZHANG, P. BRUNNER, J. T. WILLIE, ***R. CAO**, S. WANG;
Washington University in St. Louis, St. Louis, MO

Abstract: Recognizing familiar faces is a fundamental aspect of human social interaction, relying on the brain's ability to transform repeated visual exposures into stable memory representations. The human medial temporal lobe (MTL), including the amygdala and hippocampus, is critical for knowledge-based identification distinguishing familiar from unfamiliar faces. Yet, how MTL neurons coordinate and communicate during this process, and how familiarity-relevant information is transmitted from the ventral temporal cortex (VTC)—a core area of identity processing— to the MTL remains unclear. Here, we examined single-neuron and population-level (iEEG) synchronization within the MTL and between the MTL and VTC, including the fusiform gyrus (FG) and inferior temporal gyrus (ITG). We found that individual neurons synchronized with theta oscillations during face viewing, with changes in theta phase-locking as a function of face familiarity and repeated exposures to the same identity. Notably, neurons encoding face learning through theta phase-locking were distinct from those encoding it through firing rate, suggesting a novel neural code for face learning. While familiarity did not interact with the axis-based feature coding of faces in the VTC, it significantly modulated both local neuronal synchronization within the MTL and interareal synchronization between the VTC and MTL. Together, these findings provide direct evidence of dynamic neural interactions supporting face familiarity and learning, offering insights into how visual inputs are transformed into memory representations through theta oscillatory mechanisms.

Disclosures: Y. Li: None. **J. Zhang:** None. **P. Brunner:** None. **J.T. Willie:** None. **R. Cao:** None. **S. Wang:** None.

Late-Breaking Poster

LBP026: I.02. Perception and Imagery

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP026.09/LBP010

Topic: I.02. Perception and Imagery

Title: Emotional and Neurophysiological Correlates of Affective Visual Stimuli Processing

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Abstract: Affective visual stimuli significantly shape cognitive processes, including attention, decision making, and behavioural response. The present study aims to explore how the visual features (colour, font, spatial distribution and icon design) influence emotional and neurophysiological responses through a mixed-method design. The research included behavioural surveys, electroencephalography (EEG), and eye-tracking. Behavioural data were

obtained using two online surveys (N=59; N=51;18-40 years) in which subjects made arousal and valence ratings using a Janet Ann Russell-type circumplex model of affect. Participants provided arousal and valence ratings to stimuli with graphics that combined colour (blue, red, green, grey), font (serif, round), space allocated (30% versus 70%), and icon style (line versus image). Colour (F (3,59) =30.48, p =<.000) and font (F (1,59) =0.58, p =<.04) showed a statistically significant impact on arousal. In case of valence only colour (F (3,59) =3.95, p =<.01) and icon style font (F (1,59) =0.69, p =<.04) reached the level of significance. Furthermore, unlike their line-based counterparts, image-based icons reflect intense arousal (F (3,59) = 0.026, p=0.46). EEG (N=19; 18-33 years) data depict enhanced delta and theta band neural activity to red coloured stimuli, reflecting heightened engagement and attention allocation. Eye tracking (N=27; 21-35 years) mapped gaze behaviour and attentional hotspots. These results underscore the complex interplay of perceptual characteristics with affective-cognitive processes. With the triangulation of behavioural, EEG, and eye-tracking findings, this study provides insights into how structured visual input impacts emotional and attentional processing, and to a certain extent provides further insights into the neural mechanisms of visual perception and engagement.

Disclosures: D. Singh: None. **A. Tomar:** None. **M.K. Asthana:** None.

Late-Breaking Poster

LBP026: I.02. Perception and Imagery

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP026.10/LBP011

Topic: I.02. Perception and Imagery

Title: Emergence of partial conjunctions in artificial neural networks: a tractable solution to the binding problem in vision

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Abstract: The binding problem, or how separately-coded visual features are integrated into unified object representations, remains a central challenge in neuroscience. While hierarchical, hard-wired conjunction coding has been proposed as a solution, it has long been considered intractable due to the exponential number of required feature combinations for binding. A partial solution arises through partial conjunctions, which selectively encode subsets of features and thereby reduce representational demands while maintaining unambiguous object coding. Here we explored the emergence of such units in convolutional neural networks, using a ResNet-34 model as a computational proxy for human visual cortex. Unlike classical accounts that emphasize binding across spatially or temporally overlapping features, we investigated binding among different parts of the same object, a particularly challenging problem in vision. We designed a set of object-like stimuli with a controllable number of part-based features, and

trained networks under two supervised conditions: a perceptual task requiring no feature binding, and a binding task requiring recognition of part relationships. Variance partitioning was used to quantify unit tuning across network layers, and in silico lesion analyses were applied to examine functional contributions. Our results revealed the robust emergence of partial, particularly pairwise, conjunction properties across both tasks, while full conjunction units appeared selectively under binding demands. Lesion studies demonstrated that partial conjunctions are crucial for classification performance, under both perceptual and binding conditions. These findings demonstrate that partial conjunction coding naturally arises in hierarchical networks, which form a criteria-free, condition-independent basis for representing complex multi-part objects. Our work thus suggests a representational mechanism that balances efficiency and costs, offering a computationally tractable solution to the binding problem with implications for biological vision.

Disclosures: Q. Zhu: None. **G. Davis:** None.

Late-Breaking Poster

LBP026: I.02. Perception and Imagery

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP026.11/LBP012

Topic: I.02. Perception and Imagery

Support: Project no: 222S133

Title: A deep learning-based application for evaluating right-left discrimination in the upper extremity from personal perspectives

Authors: *B. DILEK[1], Y. AKGÜL[2], T. ÖCAL[3], Ö. ÇETINKAYA[3], D. ZAPALA[4], S. AKBAS[5], E. YASAR[2], E. YILMAZ[2], L. HANOGLU[5];
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Abstract: Motivation/problem statement: The clinical significance of lateralization is that it can restore body image by changing cortical reorganization in chronic pain conditions. Evaluating the lateralization stage through personal perspective is important as addresses different attentional mechanisms of body perception. The aim of this study was to develop an application program with virtual reality supported rehabilitation models, in which the right-left distinction can be evaluated through personal perspectives. The hypothesis of the present study was that there were differences in right-left discrimination according to personal perspectives (i.e. allocentric and egocentric perspective). **Methods/ approach:** The study group consisted of healthy volunteers aged 18-65 years, who scored 21 and above in the Montreal Cognitive Assessment Test. Upper extremity movements were shown from different perspectives through the avatar developed using the UNITY platform. While the user was performing the movement,

parameters such as joint movement angle (°) and movement initiation speed (ms) were estimated and recorded using deep learning-based skeleton extraction models. Users' performances were reported separately for the right and left sides. Comparison of the obtained performance values between groups in terms of perspective categories was made with analysis of variance (ANOVA) designs. Games-Howell test was used for post-hoc comparisons. **Results:** Preliminary evaluation was performed on 95 volunteers [woman/man (%): 56/44; mean age (years): 33.54 ± 11.01]. Differences were detected in terms of movement angle and movement initiation time according to perspective categories ($F_{df=4-395}$=10.53; p<0.001; $F_{df=4-395}$=3.81; p=0.005; respectively). According to post-hoc comparisons, the highest angle and fastest reaction time values were recorded in the categories of avatar videos that could easily be transformed into self-body perception. Those values were obtained in the opposite direction when the avatar videos were in an allocentric perspective (p<0.05, for all). **Conclusion/implications:** Conditions in which avatar movements were presented from different perspectives occur through different attention mechanisms. It was determined that categories requiring a greater change in mental trajectory were perceived as more difficult. In accordance with the findings derived from the healthy volunteers, this desktop application program may be utilised in patients diagnosed with pathological pain syndrome or neurological conditions.

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Late-Breaking Poster

LBP026: I.02. Perception and Imagery

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP026.12/LBP013

Topic: I.02. Perception and Imagery

Support: IITP-2025-RS-2022-00156299

Title: Risk perception in automated driving: A prefrontal fNIRS pilot with mild physical disabilities

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Abstract: Functional near-infrared spectroscopy (fNIRS) reliably measures attention, cognitive load, risk perception, and behavioral intention. This study examined prefrontal hemodynamic responses to traffic complexity during automated driving and compared risk perception sensitivity between nondisabled and physically disabled participants. Five female participants (mean age 24.4 ± 2.5 years) took part, including three nondisabled and two with mild physical disabilities (one with a focal brain lesion and one with hearing loss, mean diagnosis age 18.5 years). None held a driver’s license. Data were recorded with NIRSport 2 (20 channels, 8

sources × 7 detectors, 10.17 Hz) and Aurora software (version 2021.4). Channel coordinates were transformed into MNI space and mapped to seven regions of interest: Dorsolateral prefrontal cortex (DLPFC, both), frontal pole (FP, central and both), and orbitofrontal cortex (OFC, both). Six statistical metrics (minimum, mean, standard deviation, skewness, kurtosis, and peak value) were extracted from oxygenated and deoxygenated hemoglobin signals. This yielded 84 features for the rest condition (7 ROI × 2 Hb × 6 metrics) and 7,560 features for hazard events (7 ROI × 2 Hb × 6 metrics × 30 trials × 3 scenarios), for a total of 7,644 features. The driving simulator (RoadRunner, MATLAB R2025a) presented three hazards: sudden braking, cut-in, and pedestrian crossing. Each occurred randomly at 40-50 km/h and was repeated 30 times. The protocol lasted ~40 min with rest, trials, and recovery. Participants pressed the space bar when perceiving risk. One-sample t-tests compared rest and event distributions; Shapiro-Wilk and Mann-Whitney U tests were used if normality was not met. Multiple comparisons were corrected with the Benjamini-Hochberg method ($p < .05$). Independence of significance was tested with chi-square analysis, and 95% confidence intervals were calculated with the Wilson method. The proportion of FDR corrected significant features ($p < .05$), referred to as the significance rate, varied by ROI, scenario, and subject ($\chi^2(4)=27.14$, $p = 1.86 \times 10^{-5}$). The participant with a mild brain lesion showed the lowest rate (47.2% [95% CI: 41.1-53.4]) compared with the highest (67.5% [95% CI: 61.5-72.9]). The OFC exhibited the strongest effect, with the right OFC under the cut-in condition reaching 75.0% [95% CI: 62.8-84.2]. This preliminary study suggests reduced risk perception related hemodynamic sensitivity in participants with mild disabilities during automated driving. The findings support future human-vehicle collaboration systems that integrate subjective driver states for disabled and elderly users.

Disclosures: M. hong: None. **S. Dong:** None.

Late-Breaking Poster

LBP026: I.02. Perception and Imagery

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP026.13/LBP014

Topic: I.02. Perception and Imagery

Title: Neural Correlates of Autobiographically Salient Music

Authors: *R. CHANDRA[1], F. S. BARRETT[2];
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Abstract: Musicis central to psychedelic-assisted therapy (PAT), and the autobiographicalsalience (AS) of music—independent of drug administration—is thought to amplifyemotional responses and facilitate altered states of consciousness. Under LSD,AS has been linked to increased parahippocampal-visual cortex coupling,supporting imagery and meaning-making (Kaelen et al., 2016). Yet the neuralmechanisms of autobiographically salient music outside of drug contexts remainpoorly understood. Here, we present an EEG dataset of

extended, hour-long,within-subjects music-listening sessions with bothpersonalized/autobiographically salient (AS) and standardized playlists inpsychedelically naïve adults.

Methods

Thirty-two participants (M = 34.4 years, SD = 10.8;59% female) completed multiple counterbalanced sessions while EEG wascontinuously recorded from a 64-channel BioSemi ActiveTwo system. Data werepreprocessed with 60 Hz notch filtering, mastoid re-referencing, and spectraldecomposition across canonical frequency bands (delta-gamma).

Results

Preliminary whole-brain analyses suggested a trend-level reduction of beta power as the autobiographical salience of songs increased, independent of condition ($\beta = -0.0332$, SE = 0.0199, $t = -1.67$, $p = .096$, 95% CI [-0.073, 0.006]). No reliable differences were observed in other frequency bands (all $ps > .35$, $\eta^2 < .01$). Percent-change models across sessions explained negligible within-subject variance (< 0.2%).

Discussion

These findings converge with prior reports of alpha/low-beta suppression during emotionally significant or familiar music (Malekmohammadi et al., 2023) and mirror reductions observed during psychedelic states (Riba et al., 2002; Muthukumaraswamy et al., 2013). Autobiographical salience may modestly reduce beta activity, potentially indexing heightened emotion, imagery, and meaning-making—processes that overlap with neural mechanisms underlying psychedelic-induced altered states of consciousness.

Conclusion

These preliminary analyses provide a first whole-brain characterization of autobiographical salience during extended music listening in non-drug contexts. Future region-specific models in SPM will test for significant oscillatory clusters (e.g., posterior alpha) and examine how autobiographical salience shapes neural dynamics associated with core altered-state phenomena including insight, mystical-type experiences, flow, and challenging experiences.

Disclosures: R. Chandra: A. Employment/Salary (full or part-time); Johns Hopkins University. **F.S. Barrett:** None.

Late-Breaking Poster

LBP027: I.03. Decision Making

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.01/LBP015

Topic: I.03. Decision Making

Title: Participants show motor habit preference and loss aversion in a novel Iowa Gambling Task

Authors: T. KRATT, T. SHAW, *D. B. DORMAN;
Neurosci., Hope Col., Holland, MI

Abstract: Difficulty in controlling and appropriately modifying habitual and impulsive behavior is a shared feature of many psychiatric conditions, from addiction to OCD. In an effort to better understand how habitual and goal-directed decision making strategies change in a realistically reward-driven and uncertain environment, we created a novel version of the Iowa Gambling Task (IGT). The IGT is a widely accepted task that assesses risk-taking in opaque environments. In the original task, participants must determine fixed underlying reward and loss probabilities through trial and error. To investigate how people adapt to changing environments, we introduced two blocks to the IGT—a "trust the label" block and a "trust the position" block—in which reward and loss probabilities change depending on the block, so that optimal behavior requires cognitive flexibility in switching between habituated and goal-directed behavior. The distinguishing feature of these two test blocks is that deck labels change for each: in the "trust the label" block, the deck label ("A", "B", "C", or "D") determines the underlying reward probabilities, while in the "trust the position" block, only the position of the deck on the screen (up, down, right, or left) determines whether the deck yields more gains or losses. Participants make their deck choices by pressing arrow keys to correspond to deck positions. The distinction here is that while the labels are purely a visual stimulus in the task, participants select their choice deck based on position. 17 undergraduate students completed the modified IGT, and position and label preferences were compared using statistical methods. Results indicated that participants switch position-based strategies (but not label-based strategies) depending on the block, and that participants' choices across the entire experiment were more position-based than label-based. Additionally, when their choices were used to create GLM-HMMs (Generalized Linear Model-Hidden Markov Model, a model meant to recover distinct strategies/states over time), positional outputs were weighed much higher in their final decision. Also, participants both statistically and in GLM-HMM representations preferred options without frequent losses to more volatile ones, even when their expected value was similar. This suggests a certain amount of loss aversiveness, in which people prefer not to explore options once they find a choice that never penalizes them too strongly, even if they gain less over time. Overall, these results suggest that in a complex and changing environment, people tend to rely on motorized habituated decision making in the absence of strong penalties for doing so.

Disclosures: T. Kratt: None. **T. Shaw:** None. **D.B. Dorman:** None.

Late-Breaking Poster

LBP027: I.03. Decision Making

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.02/LBP016

Topic: I.03. Decision Making

Support: NIA Grant R01-AG067011
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Temple University College of Liberal Arts Research Award
Adelphi University Faculty Development Award

Title: Social closeness modulates neural and computational processes underlying decisions to trust others

Authors: ***Y. YANG**[1], S. WANG[1], C. SHARP[1], J. A. CLITHERO[2], D. S. FARERI[3], D. V. SMITH[1];
[1]Temple University, Philadelphia, PA; [2]Marketing, University of Oregon, Eugene, OR; [3]Psychology, Adelphi University, Garden City, NY

Abstract: Objective: Social decisions, such as trusting another with money, are complex processes influenced by social context (e.g., trustee identity). Prior research has examined trust decisions (e.g., percentage of trust decisions) and brain response to partner's reciprocation and defection (e.g., increased ventral striatum activation during reciprocation). However, the underlying computational processes and their neural correlates remain largely unknown. Here, we combine Functional Magnetic Resonance Imaging (fMRI) with Drift Diffusion Modeling (DDM, Ratcliff, 1978) to investigate how trustee identity (friend vs. stranger) modulates the computational and neural dynamics of trust decisions.
Methods: Data were acquired from 132 adults (M_{age} = 41.49, SD = 17.45) playing a modified trust game with a friend and an ostensible stranger during fMRI scanning. Part of our data has been published (Smith et al., 2024, Data in Brief). We fitted a DDM model for each participant separately to estimate participant-level trustee-identity effects on cognitive processes (e.g., drift rate, bias, boundary separation). We used these participant-level estimates in whole-brain fMRI analyses to investigate if such effects were associated with functional brain activation and connectivity of the ventral striatum (VS) and Default Mode (DMN) network. All whole brain results were corrected for multiple comparisons using a cluster-defining threshold $Z > 3.1$ and $p < 0.05$ (family-wise error rate).
Results: Behaviorally, participants are more likely to trust a friend partner compared to a stranger partner ($\beta = 1.22$, $p < 0.001$). Drift rate and boundary separation are significantly larger when playing with a friend partner compared to a stranger partner (drift rate, $\beta = 0.63$, $p < 0.001$; boundary separation, $\beta = 0.35$, $p < 0.001$). At neural level, we found positive correlations between trustee identity-related drift rate and activations in posterior cingulate cortex and precuneus . In contrast, we found a negative correlation between trustee-related drift rate and cerebellum right crus activation. We also found a positive correlation between trustee-related boundary separation and posterior insula activation.
Discussion: Our findings reveal that trust-related decision making across social context is supported by distinct cognitive and neural dynamics. These results move beyond simple behavioral differences to provide a cognitive processes-brain account of social decision making. By linking computational signatures of decision making to distinct brain systems, this work advances a mechanistic understanding of how social relationships influence trust.

Disclosures: Y. Yang: None. **S. Wang:** None. **C. Sharp:** None. **J.A. Clithero:** None. **D.S. Fareri:** None. **D.V. Smith:** None.

Late-Breaking Poster

LBP027: I.03. Decision Making

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.03/LBP017

Topic: I.03. Decision Making

Support: NIH R00CA240681
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NIH U19NS123714
Paul G. Allen Foundation

Title: Organization of the thalamic reticular nucleus across spatial scales

Authors: *K. CAO, R. FLANNERY, R. JAVERI, K. WULF, P. GROTZ, C. ARSHADI, N. OUELLETTE, M. HOOPER, M. WOODARD, X. JIANG, D. FRIEDMANN, L. ROY, M. T. SUMMERS, B. TASIC, K. SVOBODA, A. GLASER, J. V. CHANDRASHEKAR;
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Abstract: The thalamic reticular nucleus (TRN) is a shell of inhibitory neurons that gates corticothalamic and thalamocortical information flow, shaping sensory and motor processing as well as higher order cognitive functions such as attention, motivation, and decision-making. Despite its central role in these diverse multi-regional brain-wide circuits, the cell types of TRN remain only partially understood. Anatomical tracing, physiological recordings, and molecular profiling have begun to reveal sub-circuit motifs, but a comprehensive picture of the structural and molecular organization is still lacking.
To address this, we are dissecting the TRN's cellular architecture across spatial scales. Leveraging enhancer AAVs to label molecularly defined neurons and the ExA-SPIM platform for brain-wide single cell imaging, we reconstruct individual neuron morphologies for TRN inputs and outputs. Integrated with the Allen mesoscale connectivity and molecular cell-type atlases, this approach yields a multi-scale morpho-transcriptomic map of TRN circuits. We present here our efforts to study TRN using this paradigm, with a focus on corticothalamic circuits to mediodorsal thalamus.

Disclosures: K. Cao: None. **R. Flannery:** None. **R. Javeri:** None. **K. Wulf:** None. **P. Grotz:** None. **C. Arshadi:** None. **N. Ouellette:** None. **M. Hooper:** None. **M. Woodard:** None. **X. Jiang:** None. **D. Friedmann:** None. **L. Roy:** None. **M.T. Summers:** None. **B. Tasic:** None. **K. Svoboda:** None. **A. Glaser:** None. **J.V. Chandrashekar:** None.

Late-Breaking Poster

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.04/LBP018

Topic: I.03. Decision Making

Support: NIH R01134175

Title: Optical measurement of tonic and phasic dopamine fluctuations in mouse prelimbic cortex: inter-laboratory reproducibility

Authors: *B. Z. ROBERTS[1], J. W. YOUNG[2], S. BARNES[3];
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Abstract: Fiber photometry (FP) enables measurement of neurotransmission in real time in behaving animals via genetically encoded sensors that fluoresce in the presence of a given molecule and stimulation light. Dopamine signaling in frontal areas has recently become accessible by this technique with the development of the highly sensitive GPCR activation-based (GRAB) sensor, gDA3h. Here, we demonstrate: (1) the utility of gDA3h in capturing pharmacologically induced changes in tonic dopamine signaling in the prelimbic area of the mouse prefrontal cortex (PL-mPFC); and (2) the inter-laboratory reliability of this sensor in detecting task-related fluctuations in phasic dopamine signaling in this area. We expressed gDA3h (AAV9-hSyn-gDA3h-EGFP) in the PL-mPFC of male (n=2) and female (n=2) C57BL6/J mice and implanted fiber optic ferules over the infusion site. We first tested mice in a 45-min open field session concurrent with FP, administering an i.p. injection of either the dopamine releaser amphetamine (0 or 1 mg/kg; within-subjects) or the trace amine-associated receptor 1 (TAAR1) agonist R05256390 (0 or 1 mg/kg; within-subjects) after 20 min. We later conducted FP in these mice during a Pavlovian conditioning paradigm whereby illumination of a magazine predicted reward delivery. Amphetamine increased tonic PL-mPFC dopamine signal by ~4x over baseline [$t(4)=3.17$, $p=.034$], peaking ~6 min after administration and slowly decaying across the remainder of testing. TAAR1 activation did not affect this signal. Phasic PL-mPFC dopamine signaling increased during unconditioned stimulus (reward) consumption in the Pavlovian conditioning paradigm [$t(6)=3.69$, $p=.010$], but not during conditioned stimulus (light) presentation. These latter findings reproduced previous results from an auditory head-fixed paradigm. gDA3h therefore reliably captures fluctuations in tonic and phasic dopamine signaling in mouse PL-mPFC. Experiments utilizing this sensor to measure frontal dopamine dynamics during risky decision-making in a mouse model of mania are currently underway.

Disclosures: B.Z. Roberts: None. **J.W. Young:** None. **S. Barnes:** None.

Late-Breaking Poster

LBP027: I.03. Decision Making

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.05/LBP019

Topic: I.03. Decision Making

Title: Humans Flexibly Adjust Social Learning Strategies Based on Partner Characteristics

Authors: *G. MORISHITA[1,2], M. SUGAWARA[3], C. MURAWSKI[4], N. YADAV[4], S. SUZUKI[5];
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Abstract: Social learning is a hallmark trait of humans, enabling individuals to adaptively guide decisions based on others' behavior. Prior research has shown that individuals learn not only from others' rewards (i.e., simulation learning), which is driven by prediction errors about others' outcomes and encoded in the ventromedial prefrontal cortex, but also from others' actions (i.e., imitation learning), which is driven by prediction errors about others' actions and encoded in the dorsal prefrontal cortex.
However, it remains unclear how social learning strategies are adapted to the characteristics of an observed partner. In particular, when partners make noisy decisions, imitation learning may be less advantageous. We therefore hypothesized that reliance on imitation learning would decrease as partner decision noise increased, and that this behavioral adjustment would be accompanied by attenuated encoding of action prediction error signals in the dorsal prefrontal cortex (dmPFC and dlPFC).
To test this hypothesis, we conducted an fMRI experiment (N=36) in which participants performed an observational learning task with partners exhibiting different levels of decision noise. Behaviorally, reliance on partners' actions decreased as decision-noise levels increased, as confirmed by both model-free regression and model-based analyses. Ongoing neuroimaging analyses are examining whether action prediction error signals in the dmPFC and dlPFC are also modulated by partner noise, and preliminary results will be presented. These findings provide new insight into how humans flexibly adjust their social learning strategies based on a partner's characteristics.

Disclosures: G. Morishita: None. **M. Sugawara:** None. **C. Murawski:** None. **N. Yadav:** None. **S. Suzuki:** None.

Late-Breaking Poster

LBP027: I.03. Decision Making

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.06/LBP020

Topic: I.03. Decision Making

Title: Neural correlates of metacognitive learning during perceptual decision-making

Authors: *Y. NANJO;
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Abstract: Metacognitive learning adapts decision policies by comparing internal confidence with external outcomes; however, it remains unclear whether this discrepancy directly drives learning and where in the brain regions it is computed. Addressing this gap would unify metacognitive monitoring with control and explain why some errors trigger change while others are ignored. We combined a random-dot motion discrimination task with functional magnetic resonance imaging to test whether a model-agnostic confidence prediction error (conf-PE)—continuous feedback from a quadratic scoring rule minus the participant's reported confidence—organizes trial-by-trial adjustment and neural responses at feedback. On each trial, participants made a decision about the motion direction, rated confidence on a sixteen-point scale, and received continuous feedback. Learning was quantified from run-wise improvement and from a model-free update index capturing the size of the next trial change. Neuroimaging utilized a whole-brain general linear model that incorporated confidence, feedback value, and signed and unsigned conf-PE entered. Behaviorally, accuracy increased across runs; larger unsigned conf-PE predicted higher next trial adjustments, with high-confidence errors eliciting the largest corrections. In fMRI results, the anterior medial prefrontal and the pregenual cingulate cortices encoded signed conf-PE, the dorsal anterior cingulate scaled with unsigned conf-PE and the update index. Together, these results support a circuit account in which discrepancy signals in the anterior prefrontal and the pregenual cingulate link metacognitive monitoring to control implemented by the dorsal anterior cingulate. This model-agnostic framework defines concrete targets for subsequent model-based analyses of metacognitive learning.

Disclosures: Y. Nanjo: None.

Late-Breaking Poster

LBP027: I.03. Decision Making

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.07/LBP021

Topic: I.03. Decision Making

Support: CB176639
PN2463
DGAPA-UNAM, IN205417
DGAPA-UNAM, IN214520,
DGAPA-UNAM, IN214223

Title: Top-down corticostriatal gating of adaptive restraint during motivational conflict

Authors: *E. ILLESCAS-HUERTA[1], E. HERNÁNDEZ-ORTIZ[2], F. SOTRES-BAYON[3]; [1]Cell Physiology Institute, Mexico, Mexico; [2]Behavioral Neuroscience, National Autonomous University of Mexico, Mexico, Mexico; [3]National Autonomous University of Mexico, Mexico City, Mexico

Abstract: Adaptive action under learned threat requires withholding reward pursuit, yet the specific circuit basis is not known. We identify a top-down prelimbic→anterior nucleus accumbens core (PL→aNAcC) pathway that gates crossing decisions in a semi-naturalistic foraging conflict task in male rats. mPFC subregion inactivations showed that PL—but not infralimbic (IL)—is necessary for restraint, and PL effects occurred without impairing memory or motivation. Single-unit recordings in PL revealed transient firing increases time-locked to conflict crossings, and population analyses demonstrated that PL ensembles differentiate conflict from non-conflict specifically around the decision epoch, consistent with an imminent-crossing signal under threat. c-Fos mapping indicated selective engagement of PL and NAc core (NAcC)—but not shell—, with no differential activation in IL, focusing mechanistic hypotheses on a PL-NAcC axis. Accumbens subregion manipulations dissociated function: anterior NAcC was necessary for restraint, whereas posterior NAcC disruption broadly increased reward seeking irrespective of threat (nonselective disinhibition). Optogenetic silencing of PL→aNAcC terminals reproduced the aNAcC phenotype while sparing memory and motivation, and this pathway was required under learned—but not innate—threat. Together, these data define a top-down PL→aNAcC mechanism that integrates motivational signals to gate action at the moment of choice, providing a circuit-level account of flexible decision-making under danger and a translational handle on disorders marked by impaired inhibitory control and maladaptive risk-taking.

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Late-Breaking Poster

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Topic: I.03. Decision Making

Support: UCLA Friends of the Semel Institute Felloship

Title: Neural Dynamics in ACC and V1 During an Audio-visual Contextual Decision-Making Task in Mice

Authors: ***K. SAFARYAN**[1], J. SHENASSA[1], J. SHALOM[1], A. SAATI[1], S. LAM[2], E. LI[2], P. GOLSHANI[1];
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Abstract: Cognitive flexibility allows animals to make rewarding decisions in rapidly changing environments. Flexible responses to the same stimulus in different contexts require selective attention and continual appraisal of contextual variables. Yet, how distinct cortical circuits encode contextual variables is not understood. To address this problem, mice were trained to perform serial extradimensional shifts (SEDS), where cross-modal stimuli, visual gratings of 45^{o} and 135^{o}, and auditory low(5Hz)- and high(18Hz)- pitch tones, interchangeably define trial outcome or serve as distractor. The shifts between relevant modalities were covert and accompanied by immediate fast decline of the performance with consequent gradual improvement. Each block on average consisted of 90-100 trials with after-switch recovery periods found to be shorter in the auditory-attend blocks (exponential fit tau = 40.4±11.47 trials) compared to the visual-attend blocks (exponential fit tau = 48.7±17.38 trials). Simultaneously, we tracked pupil size throughout the behavioral sessions. We observed transient pupil dilations reliably occurring at trial onset. Notably, onset-aligned dilations coincided with correct (hit) trials, whereas delayed or absent dilations were associated with missed trials. In addition, baseline pupil size differed across alternating contextual blocks. Both fast (trial-related) and slow (block-related) pupil dynamics correlate with behavioral performance and task context. We performed single-cell analyses to assess neural correlates of task variables (visual stimulus, choice, and context) across alternating contexts in the anterior cingulate cortex (ACC), secondary motor cortex (M2), and primary visual cortex (V1). A generalized linear model was used to quantify the responses of individual neurons to these variables obtained from simultaneous acute Neuropixels recordings. Selective responses to visual stimuli were most prevalent in V1 (~7.4%), whereas contextual encoding was more prominent in ACC (~14.3%) and M2 (~9.3%). Choice selectivity was relatively rare across regions; however, ~40% of mixed-selectivity neurons exhibited choice-related responses. Both the ACC and VC units represent wide range of task (contextual) variables with correlated nature of the ACC and VC responses during contextual decision-making task in mice.

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Topic: I.03. Decision Making

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Title: Adolescent social interactions support action flexibility via cell-specific neurotrophin systems

Authors: *K. E. COBB[1], M. K. SEQUEIRA[2], E. H. SEO[2], S. L. GOURLEY[3];
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Abstract: The orbitofrontal cortex (OFC) is necessary for action flexibility—the capacity to dynamically alter learned behaviors to obtain a goal. Social isolation in adolescent mice (from postnatal day [P] 31-56) impairs action flexibility, causing habit-biased reward pursuit wherein familiar behaviors are engaged reflexively, irrespective of outcome. We first report that this deficit is specific to memory-dependent action flexibility, with memory-independent action flexibility remaining intact. We next reveal that housing adolescent mice with only adult conspecifics from P31-P56 mimics social isolation: mice demonstrate impaired action flexibility and elevated dendritic spine density in layer V OFC neurons. We next turned to tropomyosin receptor kinase B (TrkB), a major stabilizer of dendritic spines, hypothesizing that moderating neurotrophin tone might restore action flexibility. Previously, we identified a population of neurons in the OFC that are required for memory-dependent action flexibility. These neurons hold memories of broken action-outcome contingencies and are required to update future actions accordingly. To restrict our manipulation to memory trace cells, we created a novel Cre-dependent truncated TrkB (TrkB.T1) viral construct and infused it into c-Fos "Targeted Recombination in Active Populations" mutant mice to selectively express TrkB.T1 in memory trace OFC neurons. Selective TrkB.T1 expression rescued isolation-impaired action flexibility, and this occurs in coordination with excitatory plasticity in hippocampal-to-OFC projection neurons. Collectively, our results unveil new insights into the specific mechanisms mediating the long-term consequences of social isolation in adolescence.

Disclosures: K.E. Cobb: None. **M.K. Sequeira:** None. **E.H. Seo:** None. **S.L. Gourley:** None.

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Support: NIH Grant DA044297
NIH Grant OD011132

Title: Parallel maturation of the medial orbitofrontal cortex and action flexibility across adolescence

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Abstract: The medial orbitofrontal cortex (MO) is a frontal cortical brain region necessary for envisioning the possible outcomes of varied action strategies. This complex cognitive function evolves and strengthens across adolescent development, though mechanisms remain unclear. Here we use an operant rule-shifting task wherein mice initially develop one strategy to acquire food, then are required to adopt a new one to continue to be reinforced. Adolescents [postnatal day (P) 42] made more errors than adults (P56+) and generated lower cFos counts in the MO, measured as a surrogate for cellular activity. Meanwhile, counts in the vHC, which provides inputs to the MO, remained stable. Similarly, tract-tracing revealed that the densities of vHC-to-MO projections are stable across adolescence, while projections from the basolateral amygdala (BLA) are abundant early in life and then pruned. This developmental profile raises the possibility that adolescent mice struggle to shift due to insufficient communication between the vHC and MO or alternatively, over-exuberance of BLA projections (and potentially synaptic input), combined with poor task engagement of MO neurons. Using combinatorial chemogenetics and asymmetric infusion designs, we demonstrate that vHC-MO connections are necessary for rule shifting, their inactivation making adult mice 'appear' as if they were adolescents. Meanwhile, hyper-activation of excitatory neurons in the BLA and concurrent suppression of task-related neural activity in the MO had no impact. Thus, hippocampal inputs to the MO are likely candidates supporting the maturation of flexible behavior, providing new insight into the neurobiological bases of flexible decision making across adolescence.

Disclosures: A. Wiggins-Gamble: A. Employment/Salary (full or part-time); Graduate Student, Emory University. **S.L. Gourley:** A. Employment/Salary (full or part-time); Associate Professor, Principle Investigator, Emory University.

Late-Breaking Poster

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NIH-BSF CRCNS (2019793)

Title: The contribution of the Periaqueductal Grey to reversal learning, but not acquisition, in a flexible discrimination task assessed by fMRI in mice

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Abstract: Flexible, goal-directed behavior depends on the ability to update value representations in response to changing contingencies. While dopaminergic projections to the ventral striatum are well-established mediators of value-based learning, the role of the periaqueductal gray (PAG)—a midbrain structure classically linked to threat processing and aversive learning—remains unclear in this domain. Using functional MRI in behaving mice performing a go/no-go odor discrimination task, we compared neural activity during initial cue-reward learning (acquisition) and subsequent contingency reversal. To more precisely link neural activity to underlying learning processes, we modeled value updating using a Q-learning framework, a model-free reinforcement learning algorithm. Trial-by-trial estimates of state-action values allowed us to dissociate acquisition from reversal-related signals. As expected, ventral striatal responses tracked expected value during acquisition. However, reversal learning recruited both the ventral striatum and the PAG. PAG activity closely followed model-derived signatures of reversal learning, implicating it in the suppression of previously rewarded actions and in updating behavior in the absence of explicit punishment. These findings reveal a previously unrecognized computational role for the PAG in value-based decision-making and cognitive flexibility.

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Title: Dendritic computation for rule-based flexible categorization

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Abstract: A hallmark of intelligent behavior is the ability to flexibly respond to external sensory inputs based on dynamically changing rules. A central question is how neurons in the brain implement computations underlying intelligent behaviors. The neocortical pyramidal neurons use their elaborated dendritic arbors to segregate a plethora of inputs and dynamically integrate them—a process known as dendritic computation—which may play important roles in rule-dependent sensory processing. However, evidence directly linking dendritic computation with intelligent cognitive behaviors has been absent. Here we combine two-photon imaging and a rule-switching flexible categorization task in mice to show that a projectome-defined extratelencephalic (ET) cortical layer 5 (L5) neurons in the auditory cortex integrate dendritic rule information and somatic sensory input to enable rule-dependent flexible categorization. The apical dendrite and soma within the same ET neurons exhibit distinct compartmental representations for sensory and rule information, with the soma predominantly encoding sensory information and the dendrites representing inferred task rules. Simultaneous optogenetic dendritic inhibition and two-photon imaging revealed that dendritic rule coding is essential for somatic output of flexible categorization. Our findings indicate that nonlinear dendritic integration of rule and sensory information constitutes a neuronal computational mechanism underlying rule-switching flexible decision-making.

Disclosures: Y. Zhang: None.

Late-Breaking Poster

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Title: A novel modular labyrinth for assessing cognitive flexibility in mice

Authors: *I. LUNA[1,2], C. LIU[1], E. HOU[1,3], E. HO[1], A. ENOS[1], M. NESBIT[1], V. S. SOHAL[1];
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Abstract: Cognitive flexibility is the ability to adapt to changes in the environment and is a critical function of the medial prefrontal cortex (mPFC). Cognitive flexibility is often assessed using decision-making tasks in which the probabilities or contingencies of rewards are altered over time. In rodents, cognitive flexibility assays typically involve one decision per trial. To broaden the range of approaches available for studying neural activity during decision-making, we sought to establish a navigation-based assay that incorporates multiple decision nodes per

trial. Specifically, we developed a novel, modular labyrinth constructed from LEGO bricks to explore a low-cost and accessible assay for cognitive flexibility. The modular design features open-top corridors, dead ends, and adjustable routes, enabling paths to be altered across days. By altering the maze layout across sessions, mice are required to flexibly adjust their navigational strategies to discover efficient reward paths. In this assay, mice are first familiarized with a layout that contains both an optimal path to the reward and a longer alternative. On the following day, the optimal path is blocked by adjusting the layout of the labyrinth, requiring animals to adapt their navigational strategies. Performance was quantified by calculating deviations from the optimal path as well as the frequency of dead-end entries, providing a measure of efficiency and flexibility in navigation. Preliminary findings suggest variability across animals in exploration when adapting to a changed environment. Overall, this work introduces a scalable and inexpensive behavioral tool for assessing cognitive flexibility, with a modular design that supports potential applications for optogenetic and pharmacological manipulations in tandem with tethered neural recordings.

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Title: Frontopolar cortex neurons encode computations relevant for solving the explore-exploit dilemma

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Abstract: Explore-exploit decision making requires balancing exploitation of known options with exploration of novel ones to maximize long-term value. Prior work on the frontopolar cortex (FPC) shows it plays a critical role in learning about novel objects, guiding goal-directed behavior, and supporting cognitive flexibility in changing environments. Studies in humans and monkeys demonstrate greater exploration when reward horizons are longer—that is, when rewards are further away. In humans, the FPC encodes reward horizon and influences exploratory decisions. Here, we tested whether the macaque FPC similarly encodes reward horizon and related computations for explore-exploit behavior.We developed a three-arm bandit

task that induces explore-exploit tradeoffs by introducing novel choice options linked to the gain or loss of virtual tokens. Tokens served as secondary reinforcers, cashed out for primary juice rewards once a fixed threshold was reached. This design allowed us to assess whether monkeys adjust exploration as they approach reward horizon. In this task, the number of tokens directly reflects the reward horizon and should influence the likelihood of exploring uncertain options versus exploiting familiar ones. Monkeys were more exploratory when further from cashout (longer horizon) and more exploitative when closer to cashout (shorter horizon).We hypothesized that the FPC would encode both reward horizon and choice uncertainty. We recorded over 600 neurons from the FPC of two rhesus macaques while they performed the task and used a GLM to analyze encoding during key trial epochs. Across trials, 16.8% of neurons encoded the number of tokens at trial start—a proxy for reward horizon. About 30% encoded uncertainty about chosen and unchosen option values. Notably, there was minimal encoding of absolute reward compared with robust encoding of reward uncertainty. These results suggest that FPC activity mediates exploration under uncertainty and supports solving the explore-exploit dilemma.

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Title: Novel dopamine D4 receptor ligands differentially shape psychostimulant-induced risky choice preference without altering baseline decision making in rodents

Authors: C. P. KNAPP[1], D. J. CHANDLER[2], T. M. KECK[3], C. A. BOATENG[4], S. B. FLORESCO[5], B. D. WATERHOUSE[6], ***R. L. NAVARRA**[7];
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Abstract: Catecholamine transmitter systems, including dopamine (DA) and norepinephrine (NE), regulate prefrontal cortex (PFC)-mediated executive functions such as complex decision

making in situations involving uncertain risk/reward. Perturbations of these systems are implicated in ADHD, substance use disorders, and other neuropsychiatric conditions marked by maladaptive risky behavior. Among catecholamine receptors, the DA D4 receptor (D4R) remains least understood due to limited pharmacological tools, but novel ligands with improved specificity now enable more precise study. To examine D4R modulation of baseline and psychostimulant-induced risky choice preference, FMJ-045 (low-efficacy partial agonist), FMJ-038 (high-efficacy partial agonist), and FMJ-054 (full antagonist), were administered (1-10 mg/kg, i.p.) prior to performance of the probabilistic discounting task (PDT), where rodents choose between a small/certain reward (100% probability) and a large/risky reward (descending probabilities across blocks). PDT performance was also tested following co-administration of each ligand (10 mg/kg) with amphetamine (AMPH; 0.5 mg/kg, i.p.). Locomotor activity was measured concurrently using the open field test (OFT) to dissociate cognitive from motor effects. None of the D4R ligands altered baseline PDT measures, including choice preference, choice and magazine latencies, or win-stay/lose-shift behavior, indicating no effect on risk/reward decisions under baseline conditions. As expected, AMPH increased risky choice and reduced lose-shift behavior. FMJ-045 and FMJ-054 attenuated AMPH-induced risky choice and restored lose-shift behavior. FMJ-038 blocked AMPH-induced risky choice but this combination also reduced baseline risky choice in high-reward probability blocks and win-stay behavior. AMPH elevated locomotion, whereas none of the D4R ligands altered activity, confirming that decision making effects were independent of motor changes. These findings show that selective D4R ligands modulate psychostimulant-driven increases risky choice without affecting baseline decision making or locomotion. The full antagonist and low-efficacy partial agonist broadly reversed AMPH-induced risky choice preference and reduced sensitivity to losses, while combination with the high efficacy partial agonist disrupted stable value representation when reward probability was high. Results highlight D4R contributions to risk/reward processing under conditions of elevated PFC catecholaminergic tone and their potential as therapeutic targets for disorders involving executive dysfunction and maladaptive risk-taking.

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Late-Breaking Poster

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Topic: I.03. Decision Making

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Title: Aging alters distinct components of nucleus accumbens dopamine signals during decision making under risk of punishment

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Abstract: Aging is associated with heightened risk aversion, but such shifts in decision making toward safer options can contribute to adverse outcomes such as overly conservative financial strategies, avoidance of necessary health care, and social withdrawal, which can compromise quality of life for older adults. Here we began to investigate the neural mechanisms by which aging causes this shift in decision making toward greater preference for safe vs. risky options, using a rat model of decision making under risk of punishment. This type of risky decision making is mediated by a network of limbic-striatal brain regions and is strongly modulated by dopamine (DA), particularly in the nucleus accumbens (NAc). To elucidate how aging alters the functional role of NAc DA signals in this context, young adult (5 months, n=10) and aged (24 months, n=5) Fischer 344 x Brown Norway F1 hybrid rats of both sexes were trained to make discrete choices between a small, "safe" food reward and a large, "risky" food reward that was accompanied by varying probabilities (0%, 25%, 75%) of mild footshock punishment. As such, outcomes of the risky choice could be divided into "Wins" and "Losses", depending on whether delivery of the large food reward (which occurred on every trial) was accompanied by footshock (which was delivered probabilistically). *In vivo* fiber photometric recording of DA from the NAc core via GRAB-DA2m during task performance revealed signed prediction error-like signals such that in both young and aged rats, DA signals increased during risky Wins and decreased during risky Losses. In both age groups, DA signals tracked shock probability, such that DA signal peaks during risky Wins were larger with higher shock probabilities, and DA signal troughs during risky Losses were shallower with higher shock probabilities. Most notably, in young rats, increases in the DA signal prior to choices of the large reward ("dopamine ramps") scaled with anticipated reward value (i.e., were smaller at higher shock probabilities), whereas these increases were largely absent in aged rats. These latter results could reflect motivational deficits and/or a failure to accurately represent future outcomes in aged rats, and are consistent with the general bias away from risky options in aging.

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Late-Breaking Poster

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Support: NIMH R01MH126183

Title: Neural mechanisms underlying valence bias in reinforcement learning and episodic memory across development

Authors: *S. SIVAKUMARAN[1], N. SOSSOUNOV[1], W. YU[1], C. A. HARTLEY[2];
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Abstract: Individuals learn differently from positive and negative outcomes. Such valence biases in reinforcement learning (RL) shift across development and also yield corresponding biases in what is retained in episodic memory. In the present fMRI study, we investigate the neural mechanisms underlying the impact of valence bias on memory, and how such processes change with age.Seventy-four participants aged 8-25 (target N = 120) completed an RL task in an MRI scanner. Participants had to learn through trial and error the values and probabilities associated with five deterministic or probabilistic "point machines". Images of trial-unique exemplars from three distinct categories were paired with probabilistic wins, probabilistic non-wins, or deterministic outcomes respectively and memory for these images were probed in a surprise recognition test.To measure valence bias, we fit participants' choices with an RL model and computed an asymmetry index (AI) reflecting biases in their learning rates for positive and negative prediction errors (i.e., PE+ and PE-). Consistent with prior research, we found that individuals with more positive AI were more likely to remember the objects presented on PE+ trials, compared to those with more negative AI. A univariate analysis revealed that increased activity in both hippocampus and amygdala during outcome presentation predicted successful recognition memory, suggesting a role in episodic encoding. Further, increases in resting-state connectivity from pre- to post- learning between the hippocampus and the ventral temporal cortical ROI associated with the probabilistic non-win category predicted memory for the those exemplars more strongly in participants with more negative AI, which may reflect prioritized consolidation of PE- memories during post-encoding rest specifically in subjects with a negative valence bias. Together, these preliminary findings provide mechanistic insight into how valence bias during RL shapes memory-related neural processes. Ongoing work will examine whether AI predicts valence-specific neural activation during learning and biased offline memory reactivation during post-encoding rest, as well as potential age-related changes in these neural processes. Collectively this work provides important insights into how individual differences in learning computations shape the prioritization of valued outcomes in memory across development.

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Program #/Poster #: LBP027.18/LBP032

Topic: I.03. Decision Making

Title: Decoding intent to interact from EEG during value-based decision making in virtual reality

Authors: *Y. L. T. M. PAN;
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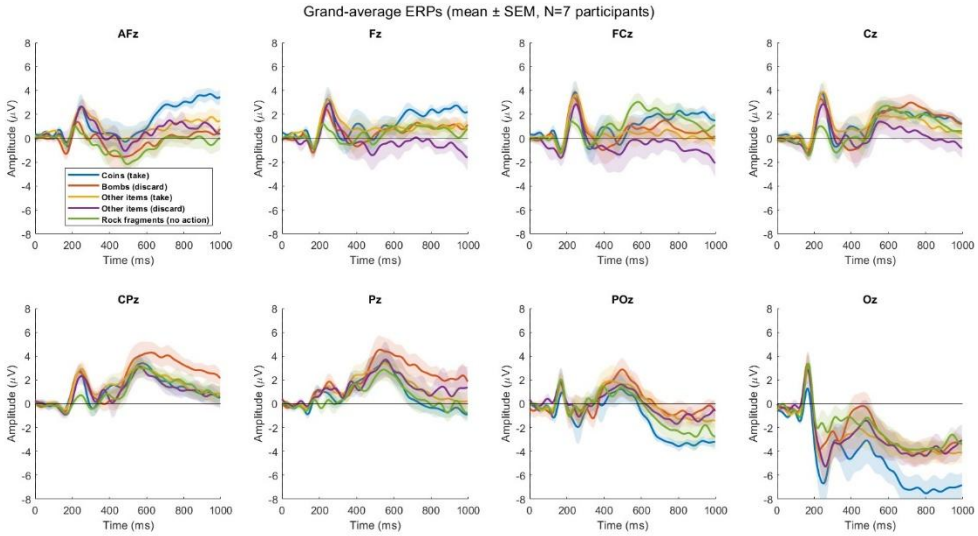
Abstract: Distinguishing intent from no intent is key to understanding how perception drives action and is closely tied to value-based decision-making. This process is a promising target for brain-computer interfaces (BCIs), with intent decoding supporting novel interactions, e.g., hands-free control in virtual reality (VR). Yet most research relies on simplified paradigms such as gambling tasks, limiting ecological validity. We developed an immersive VR paradigm to investigate the neural dynamics of value-guided interaction intent under naturalistic conditions. Participants (n=7 of 23 planned) wore a 64-channel EEG cap and a VR headset while interacting with items of varying value: coins (always beneficial), bombs (always harmful), food/armor (context-dependent gaming items), or rock fragments (irrelevant). Each trial included a 1-s observation period during which participants maintained gaze on the revealed item before being cued to act. EEG from this period was processed with independent component analysis (ICA), reduced to mean amplitude features, and used to train a shrinkage linear discriminant analysis (sLDA) classifier. The classifier achieved 68.6% ± 3.2% cross validated accuracy (mean ± SEM, n = 7) in distinguishing "take" versus "discard" decisions, above the chance level of 57.2% ± 1.6% (Wilson, mean ± SEM, n = 7). ERPs showed clear value effects: rock fragments evoked reduced N2/P3 consistent with absent intent, while value-bearing items produced enhanced centro-parietal positivity. Bombs elicited stronger late parietal activity (CPz/Pz), suggesting aversive salience, whereas coins showed greater frontal (AFz/Fz) and occipital (Oz) responses, reflecting reward-related orienting and amplified visual processing. These findings demonstrate that value representations shape both attentional and decisional EEG components, enabling distinguishing intent from no-intent and across value conditions. This work highlights the potential for developing BCI-VR games and advancing both cognitive neuroscience and intuitive interaction systems.



Disclosures: Y.L.T.M. Pan: None.

Late-Breaking Poster

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Title: Human amygdala neurons encode nutritive and taste-related attributes of visually presented food stimuli: evidence from human single neuron recordings

Authors: E. ATANGANA[1], S. ZHENG[2], S. SADEGHI[3], S. CHENG[4], A. MAMELAK[4], U. RUTISHAUSER[4], *J. P. O'DOHERTY[5];
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Abstract: Humans make decisions by selecting options with the greatest expected value. It has been hypothesized that the value of a stimulus, including of a food object, is constructed dynamically in the brain by integrating over the underlying constituent features of that stimulus, such as its taste attributes, nutritive content, and visual properties. Functional magnetic resonance imaging (fMRI) studies have provided important insights into how the human brain represents the value of food rewards as well as providing evidence for the representation of individual nutritive features of a food. However, the limited spatiotemporal resolution of this technique constrains our understanding of value construction at the neuronal level. Building on a large literature implicating the amygdala and ventromedial prefrontal cortex in reward-related processing, we examined neurons in these areas to ascertain whether individual constituent attributes of a food stimulus are represented in these regions at the level of single neurons. To test this, we examined four epilepsy patients undergoing neurosurgical monitoring for epilepsy with implanted electrodes who performed a food valuation task while we recorded neuronal activity across multiple brain regions. Poisson generalized linear models were applied to the neural spike data to determine if a neuron significantly encoded for value or features. A binomial test revealed that while food value was represented in both ventromedial prefrontal cortex ($p < .05$, 67 total neurons) and amygdala ($p < .05$, 51 total neurons) neurons, taste, nutrient, and visual feature encoding was uniquely observed in amygdala neurons ($p < .001$). Visual features ($p < .001$, 30 total neurons) and taste features ($p < .05$) were also encoded in the posterior temporal lobe, while nutrient features were represented in the hippocampus ($p < .01$, 29 total neurons). Furthermore, we examined the balance of value and feature encoding within each region by fitting models that included both predictors and compared their partial R^2 contributions. This revealed that the representation of features, in general, takes more precedence than value in the amygdala, posterior temporal lobe, and hippocampus compared to the ventromedial prefrontal

cortex. These findings, made possible through rare access to single-neuron recordings in humans, extend our current knowledge of value construction for food in the human brain beyond the limits of fMRI, and provide evidence for a potentially important role of the human amygdala in encoding food-related features as a precursor to an overall value.

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Late-Breaking Poster

LBP027: I.03. Decision Making

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP027.20/LBP034

Topic: I.03. Decision Making

Support: Glenn Greenberg and Linda Vester Foundation

Title: Effective pharmacological PTSD treatment does not mitigate pathological aversion to ambiguity

Authors: *D. YAN[1], A. VARELA[1], K. LOUIE[2], C. M. RAIO[3], P. W. GLIMCHER[4]; [1]NYU Grossman School of Medicine, New York, NY; [2]Neuroscience Institute, New York University School of Medicine, New York, NY; [3]Psychiatry, NYU School of Medicine, New York, NY; [4]New York University, New York, NY

Abstract: Uncertainty aversion is central to health behavior and psychopathology. Post-traumatic stress disorder (PTSD) and other psychiatric disorders have been linked to elevated ambiguity aversion, especially in the loss domain. Levy et al. reported heightened ambiguity aversion in combat veterans with PTSD (Ruderman et al., 2017), consistent with PTSD-related hypervigilance and heightened fear responses, underscoring the relevance of intolerance of uncertainty.However, few studies have assessed whether effective PTSD treatments reduce ambiguity aversion. Given evidence that stellate ganglion block (SGB) is effective for PTSD (Hanling et al., 2016; Rae Olmstead et al., 2020), we examined whether SGB mitigates pathological ambiguity aversion.We conducted a longitudinal randomized placebo-controlled trial to evaluate SGB for PTSD. Patients received right-sided ultrasound-guided injections of bupivacaine or saline at C4 and C6. They were followed for 4 months and completed repeated psychological assessments, including the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5) as the primary outcome measure. We also conducted pre/post-treatment fMRI scans with emotion, fear, and decision-making tasks. Patients completed a validated decision-making task (Levy et al., 2011) before and after treatment to assess their risk and ambiguity preferences. We hypothesized that ambiguity aversion in the loss domain would decrease after treatment; that reductions in CAPS scores would predict reduced ambiguity aversion while risk preferences would remain stable.We present preliminary data here from 69 participants (52 treatment, 17 placebo). Interestingly, we found a slight positive correlation between PTSD severity and both

risk and ambiguity attitudes. Participants exhibited elevated ambiguity aversion compared to historical healthy controls, consistent with prior findings (Ruderman et al., 2017). Although CAPS scores significantly decreased post-treatment, risk and ambiguity attitudes remained unchanged, suggesting symptom improvement was not mediated by alterations in ambiguity aversion.

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Late-Breaking Poster

LBP027: I.03. Decision Making

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Program #/Poster #: LBP027.21/LBP035

Topic: I.03. Decision Making

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Title: Physiological and Behavioral Signatures of Individual Decision Strategies Under Ambiguity

Authors: *Y. QIN[1,2], N. RUNGRATSAMEETAWEEMANA[2], P. SAJDA[2];
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Abstract: Ambiguity and risk present distinct cognitive challenges in value-based decision making, yet individuals differ in how they resolve such uncertainty. Moreover, the relationship between an individual's behavior in team contexts and their decision-making strategies in value based decision making task remains poorly understood. To tackle this, we developed a Lottery Choice Task (LCT) in which participants chose to either keep a fixed monetary amount or invest in a gamble with varying levels of ambiguity (0, 3, or 6) and probabilistic payoffs. Fifty-seven healthy adults (mean age = 23.68 ± 3.32 years; 25 female) completed one to three sessions each while having their electroencephalogram (EEG) and pupillometry recorded. After quality control, the final dataset included 96 behavioral, 77 pupillometry, and 89 EEG sessions, each comprising 132 trials. Based on alignment with expected value, participants were classified into three behavioral profiles: ideal (aligned), aggressive (invest despite lower expected value), and conservative (keep despite higher expected value). Our results indicate that individuals classified

as aggressive received significantly higher leadership ratings during a prior collaborative control task (Qin et al., 2025), suggesting a behavioral link between risk-seeking and perceived leadership ($F = 6.28$, $P = 0.003$). Moreover, physiological responses to both ambiguity and decision type (keep vs. invest) were most pronounced in the ideal group. Specifically, ambiguity elicited stronger pupil dilation and increased parietal EEG power in ideal participants. Likewise, investment decisions modulated EEG power in frontal and parietal regions primarily for the ideal group. These findings reveal that individuals adopt distinct, stable strategies under uncertainty, and that these strategies are reflected in both social behavior and neurophysiological responses. Our results underscore the importance of subject-level profiling in understanding the neural mechanisms of economic decision making under ambiguity.
Reference:Qin, Yinuo, et al. "Physiologically informed predictability of a teammate's future actions forecasts team performance." *iScience* 28.5 (2025).

Disclosures: Y. Qin: None. **N. Rungratsameetaweemana:** None. **P. Sajda:** None.

Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

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Program #/Poster #: LBP028.01/LBP036

Topic: I.04. Executive Functions

Support: NIH Grant NS120987

Title: Mesocortical dopamine circuits contribute to interval timing variability

Authors: *M. A. WEBER[1], K. SIVAKUMAR[2], E. TABAKOVIC[3], N. S. NARAYANAN[2]; [1]University of Iowa, Iowa City, IA; [2]Neurology, University of Iowa, Iowa City, IA; [3]Iowa Neuroscience Institute, Iowa City, IA

Abstract: The mammalian frontal cortex is densely innervated by dopaminergic projections from the ventral tegmental area (VTA) that support cognitive control processes. However, the precise role of VTA dopamine neurons during cognitive control is not well understood, and we hypothesized that VTA dopamine neurons support cognitive control processing in the frontal cortex. To test this hypothesis, we studied rodent VTA dopamine neurons during interval timing, which requires working memory for temporal rules and attention to the passage of time to estimate intervals of several seconds. In the first experiment, we delivered Cre-dependent GCaMP6s into the VTA of dopamine transporter-IRES-cre mice ($DAT^{IREScre}$; n=7) and then trained these mice in an interval timing task that requires the subject to switch response ports after enough time has passed without reward. We measured Ca^{2+}dependent changes in fluorescence using fiber photometry and found that VTA Ca^{2+} dynamics increase rapidly at the start of an interval timing trial. Interestingly, a greater change in mean VTA Ca^{2+} dynamics at trial start predicted less timing variability, suggesting that manipulating VTA dopamine neurons at the beginning of an interval timing trial will alter timing variability. In the second experiment,

we inhibited VTA dopamine neurons of $DAT^{IREScre}$ mice (n=7) using Cre-dependent halorhodopsin while simultaneously recording frontal cortex neuronal activity. Inhibition of VTA dopamine neurons increased timing variability and increased trial-by-trial variability in neuronal firing rates. These data predict that stimulating VTA dopamine neurons has the potential to decrease timing variability. We tested this idea by expressing Cre-dependent channelrhodopsin in the VTA of both intact $DAT^{IREScre}$ mice (n=7) and dopamine depleted $DAT^{IREScre}$ mice (n=7) to stimulate dopamine neurons during interval timing. Strikingly, we found that stimulation for 2 seconds at trial onset was sufficient to improve timing variability in both intact and dopamine depleted mice. Together, these results highlight the importance of VTA dopamine activity for interval timing variability, which is relevant for understanding basic mechanisms that support cognitive control as well as neurological and neuropsychiatric illnesses that affect cognition and dopamine circuits. These results may guide future therapeutics and brain stimulation interventions that improve cognition in disease.

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Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP028.02/LBP037

Topic: I.04. Executive Functions

Support: Bretagne Atlantique Ambition (BAA) and the Rennes Clinical Neuroscience Institute (INCR)

Title: Functional connectivity is dominated by aperiodic, rather than oscillatory, coupling

Authors: N. MONCHY[1], ***J. DUPREZ**[1], J.-F. HOUVENAGHEL[1], B. VOYTEK[2], J. MODOLO[1];
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Abstract: Functional connectivity (FC) is commonly used to identify specific circuits underlying brain (dys-)function. Classical methods to identify functional networks rely on filtering electrophysiological signals in canonical frequency bands and using connectivity metrics, under the assumption that FC reflects oscillatory networks. However, signals also contain non-oscillatory, aperiodic neural activity and the presence of oscillations, while presumed, is not systematically checked. This raises the question about the contribution of aperiodic activity to FC networks identified with classical methods. Here, we used two different human electroencephalography databases (n= 59, n=103), to estimate the contribution of aperiodic activity on reconstructed oscillatory functional networks in resting state, and during cognitive task recordings (n=59) as a complementary analysis. We used the specparam algorithm to

identify significant spectral peaks to only keep the pairs of regions of interest (ROIs) that displayed true oscillatory connectivity. We compared our results with the classical analysis pipeline (without checking for oscillations) in terms of ROIs displaying oscillations, kept functional connections, and classical graph theory metrics reported in the literature. Our results showed that the contribution of aperiodic activity dominated in about 99% of delta, theta, and gamma functional networks, over 90% of beta functional networks and between 23 and 61% of alpha functional networks. The drastic reduction in surviving connections after checking for oscillations was robustly found in resting state in both datasets and also during a cognitive task. The graph theory metrics were significantly impacted by whether or not the presence of oscillations was checked. Although a universal consensus on how to identify and quantify neural oscillations is yet to be reached, our results indicate that oscillatory functional networks may be drastically sparser than commonly assumed, and that conclusions regarding these networks might be biased. Most resting-state FC studies might therefore actually reflect aperiodic networks instead of oscillations-based networks. Consequently, we recommend that studies within the theoretical framework of oscillatory FC first check the actual presence of aperiodicity-unbiased neural oscillations before estimating their statistical coupling to strengthen the robustness, interpretability, and reproducibility of FC results.

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Late-Breaking Poster

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Program #/Poster #: LBP028.03/LBP038

Topic: I.04. Executive Functions

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Kent and Liz Dauten
Simons Foundation
Paul and Daisy Soros Foundation

Title: Electrophysiology of precision functional networks: Concordant insights from fMRI and iEEG in an oddball paradigm

Authors: *W. SUN[1], M. R. LIBOWITZ[2], D. FELDMAN[2], J. DU[1], T. DAVIS[2], S. RAHIMPOUR[2], E. H. SMITH[2], J. B. KING[2], R. L. BUCKNER[1], B. SHOFTY[2];
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Abstract: Precision fMRI has recently revealed insights into the topography and function of large-scale distributed networks. In this multi-modal study, we estimated precision functional

networks in pre-operative patients and then examined electrophysiology using iEEG following their surgery.

The pre-operative session (~60 min fMRI) included a visual oddball task. Using an automated pipeline, both precision functional network estimates and task responses were extracted (Du et al., 2025 *Neuron*). Individuals then underwent iEEG surgery and performed the same task post-operatively (~70 min iEEG).

The fMRI oddball effect showed robust activation of the Cingulo-Opercular Network (CG-OP) and deactivation of the Default Network (DN) consistent with expectations (Du et al., *J Neurophysiol*; for context see Dosenbach et al., 2025 *Nat Rev Neurosci*). Based on co-localization of electrode contacts with network assignments and fMRI task responses, contacts were selected *a priori* for iEEG analysis. In a first individual, the selected anterior insula contact within CG-OP showed a robust increase in high frequency broadband (HFB) power to oddball targets, while an inferior frontal contact estimated to be within the DN demonstrated a clear decrease in HFB power. In post-hoc analyses examining all available contacts localized to higher order networks, the oddball response was found to be selective, demonstrating increased power for multiple electrodes within the CG-OP and salience networks and decreased power within the DN. Replication analyses in a second individual are underway, and additional participants are being enrolled.

These results suggest a precision fMRI-iEEG framework that can be leveraged to make novel discoveries about the organization and function of human brain networks.

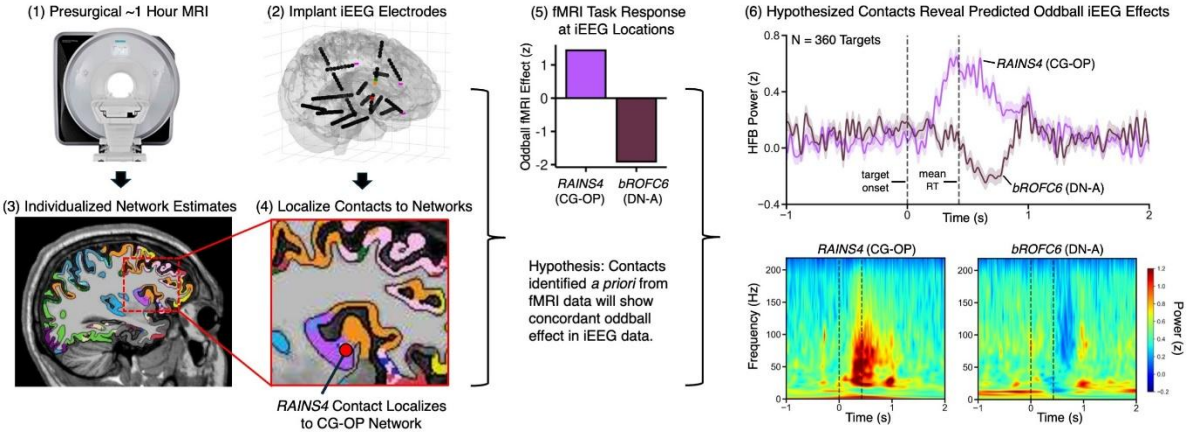
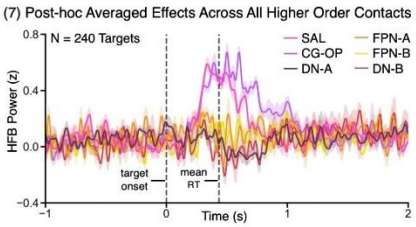


Figure 1. Precision network mapping and hypothesis-driven electrophysiology analysis. *Plots (5) and (6) represent data from individual iEEG contacts. Plot (7) represents data averaged across all available iEEG contacts within each higher order network. CG-OP: Cingulo-Opercular Network (also called the Action-Mode Network); DN-A: Default Network A; SAL: Salience; DN-B: Default Network B; FPN-A: Frontoparietal Control Network A; FPN-B: Frontoparietal Control Network B; HFB: high frequency broadband (75-175 Hz).*



Disclosures: W. Sun: None. **M.R. Libowitz:** None. **D. Feldman:** None. **J. Du:** None. **T. Davis:** None. **S. Rahimpour:** None. **E.H. Smith:** None. **J.B. King:** None. **R.L. Buckner:** None. **B. Shofty:** None.

Late-Breaking Poster

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Program #/Poster #: LBP028.04/LBP039

Topic: I.04. Executive Functions

Support: R01MH131559

Title: Task representations in a community structure

Authors: *B. HUANG[1], J. JIANG[2];
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Abstract: Cognitive flexibility enables us to switch between different tasks to accommodate change of goals. Previous studies have shown that statistical learning plays an important role in supporting cognitive flexibility by learning the probability of switch in general and the probability of switching to a specific task. Beyond transitions between two tasks, in real life tasks usually form higher-order structures. For example, tasks can group into communities (i.e., clusters of tasks with more frequent switches within than between clusters) based on context, such as data analysis tasks and cooking tasks. However, it remains unknown whether and how higher-order structure of tasks can be learned from statistical learning to support cognitive flexibility. The hippocampus and the dorsolateral prefrontal cortex (dlPFC) have been demonstrated to be engaged in the discovery of community structure from experiences of transitions between items. We hypothesize that similar neural mechanisms can be applied to identify higher-order structures of tasks in the environment and adjust neural task representations accordingly, and the neural task representation structure will affect cognitive flexibility. To test this hypothesis, participants (n = 40) learned eight perceptual discrimination tasks and switched between tasks at the trial level. Unbeknownst to the participants, the tasks are organized into two communities of four tasks each. Within each community, only one task (boundary task) has 1/3 chance to switch to the boundary task of the other community, while all other task switches are within-community. Trial sequences were generated by both Hamiltonian walk and random walk based on the community structure. Behaviorally, we focused on boundary tasks and found that participants responded more slowly and made more errors when switching across communities compared with switching within communities. fMRI analysis revealed stronger activation in the cerebellum and anterior hippocampus for between- than within-community task switches. Our findings provide initial evidence supporting that higher-order structure of tasks, such as community, can be learned to influence performance in cognitive flexibility.

Disclosures: B. Huang: None. **J. Jiang:** None.

Late-Breaking Poster

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Program #/Poster #: LBP028.05/LBP040

Topic: I.04. Executive Functions

Support: R01MH131559

Title: Active reorganization of task representation following hierarchical task learning: evidence from 7T fMRI

Authors: *W. LEE[1], J. JIANG[2];
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Abstract: Humans have an ability to learn complex tasks efficiently and generalize those learned tasks to new contexts adaptively (Lee et al., 2022). One possible mechanism underlying this ability is hierarchical task representation, which refers to the ability to use simpler tasks as building blocks for complex task learning. Previous literature suggests that the Medial Temporal Lobe (MTL) and Lateral Prefrontal Cortex (LPFC) are key regions representing tasks in cognitive map, and translating into actionable production rules (Vaidya & Badre, 2022). However, whether and how the compositional relation changes constituent simple task representations is not well understood. Here, we hypothesize that task representations in the hippocampus and LPFC change when simple tasks are used as building blocks for complex task learning. To test this hypothesis, we conducted a two-day fMRI experiment (n = 30). On day 1, participants first learned four simple tasks (A, B, C, D), each requiring participants to focus on different feature of a stimulus. Participants then performed complex tasks, which can be learned by associating two simple tasks (AB, CD). On day 2, participants repeated same simple tasks phase. We predicted that, on day 2, the neural representations of associated simple tasks will be changed more than non-associated simple task, compared to day 1. Our behavioral analysis supports the prediction by presenting faster RTs when switching between associated simple tasks than day 1 ($t(29) = -2.07$, $p = .041$), which suggests that the task representations between associated simple task has been reorganized for adaptive behavior. Furthermore, representation similarity analysis (RSA) using 7T fMRI data showed decreased pattern similarity between associated simple tasks on day 2 than day 1 in the left middle hippocampus ($t(29) = -2.13$, $p = .041$), and right dorsal LPFC in right hemisphere ($t(29) = -3.20$ $p = .003$). This finding points to the pattern separation process that may reduce interference between constituent task representations to support adaptive behavior. Overall, it suggests that the complex task learning can be achieved by actively reorganizing the neural representations of its constituent simple tasks, which supports hierarchical task learning.

Disclosures: W. Lee: None. **J. Jiang:** None.

Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP028.06/LBP041

Topic: I.04. Executive Functions

Title: Single-trial EMG signatures reveal how pause and retune processes shape human action stopping

Authors: *C. G. WADSLEY[1], I. ESPINO - MARQUEZ[1], D. A. DIESBURG[2], J. R. WESSEL[3], I. GREENHOUSE[1];
[1]University of Oregon, Eugene, OR; [2]Psychological and Brain Sciences, Brown University, Providence, RI; [3]The University of Iowa, Iowa City, IA

Abstract: The ability to stop our actions is critical for navigating our everyday environment safely. The contemporary "pause-then-retune" framework distinguishes two key processes in response inhibition: a rapid, nonspecific "pause" to interrupt an action during attentional processing, followed by a context-dependent "retune" to cancel or adjust the action appropriately. While a global pause process is well established, its duration and whether a distinct retune process is necessary for response inhibition are unclear. We aimed to characterize pause and retune processes at a single-trial level using stimulus-selective stop-signal tasks (SST) and electromyography (EMG). Human participants (n = 20) completed two SST conditions: a standard condition with relaxed effectors at trial onset and ballistic go responses, and an active condition with pre-contracted effectors and sustained press-and-hold go responses. Stop-signal reaction times and EMG cancel times did not differ between conditions (both $P > 0.09$), indicating comparable response inhibition. The frequency and timing of partial EMG (pEMG) responses in the active condition were then analyzed and defined as responses terminated before the end of the go-response period. Trial-wise analyses revealed stop failures, compared with successes, were characterized by a faster onset ($F_{1,38} = 48.98$, $P < 0.001$) and larger area ($F_{1,38} = 79.51$, $P < 0.001$) of pEMG, but not by how fast pEMG suppression occurred ($F_{1,38} = 1.29$, $P = 0.324$). Importantly, pEMG was observed in nearly all failed stop trials (96.7%) compared to ignore trials (57.2%, $W = 210$, $P < 0.001$) and correct stop trials (70.0%, $W = 190$, $P < 0.001$), where roughly one-third of stop trials in the active session were explained by instances of "not-going". The duration of pEMG suppression was also longer in failed stop trials (171.1 ms) compared to correct stop (144.0 ms, $F_{1,38} = 25.04$, $P < 0.001$) and ignore trials (108.6 ms; $F_{1,38} = 133.34$, $P < 0.001$). These results have important implications for understanding response inhibition. First, they support a pause process as the primary driver of early stopping but indicate stopping depends more on the extent of ongoing motor activity at the time of pausing than on the latency of the pause itself. Second, our data indicate stop and ignore trials diverge roughly 100 ms after the initial pause, with the retune process manifesting as either continued suppression or a resumption of motor activity, respectively. Lastly, our data highlights the limitation of inferring response inhibition solely from the absence of a button press, given the robust EMG suppression observed even on failed stop trials.

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Late-Breaking Poster

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Program #/Poster #: LBP028.07/LBP042

Topic: I.04. Executive Functions

Support: NIH grant U01NS121472
McNair Foundation

Title: A Gamified Go/No-Go Paradigm for the Epilepsy Monitoring Unit

Authors: G. LIU[1], L. MATTAR[1], R. JAFRI[1], A. WATROUS[1], D. PAULO[2], B. Y. HAYDEN[1], N. R. PROVENZA[1], J. YAU[3], S. A. SHETH[1], J. VERGARA DE LA FUENTE[3], *E. BARTOLI[4];
[1]Neurosurgery, Baylor College of Medicine, Houston, TX; [2]Neurosurgery, Henry Ford West Bloomfield Hospital, Birmingham, MI; [3]Neuroscience, Baylor College of Medicine, Houston, TX; [4]Baylor College of Medicine, Houston, TX

Abstract: The go/no-go (GNG) task is a well-known paradigm for studying reactive inhibition. While traditional GNG tasks use repetitive presentations of letters or other visual stimuli, there is an inherent disconnect between standard laboratory assessments and the application of inhibitory control in naturalistic, real-life scenarios. To understand how neural activity supporting inhibitory control generalizes to more realistic scenarios, we developed a gamified GNG paradigm. By creating a video game version, we aimed to capture the same cognitive control performance metrics as traditional GNG tasks in a more naturalistic way for use at the Epilepsy Monitoring Unit. Our objective is to compare behavioral and neural responses obtained via gamified GNG against key traditional GNG metrics. To this end, we recruited ten neurosurgical patients undergoing intracranial stereo-electroencephalography monitoring at the epilepsy monitoring unit (3 males, age range from 20 to 68). Single-unit activity in orbitofrontal cortex (OFC) was obtained through Behnke-Fried probes. The gamified GNG Task was designed in Unity. During the task, subjects are placed in a dark hallway where they observe computer-generated figures, either humans or monsters, sprinting towards them. They must quickly decide to either close a gate to prevent the figure from reaching their player ("monsters", go trials) or leave it open to allow them to pass ("humans", no-go trials, 30%). The task features dynamic difficulty adjustment based on performance, varied figure designs, and a point-based reward system associating different values with different figures. Behavioral results demonstrated that the gamified GNG successfully replicated key cognitive control behaviors seen in traditional GNG paradigms, including faster reaction times for false alarms than for go-correct trials ($p<0.001$), post-error slowing ($p=0.027$), and slowing responses with increasing difficulty (correlation between reaction times and difficulty level ranging from 0.51 to 0.84 for each

participant, all $p<0.001$). Neuronal state-space analysis of OFC units (93 units across 7 patients) revealed condition-dependent trajectories that diverged between go and no-go. These results align with existing evidence of OFC modulation by inhibitory demands, thus validating the use of this novel task to investigate inhibitory control more naturalistically across difficulty levels and in association with different action values. In the future, we plan to perform within-participants comparisons of gamified and traditional GNG signatures.

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Late-Breaking Poster

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Program #/Poster #: LBP028.08/LBP043

Topic: I.04. Executive Functions

Title: Subliminal visual stimulus triggers automatic inhibition of saccadic eye-movement and influences the pupillary dynamics.

Authors: S. PETHE[1], ***S. RAY**[2];
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Abstract: Subliminal visual stimulus triggers automatic inhibition of saccadic eye-movement and influences the pupillary dynamics
Sayali Pethe, **Supriya Ray***
Department of Psychology, Ashoka University, Plot #2, Rajiv Gandhi Education City, Sonepat, Haryana-131029
Abstract:Masked priming paradigms are essential for studying unconscious information processing. They involve a prime stimulus presented briefly, followed by a mask that prevents conscious perception of the prime. The subsequent target stimulus requires a response, usually a button press, from the participant. The subliminal prime's influence on this response is measured. These paradigms reveal two contrasting effects: the positive compatibility effect (PCE) and the negative compatibility effect (NCE). The PCE occurs when a prime compatible with the target facilitates a faster response compared to an incompatible prime. This is observed at very short prime-target stimulus onset asynchronies (SOAs), typically less than 60ms. The NCE is a paradoxical reversal of the PCE, where a compatible prime leads to slower responses than an incompatible prime. This effect is generally observed at longer SOAs (e.g., 100-200ms). This automatic response inhibition prevents the premature execution of a response to the subliminal visual prime. In order to know whether the PCE and NCE are effector-independent phenomena, and whether the subliminal stimulus influences pupillary light response (PLR), we recorded eye-movements and pupil size of healthy young participants. Our data indicate that the oculomotor

system, like the somatomotor system, is vulnerable to automatic inhibition. In addition, differential PLR dynamics was observed based on the compatibility between the subliminal prime and the visible cue to the target.

Disclosures: S. Pethe: None. **S. Ray:** None.

Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP028.09/Web Only

Topic: I.04. Executive Functions

Title: Effects of acute aerobic exercise with and without cognitive demand on executive functions in adolescents with attention-deficit/hyperactivity disorder (ADHD): a case study

Authors: *X.-J. CHAW[1], J.-L. SUN[2], H.-I. KUO[3,4];
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Abstract: Studies have found adolescents with attention-deficit hyperactivity disorder (ADHD) usually suffer from executive function (EF) deficits. Previous evidence has shown that aerobic exercise (AE) could improve EFs in adolescents. However, some researchers have indicated that AE which are not cognitively demanding often showed limited or no effects on EFs. Therefore, this case study aims to investigate the effects of acute cognitively demanding AE on EFs in adolescents with ADHD. This study recruited a female adolescent with ADHD aged 15 years old without any comorbidities and allocated her into a random sequence of three different exercise conditions: cognitively demanding aerobic exercise condition (CE), aerobic exercise condition (AE), and active control condition (AC). She was assessed by inhibitory control (Stop Signal Task), cognitive flexibility (Intra-Extra Dimensional Shift), and working memory (Spatial Memory Task) before and after every exercise conditions. Regarding CE condition, the participant showed improvements across all three executive function tasks. In cognitive flexibility, pre-extra dimensional shift errors decreased from 10 to 4 errors (-60%), adjusted total errors decreased from 12 to 5 errors (-58%), adjusted total trials decreased from 84 to 59 trials (−30%), and total latency decreased from 82,592 ms to 37,541 ms (−55%). Inhibitory control improved with stop signal reaction time (SSRT) reduced from 190.75 ms to 175.94 ms (−8%), while directional errors remained unchanged. In working memory, total errors decreased from 1 to 0 errors (-100%), and strategy scores improved from 4 to 2 scores (-50%). In contrast, AE and AC conditions showed minimal changes especially in cognitive flexibility and working memory.

In AC condition, inhibitory control improved with SSRT reduced from 215.00 ms to 201.08 ms (−7%), while directional errors remained unchanged, which showing results similar to CE condition. This case study found acute bout of CE conditions may enhance EFs (especially in cognitive flexibility and working memory) in an adolescent with ADHD compared to AE and AC conditions. These results highlight the potential value of incorporating cognitive demands into AE interventions which may further enhance EFs. Future study with larger sample sizes is needed.

Disclosures: X. Chaw: None. **J. Sun:** None. **H. Kuo:** None.

Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP028.10/LBP044

Topic: I.04. Executive Functions

Support: National Science and Technology Council, Taiwan Grant 112- 2314-B-002-119-MY3

Title: Effects of virtual reality-based aerobic exercise intervention on executive functions and cortical excitability in adolescents with attention-deficit/hyperactivity disorder (ADHD)

Authors: *J.-L. SUN[1], X. CHAW[2], H.-I. KUO[3];
[1]School and graduate institute of physical therapy, National Taiwan University, New Taipei City, Taiwan; [2]Graduate Institute of Physical Therapy of National Taiwan University, Taipei City, Taiwan; [3]National Taiwan University, Taipei, Taiwan

Abstract: Aims: Previous evidence found that adolescents with attention-deficit hyperactivity disorder (ADHD) are usually accompanied by executive function (EF) deficits, and the underlying mechanism might be due to brain physiology. Studies also indicated that aerobic exercise showed a positive impact on EFs in the ADHD population, and virtual reality (VR)-based intervention might enhance EFs and engagement of the young population with ADHD. Therefore, this study aims to explore the effect of long-term VR-based aerobic exercise intervention on EF performance and cortical excitability in adolescents with ADHD. **Methods:** Ten adolescents with ADHD, aged 13-17 years and free of comorbid conditions, were recruited and randomly assigned to one of the three groups: VR-based aerobic exercise group, aerobic exercise group, or control group. All participants completed EF assessments, including the Stop Signal Task (SST), Continuous Performance Test (CPT), and Wisconsin Card Sorting Test (WCST), as well as cortical excitability measurements using transcranial magnetic stimulation (TMS), both before and after the 5-week intervention. **Results:** Our findings indicated no significant differences among the three groups on SST and CPT from pre- to post-intervention. However, a significant time × group interaction was observed on WCST between the control group and the VR-based aerobic exercise group, specifically for perseverative responses (p =

0.036) and perseverative errors (p = 0.046). Cortical excitability analyses revealed no significant between-group differences from pre- to post-intervention; however, the 2-ms short-interval intracortical inhibition (SICI) exhibited a decreasing trend in the VR-based aerobic exercise group compared to the other two groups. **Conclusions:** This study found that VR-based aerobic exercise may enhance cognitive flexibility and working memory in adolescents with ADHD, as evidenced by significant improvements on the WCST. No significant effects were observed for inhibitory control, attention, or overall cortical excitability; however, a trend toward decreased 2-ms SICI was noted in the VR-based aerobic exercise group, suggesting potential modulation of intracortical inhibition following the 5-week intervention.

Disclosures: J. Sun: None. **X. Chaw:** None. **H. Kuo:** None.

Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP028.11/LBP045

Topic: I.04. Executive Functions

Support: NIH/NIDDK R01DK09933-01A1

Title: Body Mass Index and Sex Interaction Moderates the Relationship Between Number of White Matter Hyperintensities and Set Switching in a Sample of Adults with Obesity

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Abstract: Metabolic syndrome is associated with small vessel ischemia in the brain, contributing to the development of white matter hyperintensities (WMH). Small vessel ischemic disease is associated with deficits in executive functions and processing speed. Sex differences are a current area of interest with respect to WMH due to the higher prevalence of WMH in women than men. This study examined whether baseline WMH burden is associated with cognitive flexibility, measured by a set-shifting task, in individuals with obesity undergoing bariatric surgery evaluation. We also aimed to examine whether the interaction between sex and BMI moderate the relationship between number of WMH and cognition. T2 Flair MRI from participants (n=64, m/f=11/53, BMI=45.90±8.43) WMH were used to assess volume/burden using the lesion growth algorithm implemented in the LST toolbox version 3 for SPM12. Using the PROCESS macro on SPSS, we evaluated the interaction of sex and BMI on the relationship between number of WMHs and Trails B raw performance, controlling for age, education, and race. The overall model was significant, F(10, 53)=3.65, p=0.000. There was a main effect of the

number of WMH on Trails B performance (B=-44.98, p=0.020). While both BMI and sex were significant moderators, there was a WMHs x BMI x sex interaction, which moderated the relationship between the number of WMHs and Trails B performance (β=-0.57, p=0.008). Patterns of findings were disparate between males and females, with females improving in Trails B performance as BMI got higher. In individuals with obesity participating in a study on bariatric surgery, we found evidence for an association between WMH and set shifting. This association is moderated both sex and BMI, as well as a sex x BMI interaction. Future analysis may include immune factors and metabolic syndrome to control confounding.

Disclosures: A.A. Uribe: None. **B. Defeis:** None. **J. Juhasz:** None. **K.J. Johnson:** None. **M. Britton:** None. **H. Hoogerwoerd:** None. **J.B. Williamson:** None. **R. Cohen:** None. **E.C. Porges:** None.

Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP028.12/LBP046

Topic: I.04. Executive Functions

Title: Causal modulation of triple-network connectivity in the human brain with transcranial ultrasound

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Abstract: The triple-network system comprising the salience (SN), default mode (DMN), and central executive (CEN) networks plays a critical role in detecting and mapping salient internal and external events, supporting adaptive cognition and behavior. Aberrant interactions among these networks are a hallmark of many psychiatric and neurological disorders, highlighting the need for solutions to causally and precisely modulate triple-network connectivity in the human brain.Transcranial ultrasound stimulation (TUS) provides a promising noninvasive approach to achieve such modulation. Here, we leveraged theta-burst TUS to investigate whether stimulating a SN hub (anterior cingulate cortex; ACC) versus a DMN hub (posterior cingulate cortex; PCC) would differentially alter functional connectivity within the triple-network system.Twenty-four healthy adults (14 females, 22-53 years) completed three randomized and counterbalanced TUS/MRI sessions, each spaced at least one week apart, in which theta-burst TUS targeted either the left ACC, the left PCC, or was delivered in a sham condition, with resting-state fMRI acquired immediately after each session. Six regions of interest representing the triple-network system were defined: anterior insula (AI), ACC, PCC, ventromedial prefrontal cortex, dorsolateral prefrontal cortex, and posterior parietal cortex (PPC). Static connectivity was assessed using Pearson correlations among the six regional fMRI time series and effective connectivity using multivariate Granger causality. Analyses revealed no significant differences in static functional connectivity across conditions. In contrast, effective connectivity showed a

selective effect: ACC stimulation significantly increased directed influence from AI to PCC and from AI to PPC compared to PCC stimulation ($p < 0.005$). No other directed edges were significantly altered. These findings demonstrate a dissociation between static and effective connectivity measures. TUS to ACC enhanced salience network influence on both DMN and CEN nodes, consistent with the SN's proposed role in causally influencing inter-network dynamics through AI. PCC stimulation, by contrast, did not produce comparable effects, highlighting the region-specific capacity of ultrasound neuromodulation to modulate directed interactions between large-scale networks. The findings also underscore the importance of effective connectivity metrics for detecting nuanced state-dependent effects of noninvasive brain stimulation and point toward the potential of TUS for modulating causal network-level mechanisms relevant to cognition and psychopathology.

Disclosures: S. Phadtare: None. **K. Supekar:** None.

Late-Breaking Poster

LBP028: I.04. Executive Functions

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP028.13/LBP047

Topic: I.04. Executive Functions

Support: NIH Grant R01MH119091

Title: Differences in the relationship between emotion regulation and gray matter volume across sub-types of ADHD

Authors: N. TRUELOVE[1], J. R. COHEN[2], ***S. ASHBURN**[3];
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Abstract: Impaired emotion regulation (ER) is reported in over half of children with attention-deficit hyperactivity disorder (ADHD) and it has been proposed to consider ER among the core symptoms of ADHD. Neuroimaging studies have found reduced gray matter volume (GMV) in individuals with ADHD in comparison to typically developing (TD) controls, particularly within the basal ganglia, frontal and temporal lobes, and the cerebellum (Stoodley et al., 2014). Notably, these regions with altered structure coincide with regions that have been separately implicated in ER (Turkia et al., 2021). However, studies have yet to examine the relationship between ER, GMV, and the sub-types of ADHD: inattentive (ADHD-I), and combined (ADHD-C). Therefore, the present study investigated the relationship between ER and GMV compared across sub-types of ADHD and TD children. We included 127 children, aged 10 to 12 years old, 30 ADHD-I (mean age =11.53, SD = 0.97), 57 ADHD-C (mean age = 11.35, SD = 0.94), and 40 TD (mean age = 11.18, SD = 0.98). Participants completed behavioral tests for IQ (Weschsler 2014), ADHD assessments (Conners 2008; Shaffer at et al., 2000), and the Emotion Regulation

Checklist to measure ER (Shields & Cicchetti, 1997). T1-weighted images were reoriented to the anterior commissure, co-registered, and segmented (grey matter, white matter, and cerebrospinal fluid). We used DARTEL to create a study specific template which was then normalized to MNI space. We also used CAT12 to calculate total intracranial volume and to check for noise outlier and deviating data. We performed a one-way ANOVA (TD vs. ADHD-I vs. ADHD-C), dummy coded for group while controlling for total intracranial volume, to test for group differences in the relationship between ER and GMV. In agreement with previous studies, there was a significant difference in ER between groups, such that ADHD-C exhibited poorer ER than ADHD-I and TD groups. When testing for group differences in the relationship between ER and GMV, we found significant group differences in 24 brain regions, primarily within frontal, temporal-parietal, and basal ganglia regions. Post-hoc partial correlations revealed that higher ER scores, corresponding to poorer ER, was associated with more GMV in the right supramarginal gyrus in the ADHD-I group; however, there was no such relationship within this region for the ADHD-C and TD groups. This study fortifies prior behavioral findings that suggest divergent roles of ER across ADHD subtypes and it also provides evidence of paralleling structural differences.

Disclosures: N. Truelove: None. **J.R. Cohen:** None. **S. Ashburn:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP029.01/LBP048

Topic: I.05. Working Memory

Title: Multiple routes to metacognitive judgments of working memory in the macaque prefrontal cortex

Authors: *C. NING[1,2], G. FU[2], Y.-Y. ZHANG[2,3], F. MEYNIEL[4,5], L. WANG[2];
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Abstract: The ability to evaluate one's own memory is known as metamemory. Whether metamemory is inherent to memory strength or requires additional computation in the brain remains largely unknown. We investigated the metacognitive mechanism of working memory (WM) using two-photon calcium imaging in the prefrontal cortex of macaque monkeys, who

were trained to memorize spatial sequences of varying difficulties. In some trials, after viewing the sequence, monkeys could opt out of retrieval for a smaller reward, reflecting their confidence in WM (meta-WM). We discovered that PFC neurons encoded WM strength by jointly representing the remembered locations through population coding and their associated uncertainties. This WM strength faithfully predicted the monkeys' recall performance and opt-out decisions. In addition to memory strength, other factors—trial history and arousal—encoded in baseline activity predicted opt-out decisions, serving as cues for meta-WM. We identified a code of meta-WM itself that integrated WM strength and these cues. Importantly, WM strength, cues, and meta-WM were represented in different subspaces within the same PFC population. The dynamics and geometry of PFC activity implement metacognitive computations, integrating WM strength with cues into a meta-WM signal that guides behavior.

Disclosures: C. Ning: None. **G. Fu:** None. **Y. Zhang:** None. **F. Meyniel:** None. **L. Wang:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP029.02/LBP049

Topic: I.05. Working Memory

Support: NIH Grant R34NS127100

Title: Optotagging SST interneurons in primate prefrontal cortex reveals their heterogeneous physiology and task modulation

Authors: *R. MOZUMDER[1], Z. WANG[2], C. MAO[1], P. CHEN[1], A. KARIMI[1], K. K. DHILLON[2], T. A. HACKETT[3], B. ZEMELMAN[4], C. CONSTANTINIDIS[1];
[1]Biomedical Engineering, Vanderbilt University, Nashville, TN; [2]Program in Neuroscience, Vanderbilt University, Nashville, TN; [3]Hearing & Speech Sciences, Psychology, Vanderbilt University, Nashville, TN; [4]Neuroscience, University of Texas at Austin, Austin, TX

Abstract: Working memory (WM) relies on prefrontal cortex (PFC) circuits, yet the contribution of specific interneuron classes remains poorly defined in primates due to limited cell-type targeting tools. Capitalizing on recent advancements in optogenetic techniques, we developed a primate model to selectively target somatostatin (SST) expressing interneurons in macaque lateral PFC (areas 8a, 46) by co-injecting two AAV vectors: one carrying the h56D GABAergic promoter linked to a floxed tdTomato and BreaChES, and one carrying an SST regulatory domain linked to the Cre recombinase to ensure selective infection of SST interneurons only. After 6 weeks, we opto-tagged neurons with 589 nm laser pulses during the inter-trial interval while monkeys performed the oculomotor delayed response (ODR) task and a variant task involving a distractor presentation after the cue (ODR-d). Across 68 sessions in two monkeys, we recorded 4,418 units (3,333 single; 1,085 multi). Fifty-one well-isolated neurons

showed significant light-evoked increases in firing (Mann-Whitney U, $p<0.01$) exceeding 2 SD above baseline and exhibited highly similar waveforms during laser and non-laser periods ($r=0.998\pm0.009$), confirming reliable tagging. These tagged neurons displayed heterogeneous activation dynamics with three latency profiles: sustained activation (peak activation at 5.5±2 ms after pulse onset), transient activation (2.8±0.6 ms), and gradual delayed activation (12.2±1.7 ms). Physiologically, these opto-tagged neurons spanned a broad range of baseline firing rates and spike widths but, on average, exhibited higher baseline activity with predominantly narrow spike waveforms. Most tagged neurons exhibited robust task-related modulation, including cue- and delay-period activity. Notably, 33% of the tagged neurons exhibited "inverted tuning" during the delay period of the ODR task; this proportion was significantly higher than non-tagged units (Fisher's exact test, $p=0.016$). In a separate series of experiments, we stimulated the tagged neurons with light during the delay period of the ODR-d task. A net decrease in firing rate was observed in non-tagged neurons at that interval, confirming the inhibitory influence of these tagged neurons on local circuits. These results provide the first cell type-specific characterization of SST interneurons in primate PFC during WM.

Disclosures: R. Mozumder: None. **Z. Wang:** None. **C. Mao:** None. **P. Chen:** None. **A. Karimi:** None. **K.K. Dhillon:** None. **T.A. Hackett:** None. **B. Zemelman:** None. **C. Constantinidis:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP029.03/LBP050

Topic: I.05. Working Memory

Title: Forming generalizable sequence memory through module-based abstract control in frontal cortex

Authors: Y. ZHANG[1], X. LI[2], L. WANG[3], ***B. MIN**[1];
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Abstract: Humans and animals can flexibly assemble or re-assemble complex sequences and effortlessly generalize this ability to novel ones. How this compositional generalization ability is achieved remains elusive. Here, we found that compositional generalization requires abstract rather than specific content-based cognitive control, which can be readily implemented by the coordination of multiple functional neural modules. By introducing a novel *neural control state space*, with its dimensionality equal to the number of functional modules, we clarified not only how the abstract control state gets reconfigured during either sequence assembly or sequence re-assembly but also how the alignment between control state and network connectivity structures directs the information flow propagation required by task demands. Together with the confirmation of the predicted neural modular structure in monkey frontal cortex during spatial

sequence assembly and re-assembly, this work provides a general previously-unknown control-centric, rather than commonly-used representation-centric, theory for generalizable sequence memory formation in frontal cortex.

Disclosures: Y. zhang: None. **X. Li:** None. **L. Wang:** None. **B. Min:** None.

Late-Breaking Poster

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Program #/Poster #: LBP029.04/LBP051

Topic: I.05. Working Memory

Support: PMUB Grant B46G670083
NRCT Grant N34A660627

Title: Differential roles of left and rightposterior parietal cortexin attention: evidence from tdcs and eeg

Authors: N. CHUKASEMRAT[1], C. SAE-CHUENG[1], J. WONGTA[1], S. ITTHIPURIPAT[2], ***D. WIWATRATANA**[2];
[1]King Mongkut's University of Technology Thonburi, Darunsikkhalai Science School SciUS Program, Bangkok, Thailand; [2]Neuroscience Center for Research and Innovation, Learning Institute, KMUTT, Bangkok, Thailand

Abstract: Electrical brain stimulation has been shown to modulate neural activity across multiple cortical regions. While the posterior parietal cortex (PPC) is primarily associated with attentional control, the dorsolateral prefrontal cortex (DLPFC) plays a central role in working memory. This study investigated the contributions of the left PPC (lPPC), right PPC (rPPC), and right DLPFC (rDLPFC) to working memory capacity and the transfer of information into long-term memory using transcranial direct current stimulation (tDCS). Nineteen healthy adults (ages 18-35) performed an attentional task following 20 minutes of 2 mA tDCS applied to the PPC or DLPFC. EEG was recorded to assess neural dynamics during the task. Stimulation of the rPPC and rDLPFC produced no significant changes in attentional performance or EEG indices. In contrast, stimulation of the lPPC significantly increased N2pc amplitude ($p = 0.048$) while impairing behavioral accuracy ($p = 0.038$). These findings suggest that lPPC activation disrupts, rather than enhances, temporal attentional processing, highlighting functional asymmetries between left and right PPC in attentional control and working memory dynamics.

Disclosures: N. Chukasemrat: None. **C. Sae-chueng:** None. **J. Wongta:** None. **S. Itthipuripat:** None. **D. Wiwatratana:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

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Program #/Poster #: LBP029.05/LBP052

Topic: I.05. Working Memory

Support: NIH/NINDS K12 Grant K23 NS114178
NIMH grant MH122023

Title: Type of sensory information held in working memory can be decoded from sensory cortices with MiniRocket time series classification

Authors: *P. D. HACKETT[1], B. KUNDU[2];
[1]Neurosurgery, University of Missouri, Columbia, GA; [2]Neurosurgery, University of Missouri, Columbia, MO

Abstract: Working memory (WM) involves actively manipulating information in the short term. We addressed whether the type of sensory stimuli being held in memory (e.g. auditory tones, visual colors) can be decoded from sensory areas such as the superior temporal gyrus (STG) and the ventral visual stream, based on the sensory recruitment hypothesis that stimulus information is maintained within sensory cortex. Patients (n=10) with intracranial electroencephalography electrodes participated in a multimodal, load 3, WM task with 4 types of sensory stimuli. We applied a MiniRocket convolutional feature layer plus ridge regression to each channel and sensory stimuli type to decode sensory information held in memory during the first 1500 ms of memory maintenance period (MP1). We used outer cross-fold validation (3-fold, 70/30 split) on the training window to estimate accuracy. A region of interest (ROI) was predictive of class if >1 channels accurately predicted class during MP1 over fixation (FIX) with paired McNemar's $p < 0.05$, and >0 channels predicted class during MP2 and stimulation (STIM) over FIX. We found bilateral anterior STG is predictive of tone (LantSTG MP1: 2 sig chans/9 total, acc = 66.3%, SE = 4.9%; RantSTG MP1: 2 sig chans/4 total, acc = 80%, SE = .6%). R Fusiform Gyrus (RFUS) and R Inferior Temporal Gyrus channels predicted color class (RFUS MP1: 2 sig chans/13 total, acc = 71.7 %, SE = 1.7). The bilateral middle temporal gyri (MTG) predicted all classes during STIM but not during MP. These results suggest sensory cortex supports sensory modality specific memory, supporting further work to explore specific neural signatures of item specific information, which may be held within sensory areas.

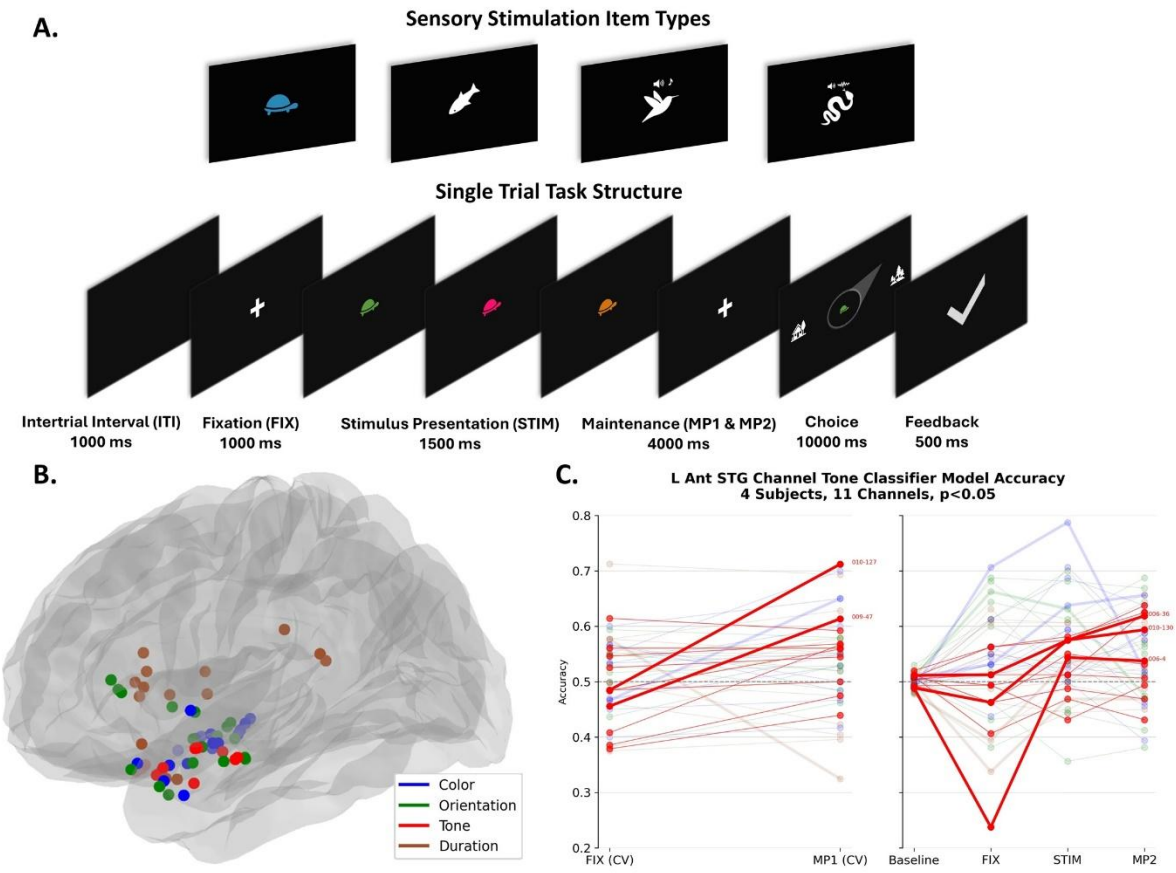

Figure 1. A. A single trial of a load-3 delayed recognition task. 120 trials are balanced across four sensory trial types: color turtles (visual), fish orientation (visual spatial), bird tones (auditory pitch), or snake hiss duration (auditory temporal). **B.** Channels significantly predictive of trial sensory class shown in MNI space ($p<0.05$ across all MP and STIM epochs > fixation). **C. Left Plot:** Example ROI shown of significant CV accuracy of MP1 over FIX in the L Ant STG. Significant channels are bold lines. **Right Plot:** MP1 Trained model on all trials shows significant accurate replay during STIM and MP2 compared to FIX.

Disclosures: P.D. Hackett: None. **B. Kundu:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

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Program #/Poster #: LBP029.06/LBP053

Topic: I.05. Working Memory

Support: NIH Grant 1R01MH131678-01A1

Title: The effects of single-pulse TMS on the representation of priority in working memory

Authors: *J. M. FULVIO[1], B. R. POSTLE[2];
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Abstract: In the double-serial retrocuing (DSR) paradigm, two items are presented as samples, then one is cued as the one that will be tested first, thereby assuming the status of "prioritized memory item" (PMI). The uncued item becomes an "unprioritized memory item" (UMI) that may or may not be cued after the first test. In previous work, a single pulse of transcranial magnetic stimulation (spTMS) delivered after the first cue prompted the involuntary retrieval of the UMI, and here we assessed the neural bases of this effect by recording EEG during performance of DSR and a matched control condition, a single retrocue (SR) task that does not produce a UMI. spTMS triggered an immediate rescue of MVPA decodability of the UMI but not of "irrelevant memory items" (IMI) produced by the second cue of DSR and by the cue during SR. Bandpass filtering indicated that this effect was carried by the alpha (8-13 Hz) and low-beta (13-20 Hz) bands. The first cue of DSR was uniquely associated with elevated phase locking in low beta, as was spTMS delivered during this epoch. Demixed (d)PCA was used to define priority-related subspaces, and these revealed rotational patterns unique to the first cue of DSR and to spTMS delivered during this epoch. Together, these results are consistent with the idea that dynamics in the low-beta band encode priority status in working memory, and that the effects of spTMS on decoding and on performance are due to disruption of this mechanism.

Disclosures: J.M. Fulvio: None. **B.R. Postle:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

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Program #/Poster #: LBP029.07/LBP054

Topic: I.05. Working Memory

Support: NSF 2120539

Title: Does rhythmic sampling modulate multiple stages of working memory?

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Abstract: Frequency-specific neural activity phasically modulates the strength of item representations being maintained in working memory and the attention-related sampling of item representations being maintained in working memory. Whereas previous work has primarily focused on how rhythmic neural processes influence item representations during a memory delay, here we focused on whether and how rhythmic neural processes modulate multiple stages of working memory: (1) the encoding of behaviorally important information from the external environment into internal representations, (2) the retrieval of behaviorally important information from internal representations, and (3) the maintenance of behaviorally important internal

representations despite interference from behaviorally irrelevant external stimuli (i.e., environmental distractors). To investigate these questions, we recorded EEG from human participants during a visual working memory task. On each trial, participants memorized a briefly presented grating (i.e., a to-be-remembered item) to reproduce the orientation after a variable delay. On half of the trials, a task-irrelevant grating (i.e., a distractor) occurred during the maintenance period. Our preliminary behavioral results confirm that the distractor reduced participants' behavioral performance (i.e., accuracy) by decreasing memory precision and increasing response variability. Our preliminary EEG results indicate frequency-specific phase-behavior relationships that span multiple stages of working memory. To address our main hypotheses, we will continue to test (1) whether pre-encoding, pre-distractor, and pre-probe EEG phases (e.g., theta- and alpha-band activity) can predict behavioral outcomes, (2) whether these encoding-, maintaining-, and retrieval-related neural processes share the same frequency, phase tuning, and scalp topographies, and (3) whether information about the orientation of to-be-remembered items can be differentially decoded during different phases of frequency-specific neural activity. These analyses will reveal how the rhythmic sampling of external and internal information, across different stages of working memory, shapes behavioral outcomes.

Disclosures: Y. Ding: None. **P. Cavanah:** None. **I.C. Fiebelkorn:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP029.08/LBP055

Topic: I.05. Working Memory

Support: DFG Emmy Noether Research Group Grant, CH 1674/2-1

Title: Shared and distinct cortical representations enable storage of multiple items in working memory

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Abstract: Working memory allows us to maintain and manipulate information in mind, but has a limited capacity. To understand how this limitation arises, it is crucial to investigate how multiple items compete for neural resources. In an fMRI study, participants (n = 23, 4 sessions, age range = 20-38 years) had to remember one, two, three or four sequentially presented orientations and, after a 14.4 second delay, recall the cued orientation continously. We applied periodic support vector regression to multivariate fMRI data and reconstruct the remembered orientations throughout the delay. We show that visual (V1-V3) and parietal (IPS) areas maintain information across all set sizes (1-4). However, as set size increases, behavioural performance as

well as decoding accuracy in both regions declines. Control-related activity about a selection cue, presented to indicate which item should be recalled, can be predominantly decoded from parietal areas, suggesting that IPS is more involved in selection. Our results indicate that when set size increases, the overlapping representations in visual cortex are affected from encoding to recall. Parietal regions allow for less precise reconstructions, potentially as a result of context representation necessary to enable selection. Taken together, our results highlight the shared and distinct roles of distributed regions for visual working memory storage of multiple items.

Disclosures: V. Chopurian: None. **C.E. Curtis:** None. **T. Christophel:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP029.09/LBP056

Topic: I.05. Working Memory

Support: NIH R01 AG068990

Title: Age moderates the links between 2-back drift-diffusion model components and neuropsychological factor scores

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Abstract: The Hierarchical Drift-Diffusion Model (HDDM) provides a principled framework for decomposing task performance into latent cognitive processes. Despite its increasing applications to better understand human higher order cognition, its application has been largely limited to individually developed computerized tasks within a narrow range of populations. In order to assess age-group differences and the clinical relevance of HDDM parameters, we applied HDDM to a 2-back face and scene working memory (WM) task, which primarily index frontoparietal control networks and visual association cortices, with data from 87 cognitively normal participants (34 young (mean age = 27.24) and 53 older (mean age = 70.19)) and examined how these HDDM model components relate to broader cognitive abilities measured by standardized neuropsychological tests between young and older adults. Relative to younger adults, older adults exhibited lower evidence accumulation rates ($p<0.001$), lower decision thresholds ($p<0.001$), and longer non-decision time (($p<0.05$). In addition, greater drift rate, but not decision threshold and non-decision time, was significantly associated with better performance in executive functions, working memory, and visual memory assessed by a comprehensive neuropsychological battery. The predictive utility of model parameters, drift rate in particular, was further moderated by age group such that the directionality of evidence accumulation rate predicting Mini-Mental-State-Examination (MMSE) scores ($p<0.01$) and visual memory ($p<0.05$) differed by age group, with a marginal interaction for executive functions ($p<0.1$). Parameter-by-age interactions were further observed for the decision threshold

on semantic knowledge ($p<0.01$) and marginally on working memory ($p<0.1$) as well as for non-decision time on semantic knowledge ($p<0.01$). Our findings of age-related differences in decision threshold and non-decision time are consistent with the behavioral observation of older adults often making fast errors and immediately recognizing their mistakes during 2-back WM tasks. These results further indicate that HDDM parameters capture age-related differences in latent cognitive processes, such as evidence accumulation rate, independent of non-decision time, and highlight domain- and age-specific sensitivity of the HDDM parameters to neuropsychological test performance.

Disclosures: X. Hu: None. **H. Oh:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP029.10/LBP057

Topic: I.05. Working Memory

Title: ASL Fluency and Deafness as a Factor of Visuospatial Recall Refinement

Authors: *S. SAADE NEEDHAM[1], **C. CHIU**[2];
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Abstract: The conception of working memory has been an ongoing area of discussion within the field of cognition. In Baddeley's working memory model, his interpretations of the phonological loop, visuospatial sketchpad, and central executive describe the functional processes of working memory among verbal speakers. However, one area of interest lies in the functional changes of this model for deaf individuals. Recent studies have found that ASL users exhibit greater activation of the dorsal visuomotor system during fingerspelling tasks, revealing the potentiality of a more succinct visual memory. Despite these outcomes, the current findings reveal ambiguity within the activation of the dorsal visuomotor pathway and, further, the impact of ASL fluency on the working memory capacity of deaf signers. The present study assessed differences in the working memory capacity of 15 native English speakers and 7 fluent ASL users ($N = 22$) enrolled at California State University, Long Beach, positing that ASL acquisition and fluency strengthens visuospatial recall. Both female and male students were recruited, but no evaluations of performance differences were conducted. Participants for this study completed a 2-back test, which measured visuospatial recall of varying facial and emotional expressions, and a reading span task, which assessed verbal recall. Counterbalancing was implemented to address order effects. Preliminary findings revealed that verbal speakers performed better on the reading span task compared to the 2-Back test. However, most notably, current results indicate that ASL users performed better on the 2-Back test but had lower accuracy on the reading span task compared to verbal speakers. These findings reveal that ASL fluency improves memory recall of visuospatial cues, including facial features, expressions, and emotions. Additionally, these results indicate

that the presence of auditory encoding lessens solely visuospatial memory retention, which, in application with ASL fluency and phonological deficits among deaf individuals, reveals the potentiality of an innate refinement of visuospatial recall. Together, these outcomes can be applied to modify the current working memory model for deaf signers to include a phonological store for sign-based phonological codes, expanding our understanding of the neural mechanisms involved in memory recall among those with sensory impairments.

Disclosures: S. Saade Needham: None. **C. Chiu:** None.

Late-Breaking Poster

LBP029: I.05. Working Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP029.11/LBP058

Topic: I.05. Working Memory

Support: GIFT Future Scholar Program

Title: Region- and Frequency-Specific Effects of Temporal Interference Stimulation on Working Memory

Authors: *Y. XIA[1], C. LI[1], X. MA[1], W. LI[2];
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Abstract: Temporal Interference (TI) stimulation, a non-invasive neuromodulation technique, is a potential therapeutic option for enhancing cognitive performance. However, the effects of stimulation frequency and sites remain underexplored. In this study, we hypothesized that TI stimulation applied at specific frequencies to specific brain regions would enhance WM performance. Specifically, we investigated how TI at different frequencies applied to the dorsolateral prefrontal cortex (DLPFC) or the dorsal anterior cingulate cortex (dACC) modulates spatial and temporal WM in healthy adults. Eighteen healthy adults (12 males, 6 females) participated in this study, receiving TI stimulation at five frequencies (10 Hz, 20 Hz, 40 Hz, 80 Hz, Sham) and a no-stimulation control during the N-back task and the Spatial Working Memory and Attention Test on Paired Symbols (SWAPS). One group (n = 9) received stimulation over the dACC, and the other (n = 9) over the DLPFC. WM accuracy and reaction time (RT) were recorded for all 12 sessions. Non-parametric statistical analyses were employed to evaluate stimulation effects. We found that dACC stimulation at 10Hz significantly enhanced 3-back performance (10Hz stimulation -0.262 ± 0.683 vs sham -1.466 ± 0.978; p = 0.017; n=9) and reduced the accuracy decline from 2 to 3 back (p = 0.016), with 80Hz showing similar trends with marginal significance (-0.523 ± 0.931; p = 0.063). dACC stimulation showed no significant effects on SWAPS task performance. Conversely, DLPFC stimulation improved SWAPS task performance at 10Hz (0.22 ± 0.75 vs pseudo 0.87 ± 0.78; p = 0.19; n=9) and significantly

reduced RT, particularly at 20Hz ($p = 0.019$), while demonstrating no significant effects on N-back performance. Results indicated that 10 Hz stimulation produced the most substantial enhancement in working memory, an effect potentially mediated by the entrainment of endogenous alpha oscillations — a mechanism thought to facilitate neural synchronization and reduce distractibility. Furthermore, we found that dACC stimulation improves the temporal task, whereas DLPFC stimulation benefits the spatial task. This dissociation likely reflects their distinct functional roles: the dACC is critically involved in performance monitoring and sequencing behavior across time, while the DLPFC is specialized for spatial manipulation and monitoring concurrent processes. Our findings demonstrate clear region-specific and frequency-specific preferences in the effects of TI stimulation on cognitive performance, providing a foundation for developing targeted TI interventions.

Disclosures: Y. xia: None. **C. Li:** None. **X. Ma:** None. **W. Li:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.01/LBP059

Topic: I.06. Social Cognition

Support: NIMH Grant R01MH129648

Title: From seeing to being: stronger neural activity in the social perception network during active interaction

Authors: *Q. LIANG, E. FINN;
Dartmouth College, Hanover, NH

Abstract: Perceiving, understanding, and engaging in social interaction is crucial to humans' survival and everyday life. Previous studies on social perception have mostly used passive-viewing paradigms, overlooking potential differences in this process between people as external observers versus active participants in the interaction. Here, to directly compare neural activity underlying first- and third-person social perception, we created simple visual scenes where one agent, represented as a dot, might be chasing another. To vary social information, we manipulated chase directness (i.e., the degree to which the chasing dot headed directly toward the chased dot versus deviating from that ideal trajectory). We used these visual scenes as stimuli in an fMRI study with three trial types: 1) third person, in which participants passively viewed 5 s animations of trajectories generated by an independent set of online participants; 2) first person, in which participants themselves controlled one dot with a trackball while the other dot chased them with varying degrees of directness, and 3) a control condition in which participants used the trackball to move a dot along a predetermined trajectory presented on the screen (to control for effects of planning and executing movements); the chasing dot’s movement was also horizontally mirrored and played to preserve similar visual inputs while removing social

contingencies. In both first- and third-person trials, participants reported whether they thought one dot was chasing the other dot (third person) or the dot they controlled (first person) versus moving independently. We found that, in the first-person compared to the control condition, right-lateralized middle temporal region MT and posterior superior temporal sulcus (pSTS)—regions proposed to form part of a "third visual pathway" specialized for social perception—as well as insula, inferior frontal gyrus (IFG) and dorsolateral prefrontal cortex (DLPFC) showed stronger activation, suggesting their engagement in processing social information during active interaction. Further analysis showed that while most of these regions (all except DLPFC) were also engaged during third-person observation, they showed greater activation during active engagement than passive viewing. Moreover, there was an interaction with behavioral reports in that activity in these regions was even further increased when participants reported actually perceiving a social interaction. In summary, our findings indicate that while largely overlapping neural systems underlie first- and third-person social perception, active participation amplifies engagement of these systems.

Disclosures: Q. Liang: None. **E. Finn:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.02/Web Only

Topic: I.06. Social Cognition

Support: National Research Foundation of Korea (NRF-2017S1A3A2067165), funded by the Ministry of Education, Science, and Technology

Title: Neural Pattern Signature of Theory of Mind Moderates Social Network Betweenness Centrality and Loneliness in Older Adults: A Multivariate Pattern Analysis

Authors: *S. CHUNG, H. KWAK, J. CHEY;
Seoul National University, Seoul, Korea, Republic of

Abstract: Loneliness in late life is shaped not only by the size of one's social circle but also by one's structural position within the broader network. Betweenness centrality, indexing how often an individual lies on shortest paths between others, may reduce loneliness by widening access to diverse contacts and support; however, such connective positions can also impose coordination demands. The role of Theory of Mind (ToM) — the ability to infer mental states of others — may be relevant for understanding how social network position relates to emotional well-being. This study aimed to investigate whether individual differences in neural signature response to ToM moderate the association between betweenness centrality and loneliness in older adults. To address this question, we applied multivariate pattern analysis (MVPA) to fMRI data collected from 38 older adults participating in the Korean Social Life, Health, and Aging Project (KSHAP). Participants completed the Frith-Happé animation task designed to elicit ToM and

control (random) conditions. The fMRI pattern classifier trained to distinguish ToM from random conditions achieved a classification accuracy of 0.632 and an AUC of 0.730. Voxel-level and region-level feature importance analyses demonstrated that the areas contributing most to the prediction included regions associated with ToM and social processing, including the cerebellum, middle temporal gyrus, medial prefrontal cortex, posterior cingulate cortex, anterior cingulate cortex, and the temporal poles. Whole-village social networks were mapped to compute global betweenness centrality for each participant. We computed pattern difference scores between ToM and random conditions and investigated whether these neural responses moderated the relationship between betweenness centrality and loneliness, which was measured by the Korean version of the Revised UCLA Loneliness Scale (UCLA-r). Results showed that higher betweenness centrality was associated with lower loneliness, adjusting for sex, age, and education. Results showed that this association was moderated by individual differences in neural sensitivity to ToM stimuli: higher betweenness centrality was associated with lower loneliness among individuals with greater neural sensitivity to ToM stimuli. However, this association was reversed as the neural sensitivity decreased. These findings suggest that the benefits of occupying connective network pathways hinge on the strength of ToM-related neural sensitivity, linking brain-based social cognition with social network position in understanding loneliness among older adults.

Disclosures: S. Chung: None. **H. Kwak:** None. **J. Chey:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.03/Web Only

Topic: I.06. Social Cognition

Title: The Dynamic Role of the Temporal Lobe in Personality: Divergent Age-Related Trajectories in Males and Females

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Abstract: The temporal lobe is a critical hub for social and emotional processes, yet its specific contribution to personality development across early adulthood remains unclear. This study investigates how the associations between temporal lobe structure and big five personality dimensions differ between young adults in their early twenties and their early thirties, and examines the distinct developmental patterns between sexes. We analyzed data from the Human Connectome Project (HCP) young adult dataset. Participants were stratified by sex into two age cohorts: younger (22-26 years; 90 female / 157 male) and older (31-35 years; 268 female / 150 male). Thickness and surface area measures were extracted from 36 bilateral temporal lobe

regions—defined by the Desikan-Killiany atlas—using FreeSurfer and HCP preprocessing pipelines. Statistical significance of group differences was assessed using permutation testing (50,000 iterations), with false discovery rate (FDR) correction applied at $q < 0.05$. Bayesian variable selection identified the most predictive regions for each trait, followed by non-parametric Spearman correlation analysis with FDR correction. While younger adults showed limited temporal involvement with neuroticism and openness, neural-personality associations became increasingly differentiated with age through sex-specific pathways. Females exhibited progressive integration of social-emotional regions: by early thirties, agreeableness correlated with bilateral banks of the superior temporal sulcus (BanksSTS) and entorhinal morphology, while openness linked to parahippocampal structure. Conversely, males demonstrated reorganization toward distributed networks, with conscientiousness showing inverse correlations with thickness in bilateral mid/superior temporal and entorhinal regions. These results indicate that the temporal lobe's contribution to personality organization undergoes significant reorganization between the early twenties and early thirties, following distinct trajectories in males and females. The emerging patterns suggest that personality development in females becomes increasingly supported by temporal lobe structures involved in social cognition and emotional processing, while personality organization in males may reflect mechanisms of neural refinement or efficiency during this developmental period. These findings highlight the importance of considering both age and sex when examining the neurobiological foundations of personality.

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Late-Breaking Poster

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Program #/Poster #: LBP030.04/LBP060

Topic: I.06. Social Cognition

Support: NIBIB Grant R01EB026549

Title: Differential contributions of social cognitive features to neural correlates of social interactions and ToM

Authors: *Z. MIAO[1], H. JUNG[2], P. A. KRAGEL[3], K. BO[1], P. SADIL[4], M. LINDQUIST[4], T. D. WAGER[1];
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Abstract: Perceiving social interactions frequently involves theory of mind (ToM). However, it is unclear whether social interaction processing and ToM are supported by separate or shared brain regions, and how those regions respond to other features during comprehension of written narratives. Here, we asked participants ($N = 231$) to provide moment-by-moment ratings of four

text and four audio narratives on presence of social interactions and usage of ToM. We quantified other features in the same narratives by collecting additional ratings on the presence of multiple people (N = 103), intentional actions (N = 101), and biological motion (N = 106), and annotating speaking, physical interactions, indoor/outdoor scenes, and sentiment. Another group of participants (N = 90) experienced the narratives during fMRI scans without explicit tasks. We regressed brain activity on time courses of social interactions, ToM, and other features to generate maps for each. Results show that social interaction and ToM activity maps generalized across the text and audio modalities (spatial r = .60 and .58, respectively). Both were positively associated with neural activity in canonical mentalizing regions across modalities (6.05% of all voxels; FDR q < .01), including bilateral precuneus, dorsomedial prefrontal cortex, superior temporal sulcus (STS), and left temporoparietal junction (TPJ). Social interactions uniquely engaged portions of left STS (0.07% of all voxels), while ToM uniquely engaged regions within right lateral occipitotemporal cortex, left anterior intraparietal sulcus, right TPJ, and premotor cortex (1.65% of all voxels). Among other features, social interaction and ToM shared regions significantly responded to presence of multiple people and speaking across modalities (ps < .001), but not physical interactions, indoor/outdoor scenes, actions/motion, or sentiment. No other features explained neural activity better than social interactions or ToM in canonical mentalizing regions. Besides, annotation with Neurosynth meta-analytic term maps showed that social interactions and ToM shared maps were most strongly associated with maps for “person”, “social”, and “mental”. Social-interaction-selective regions were associated with “sentences”, “comprehension”, and “text”, and ToM-selective maps were associated with “action”, “execution”, and “hand”. Together, the findings indicate that merely processing social interactions in narratives engages ToM regions, possibly through the involvement of multiple people and their verbal communications, but not through their physical actions.

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Late-Breaking Poster

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Topic: I.06. Social Cognition

Support: NIH R01 Grant MH123069
NIH T32 Grant MH087004

Title: Neurobehavioral characterization of social navigation in borderline personality disorder

Authors: *C. E. LE ROUX[1], S. A. RHOADS[2], X. GU[3], H. KOENIGSBERG[4], D. SCHILLER[2]; [1]Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Neuroscience, Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY; [3]Psychiatry, Data Science, Yale University, New Haven, CT; [4]James J Peters VA Medical Center, Bronx, NY

Abstract: Borderline personality disorder (BPD) is a serious psychiatric condition that affects 1.7% of the general population and up to 22% of patients in psychiatric hospitals. The core social features of BPD (i.e., unstable relationships, frantic avoidance of abandonment) often persist following treatment and wreak havoc on individuals' lives, eroding their social networks, and catalyzing self-harm and suicidality. Although these dynamics primarily manifest in close interpersonal relationships, most experimental investigations of social cognition in BPD have examined participants' responses to static encounters with unfamiliar, simplistic social stimuli. Moreover, traditional task-based neuroimaging approaches have fallen short of disentangling specific social cognitive computations that could serve as treatment targets. We previously used the Social Navigation Task (SNT), a naturalistic role-playing game, to demonstrate the involvement of the precuneus and hippocampus in computing the polar coordinates (distance, angle) of simulated relationships within a two-dimensional (affiliation-power) social space "map" in healthy individuals. To assess the integrity of these computations in BPD, we administered the SNT to male and female participants with BPD (n=23), avoidant personality or social anxiety disorders (n=29; AvPD/SA), and healthy controls (n=45; HC) during 7T functional magnetic resonance imaging. In the HC and AvPD/SA groups, exploratory whole-brain analyses revealed clusters in regions including the precuneus and temporoparietal junction where activity was predicted by the distance coordinate of SNT relationships in social space. By contrast, no such clusters were identified in the BPD group. Furthermore, despite minimal group differences in SNT behavior, distance tracking was significantly weaker in a precuneus cluster in BPD relative to HC participants, yet comparable between HC and AvPD/SA groups. While further inquiry is needed to confirm the presence of a true neurocognitive impairment, these preliminary findings suggest that neural computations supporting social cognitive mapping may be abnormal in people with BPD. Such disruption could affect individuals' ability to make "map-based" inferences while planning goal-directed interpersonal behavior and anticipating outcomes, leading to frequent miscalculations. Overall, this study provides compelling initial evidence of a precise neural mechanism that may contribute to relationship dysfunction in BPD, underscoring the utility of the SNT for neurocomputational phenotyping of social deficits in psychiatric disorders.

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Late-Breaking Poster

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European Union's Horizon Europe research and innovation programme under grant agreement No 101087124.

Title: The neural underpinnings of the normative decision-making processes: A scoping review.

Authors: *P. ŠIMKO[1,2], A. RUŽICKOVÁ[2], K. BORHANI[2], M. LANG[2];
[1]ICRC - FNUSA, Brno, Czech Republic; [2]LEVYNA: Lab. for the Exptl. Res. of Religion, Masaryk Univ., Brno, Czech Republic

Abstract: Background. Social norms guide everyday choices, yet the neural processes that translate norms into actions remain underspecified. We scoped the decision-neuroscience literature to characterize the neural substrates of normative decision-making (DM) and assess whether evidence accumulation (EA) offers a unifying framework across perceptual, value-based, social, and normative domains.
Methods. Following a preregistered protocol (OSF DOI: 10.17605/OSF.IO/G379N) under JBI/PRISMA-ScR guidelines, we screened PubMed and Scopus (1990-2024) for task-based human studies using fMRI/fNIRS, EEG/ERP, or noninvasive brain stimulation. Eligible studies involved healthy adults, task-evoked activity, and excluded clinical, pharmacological, or resting-state designs. Data were charted by domain, task manipulations, neural readouts, loci, and temporal markers.
Results. We included 209 studies (142 fMRI/fNIRS; 67 EEG). Across domains, core decision circuits were recurrently engaged with domain-specific weighting. In normative DM (n=54 fMRI/fNIRS), lateral PFC (dlPFC, ~44%) was most frequent, followed by mPFC/vmPFC (~37%), anterior insula (~22%), and ACC (~22%). Social DM recruited broader networks (lateral/medial PFC, TPJ, insula, ACC). EEG revealed dual-stage, multi-timescale dynamics with MFN/FRN and P3 most prominent, and late components (LPP, N2) modulated by fairness, partner type, and moral framing; social tasks additionally showed affective markers (N1/EPN). EA signatures (e.g., CPP) were robust in perceptual tasks but scarce elsewhere; only a few studies showed ramping dynamics in value-based or social contexts, and none paired normative tasks with explicit EA modeling.
Conclusions. Normative DM reliably engaged control-valuation networks (dlPFC-vmPFC-insula-ACC) and shared temporal markers with social DM, but its moment-to-moment shaping by norms remains underspecified. We propose neurally informed EA models as a bridge: norms may bias starting points, drift rates, and thresholds. At the neural level, normative DM likely recruits parietal accumulators modulated by dlPFC conflict monitoring and vmPFC valuation. Future designs should manipulate norm salience, identity, and fairness while constraining models with trial-level neural signals (e.g., P3/CPP), aiming to unify accounts of perceptual, value-based, and normative decisions. Methodological hurdles include defining “normative evidence,” handling compound manipulations, and ensuring parameter recovery—arguing for multimodal EEG-fMRI, slowed decisions, and preregistered model-validation pipelines.

Disclosures: P. Šimko: A. Employment/Salary (full or part-time); LEVYNA: Laboratory for the Experimental Research of Religion, Masaryk University, Brno, Czech Republic, ICRC, St. Anne's University Hospital, Brno, Czech Republic. **A. Ružicková:** A. Employment/Salary (full or part-time); LEVYNA: Laboratory for the Experimental Research of Religion, Masaryk University, Brno, Czech Republic. **K. Borhani:** A. Employment/Salary (full or part-time); LEVYNA: Laboratory for the Experimental Research of Religion, Masaryk University, Brno,

Czech Republic. **M. Lang:** A. Employment/Salary (full or part-time); LEVYNA: Laboratory for the Experimental Research of Religion, Masaryk University, Brno, Czech Republic.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP030.07/LBP063

Topic: I.06. Social Cognition

Support: NIH Grant R01MH135267

Title: Gaze patterns reflect perception of changes in the social status of observed individuals

Authors: *M. KRAUSE[1], **M. H. LYNCH**[1], M. T. KABIR[1], K. M. GOTHARD[2];
[1]Univ. of Arizona, Tucson, AZ; [2]Physiol., Univ. of Arizona, Col. of Med., Tucson, AZ

Abstract: Successful interactions within a hierarchical social group require individuals to learn the status of all members of the group. In this study, we asked how observers of pairwise dominant-subordinate interactions extract the social status of multiple individuals within a linear hierarchy. Previous work from our and other laboratories demonstrated that higher status individuals draw more visual attention than those of lower status even in the absence of overt displays of dominance. We hypothesized that status-dependent allocation of fixations reflects the viewers' use of transitive inference to appropriately place each individual in a social hierarchy. We further predicted that status-related looking patterns would reorganize to incorporate new individuals that are introduced to the hierarchy. To test these hypotheses, two subject monkeys watched videos depicting pairwise dominant-subordinate interactions among three female individuals. To establish that looking patterns are due to status and not to facial expressions, the same three individuals were presented with neutral faces. By the third training day, viewer monkeys looked significantly longer at the dominant individuals while watching the neutral videos as demonstrated by a Kruskal-Wallis test for each monkey ($H(2) = 10.0$, $p = .007$ and $H(2) = 7.03$, $p = .03$). After one of the viewer monkeys learned the three-monkey hierarchy, we introduced two new monkeys, one as the second highest ranking individual and the other as the second lowest ranking. A Wilcoxon rank sum test showed that looking time on expression videos was significantly higher for the novel monkeys compared to the familiar ones ($z = -3.59$, $p = .0003$). Interestingly, the viewer monkey did not look at the novel monkeys longer during the neutral videos. Rather, the natural tendency to look longer at novel individuals was overridden by allocating attention to the most dominant monkeys in the absence of aggressive behaviors as determined by a Kruskal-Wallis test ($H(4) = 21.5$, $p = .0003$). Taken together, these results suggest that the increased attention toward novel monkeys is linked to the observed social behavior and that perception of social status adapts to changes in a hierarchy. Further analysis will determine the dynamics of social learning and its neural correlates in the hippocampus and will extend these results to a male hierarchy.

Disclosures: M. Krause: None. **M.H. Lynch:** None. **M.T. Kabir:** None. **K.M. Gothard:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.08/LBP064

Topic: I.06. Social Cognition

Support: Intramural Research Program of the NIH, National Institute on Aging

Title: Social aging beyond memory decline: Insights from a rat model

Authors: *S. DUTTA GUPTA[1], K. HUILLCA-JARA[1], E. PEREZ[2], J. M. LONG[3], P. R. RAPP[4];
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Abstract: Research on social cognition has expanded across the lifespan, with growing recognition of its vulnerability to age-related decline. While studies in humans and non-human primates have yielded valuable insights, they are often confounded by extraneous factors such as personality traits, demographics, and cultural influences. In the present study, we utilized a well-characterized rat model to investigate age-related changes in sociability and social novelty preference, and their relation to broader cognitive function and neuromodulatory intervention outcomes. Young (6 months) and aged (24-25 months) male Long-Evans rats were tested using the three-chamber social test paradigm. Sociability was preserved in aged rats; however, during the social novelty trial, a substantial subset of aged rats preferred interaction with a familiar conspecific rather than a novel one, unlike that seen in the young rats. This age-related shift in social novelty preference was dissociable from the hippocampal-dependent spatial memory performance in the water maze, suggesting that the observed changes reflect a distinct dimension of social cognition rather than a broader memory decline. Furthermore, neuromodulation via transcranial magnetic stimulation (TMS) produced phenotype-specific effects where aged rats with a pre-treatment socially introverted phenotype exhibited enhanced novelty preference following TMS, while socially extroverted aged rats showed a decrease. These observations open new avenues for exploring potential underlying mechanisms, such as alterations in oxytocin signaling or excitatory-inhibitory balance in the brain's social network. Together, the findings establish a robust preclinical framework for better understanding individual differences in vulnerability and responsiveness to intervention, encouraging tailored therapeutic strategies to promote healthy social functioning in later life.

Disclosures: S. Dutta Gupta: None. **K. Huillca-Jara:** None. **E. Perez:** None. **J.M. Long:** None. **P.R. Rapp:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.09/LBP065

Topic: I.06. Social Cognition

Support: Honors Stipend

Title: Evaluating the performance of automated and machine learning tracking systems in characterizing negative geotaxis in zebrafish (Danio rerio)

Authors: *R. PAGKALINAWAN[1], K. KINSLOW[2], E. HOFFMAN[3], R. BUCK[3], J. KANAPALA[3], H. DEWITT[2], T. KIRCHOFF[3], J. MEDLIN[3], M. DWYER[4], S. CHAARI[3], A. J. VELKEY[2];
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Abstract: Zebrafish (Danio rerio) are a commonly used model organism in behavioral neuroscience, particularly for investigating stress and anxiety related responses, including negative geotaxis (i.e. bottom dwelling). The present study examined negative geotaxis in individual subjects (N = 60, 30 males & 30 females) responding visually to mixed-sex shoals in an adjacent tank that were exposed to a synthetic alarm substance, Hypoxanthine-3 N-Oxide (H3NO). Adult short fin wild type zebrafish were housed under standard laboratory conditions and tested in the 3 Chamber Open Tank Free-Swim Task (3COFT) in 10-minute sessions. Stimulus shoals were exposed to three different concentrations of H3NO, and subjects' behaviors were recorded for later analysis. Digital video recordings analyzed with both EthoVision XT, an established application for automated analyses, and DeepLabCut, an open source machine learning program designed for behavioral tracking. Both EthoVision and DeepLabCut revealed significant increases in bottom dwelling following adjacent shoals' exposure to H3NO compared with intact shoals, consistent with an anxiogenic response. EthoVision analyses demonstrated that subjects exposed to H3NO-alarmed shoals spent more time in the bottom zone, with longer cumulative durations and more frequent entries compared to controls. At higher concentrations, particularly 5nM, a greater cumulative duration in the negative zone and increased total distance moved were revealed. Group level averages were consistent across replicates, with greater variability in observed velocity. DeepLabCut analyses revealed details regarding individual differences and incremental changes in movement compared to EthoVision. EthoVision provided standardized and reproducible measures averaged across replicates, making it efficient for group analysis. DeepLabCut is more sensitive to differences between subjects and smaller changes in movement. These strengths suggest that EthoVision supports reliable group comparisons (quantal approach), while DeepLabCut may be better for capturing detailed behaviours (graded

approach). Characterizing the strengths of each application will help future researchers develop zebrafish models of stress and anxiety.

Disclosures: R. Pagkalinawan: 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.; Honors Stipend. **K. Kinslow:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Research grant. **E. Hoffman:** None. **R. Buck:** None. **J. Kanapala:** None. **H. Dewitt:** None. **T. Kirchoff:** None. **J. Medlin:** None. **M. Dwyer:** None. **S. Chaari:** None. **A.J. Velkey:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.10/LBP066

Topic: I.06. Social Cognition

Support: NIMH award 5T32MH106454

Title: The effects of social isolation and environmental enrichment on social behavior in rats

Authors: *S. A. TOWERS[1,2,3], L. L. COLGIN[1,2,3];
[1]Neuroscience, University of Texas at Austin, Austin, TX; [2]Interdisciplinary Neuroscience Program, University of Texas at Austin, Austin, TX; [3]Center for Learning and Memory, University of Texas at Austin, Austin, TX

Abstract: Individually housing laboratory rodents after surgery is a standard precaution to prevent injury and protect implanted devices. Yet, this practice introduces social isolation-induced stress that can confound behavioral experiments. Environmental enrichment (EE) is typically provided to counteract isolation, but whether physical enrichment alone is a sufficient buffer against the effects of isolation on social behaviors remains unclear. Moreover, sex differences in this context are poorly understood, despite studies reporting sex differences in social structures and responses to stress. We conducted a pilot study assessing motivation to explore social stimuli and preference for social novelty in male and female rats exposed to different housing and EE conditions. Specifically, we used a 3-chamber sociability test to assess the behavior of 24 adult male and female Long-Evans rats after seven days of housing in either groups of three or in isolation and with or without EE. Pilot data suggest that social isolation was the factor that most strongly affected rats' motivation to explore social stimuli. That is, the preference to explore a social stimulus more than an object tended to be stronger in isolated rats than in group housed rats. We also assessed behavior of the same groups of rats in a 3-chamber social novelty test, in which a familiar rat and a previously unencountered rat were presented. Preliminary results suggest that preference for social novelty, and the effects of isolation on

social novelty preference, may depend on sex. The preference to explore a familiar rat over a novel rat tended to be higher in isolated males than in group housed males across both EE conditions. Conversely, in females, the potential effects of social isolation may differ between EE and non-EE groups. Also, compared to male rats, female rats appeared to exhibit a stronger preference for novel rats over familiar rats across all conditions. These preliminary findings suggest that social isolation, even for periods as short as one week, can alter social behavior in Long-Evans rats. Moreover, our pilot results suggest that EE may not consistently buffer against effects of social isolation on social behaviors. These pilot data highlight the importance of considering sex-specific responses, and potential effects of housing conditions, in experiments testing social behaviors in rodents.

Disclosures: S.A. Towers: None. **L.L. Colgin:** None.

Late-Breaking Poster

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Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.11/LBP067

Topic: I.06. Social Cognition

Support: Natural Sciences and Engineering Research Council of Canada (Grant No. 05426 - T.J.H)
Start-up fund, University of Alberta, Canada (Grant No. RES0052505)

Title: One Trip or Many? Exploring the Effects of Acute and Repeated LSD Exposure on Anxiety-like Behaviour in Zebrafish

Authors: *E. V. HAGEN[1], M. P. SCHALOMON[2], Y. ZHANG[3], T. J. HAMILTON[4];
[1]Psychiatry, University of Alberta, Saint Albert, AB, Canada; [2]Faculty of Arts & Science Administration, MacEwan University, Edmonton, AB, Canada; [3]Psychiatry, University of Alberta, Edmonton, AB, Canada; [4]Macewan University, Edmonton, AB, Canada

Abstract: Psychedelic drugs are gaining popularity for the potential treatment of various mental health conditions. Animal models are essential to investigate the molecular, cellular, and behavioural effects to establish a framework for human use. Zebrafish (*Danio rerio*) are commonly used to test novel pharmacological compounds in validated and reliable behavioural tests. In this project, zebrafish were exposed to either acute 30-minute exposures of LSD (0, 1.5, 15, or 150 µg/l) or daily 30-minute LSD doses (0, 1.5, 15, or 150 µg/l) for 10 days. Motion tracking software (EthoVision) was used to record, track, and analyze zone preference and locomotion in an open-field test followed by a novel object approach test. Testing occurred immediately following acute dosing, or after 10 days of repeated exposure with follow up testing after 7 days of 'withdrawal'. In an open field test, there was a significant decrease in high mobility at 1.5, 15, or 150 µg/l doses after acute exposure, and no effect on time in the outer (thigmotaxis) transition or inner zones. In fish repeatedly exposed, there was no significant

difference in any variable after 10 days, or after the withdrawal period when compared to controls. Overall, these findings suggest a low probability of side effects with repeated doses of LSD in zebrafish.

Disclosures: E.V. Hagen: None. **M.P. Schalomon:** None. **Y. Zhang:** None. **T.J. Hamilton:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.12/LBP068

Topic: I.06. Social Cognition

Support: NIH grant MH109302
NIH grant MH122622
NIH grant MH110212

Title: Brain-derived estrogens differently modulate social recognition and aggression in Syrian hamsters of both sexes

Authors: *D. ASPESI[1], H. ALBERS[2];
[1]Georgia State University, Atlanta, GA; [2]Georgia State University Neuroscience Institute, Atlanta, GA

Abstract: Gonadal steroid hormones such as testosterone (T) strongly influence social behaviors, yet whether their effects arise from direct androgenic signaling or from aromatization into 17β-estradiol (E2) remains unresolved. In many social species, both T and E2 regulate distinct dimensions of sociality, including social recognition (SR), the capacity to discriminate and remember conspecifics, and aggression. Increasing evidence further implicates neurosteroids, locally synthesized within the brain, as rapid and dynamic modulators of behavior, though their mechanisms and potential sex differences remain underexplored. To address this gap, we investigated the contribution of brain-derived estrogens to SR and aggression in male and female Syrian hamsters, an unconventional yet powerful model for dissecting sex-specific neuroendocrine mechanisms of social behavior. Using intracerebroventricular infusions, we administered the aromatase inhibitor letrozole followed by T or E2 in intact or gonadectomized animals. SR was assessed in a two-phase odor recognition task, and aggression was evaluated using the resident-intruder paradigm. Our results show that aromatase inhibition disrupted SR in both sexes, and that subsequent E2, but not T, administration restored performance, demonstrating a critical requirement for brain-localized E2 synthesis in SR. Aggression, however, was regulated in a sex-specific manner: T suppressed aggression in males, whereas E2 reduced aggression in females. Notably, letrozole treatment paradoxically increased aggression in ovariectomized females, underscoring the essential role of estrogens in constraining female aggression. Preliminary cFos mapping revealed widespread activation during SR, with males

showing greater recruitment of regions such as the lateral septum, prefrontal cortex, and amygdala compared to females. Castration, but not ovariectomy, markedly reduced cFos activity, further suggesting sex-dependent reliance on gonadal versus brain-derived steroids. Altogether, our findings reveal that aromatase activity and rapid estrogenic signaling are indispensable for SR across sexes, while aggression is governed by distinct, sex-specific steroidal pathways. By leveraging Syrian hamsters as a nontraditional model, this work highlights how brain-derived estrogens contribute differentially to male and female social behavior. These insights advance our understanding of the neuroendocrine substrates underlying social cognition and aggression, and emphasize neural aromatization as a key mechanism linking steroids to behavior.

Disclosures: D. Aspesi: None. **H. Albers:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.13/LBP069

Topic: I.06. Social Cognition

Support: NIMH Intramural Research Program (ZIAMH002887)
NIH Graduate Partnerships Program

Title: Unilateral damage to anterior cingulate cortex and amygdala differentially disrupts socioemotional responses in macaque monkeys

Authors: *S. J. WATERS[1,2], D. LUNDGREN[1], M. K. BALDWIN[1], R. AZADI[1], J. D. FLORES[1], E. A. MURRAY[1];
[1]National Institute of Mental Health, Bethesda, MD; [2]Interdisciplinary Program in Neuroscience, Georgetown University, Washington, DC

Abstract: Our laboratory is interested in identifying the neural bases of socioemotional responses. With that goal in mind, we developed a novel behavioral paradigm—the Empathic Arousal and Partner Proximity (EAPP) test—designed to assess socioemotional and empathic responses in nonhuman primates. The EAPP measures changes in behavior and physiological arousal (e.g., heart rate) in a subject (i.e., "observer") monkey that arise from being paired with a "demonstrator" monkey. Prior to pairing, the affective state of the "demonstrator" monkey is pharmacologically manipulated via intramuscular injection of an anxiolytic drug (midazolam, 0.4 - 0.8 mg/kg), anxiogenic drug (β-CCE, 0.4 - 0.8 mg/kg), or saline (0.9%). We used the EAPP to study the effect of selective brain damage on socioemotional responses in four male rhesus monkeys (*Macaca mulatta*) that participated as observers in the EAPP test; additional rhesus monkeys served as familiar or novel demonstrators. Each observer was tested before and after receiving unilateral neurotoxic lesions of either the anterior cingulate cortex (ACC; $n = 2$) or amygdala ($n = 2$). Preoperatively, observers' behavior and physiological arousal were both significantly influenced by social context. Notably, every observer exhibited elevated heart rate

and increased vocalizations when separated from a familiar demonstrator but exhibited sustained arousal and hesitancy to approach when paired with a novel demonstrator. Post-operatively, observers with unilateral damage to the ACC (but not those with amygdala damage) exhibited significantly fewer vocalizations when separated from a familiar partner. In contrast, observers with unilateral damage to the amygdala (but not those with ACC damage) were more likely to approach and maintain close proximity to a novel demonstrator. These preliminary data suggest the ACC and amygdala make separate contributions to socioemotional responses in macaques. We conclude that the EAPP is a valuable tool for studying the neural underpinnings of socioemotional functioning and empathy in nonhuman primates. This type of information would inform both basic research and translational applications.

Disclosures: S.J. Waters: None. **D. Lundgren:** None. **M.K. Baldwin:** None. **R. Azadi:** None. **J.D. Flores:** None. **E.A. Murray:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.14/LBP070

Topic: I.06. Social Cognition

Support: Natural Sciences and Engineering Research Council of Canada (NSERC)
Canadian Institutes of Health Research (CIHR)

Title: The Approach to a Familiar in Pain: An Opioid Mediated Behaviour.

Authors: *C. Y. Y. MUI, N. K. LIDHAR, J. L. BAUMBACH, L. J. MARTIN;
University of Toronto, Toronto, ON, Canada

Abstract: Socialinteractions profoundly influence pain perception and consoling behaviourstoward distressed individuals. However, it is unclear on the extent familiaritywith the individual in pain shapes behavioural responses to a conspecific inpain and the neural mechanisms underlying such behaviours. To address this, weemployed the one-on-one social interaction and social affective preference taskwith male and female CD-1 mice. Interaction periods were analyzed in SLEAP, adeep-learning framework for multi-animal tracking, to quantify approach andavoidance behaviour toward a conspecific in pain. Males had no preferenceinteracting towards a familiar in pain or not in pain, whereas females did.When exposed solely to a mouse in pain, both sexes had increased interactionwith the familiar in pain compared to familiar not in pain. This preference wasmediated in part by the opioid system, as several opioid antagonists blockedthe social approach toward another in pain within familiar females. Thesefindings highlight the importance of familiarity on the social response topain, and the critical role opioid receptors have in modulating thesebehaviours. Understanding the interplay between relationship dynamics, socialbehaviour and pain may offer insights into the neural basis of the socialmodulation of pain and empathy.

Disclosures: C.Y.Y. Mui: None. **N.K. Lidhar:** None. **J.L. Baumbach:** None. **L.J. Martin:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.15/LBP071

Topic: I.06. Social Cognition

Title: Understanding the functional organization of the infant brain using precision fMRI.

Authors: *I. NICHOSON, B. M. DEEN;
Tulane University, New Orleans, LA

Abstract: Understanding the functional organization of the infant brain using precision fMRI.Isabel Nichoson[1] and Ben Deen[1,2]1Neuroscience Program, Tulane Brain Institute and [2]Department of Psychology, Tulane University
The Default Network (DN) is a system of regions in the association cortex implicated in a range of high-level cognitive functions, including long-term memory and social cognition. Recent work studying the precise organization of the DN within individuals has found that it comprises two distinct but neighboring networks, termed DN-A and DN-B. Although the presence and functional organization of these networks has been reliably demonstrated in adults, little is known about how they develop: whether the two systems are separated from birth based on differences in anatomical connectivity, or whether they separate over time through activity-dependent processes. We therefore investigated the development of DN-A and DN-B organization in infants using precision fMRI, densely sampling individuals in order to assess patterns of functional connectivity within each participant. Three participants (two female, one male) were repeatedly imaged between the ages of two and nine months across two to five scanning sessions, providing at least two hours of resting-state data per participant. This allowed us to precisely localize DN-A and DN-B in each participant and to track connectivity patterns longitudinally. The results show that DN-A and DN-B are differentiated as early as three months of age, suggesting that the formation of large-scale functional networks occurs very early in development.

Disclosures: I. Nichoson: None. **B.M. Deen:** None.

Late-Breaking Poster

LBP030: I.06. Social Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.16/LBP072

Topic: I.06. Social Cognition

Support: The study was funded by the "One case, one policy" grant from Shandong Province (China) awarded to BH

Title: A neural metacontrol indicator (aperiodic brain activity) predicts assimilative and accommodative coping strategies

Authors: *J. YAN[1], H. ZHANG[1], L. S. COLZATO[2], B. HOMMEL[3];
[1]Shandong Normal University, Jinan, China; [2]Faculty of Psychology & Shandong Provincial Key Laboratory of Brain Science and Mental Health, Shandong Normal University, Jinan, China; [3]Psychology, Shandong Normal University, Jinan, China

Abstract: Adaptive behavior requires flexible regulation of neural control states to balance stability and change. Within the metacontrol framework, this adaptivity is conceptualized as a dynamic trade-off between persistence (goal-maintenance, stability) and flexibility (openness to updating). Recent evidence suggests that this trade-off is instantiated at the neurophysiological level through variation in the aperiodic exponent of the EEG power spectrum, which indexes large-scale excitation-inhibition (E/I) balance. Steeper exponents are associated with persistent, stability-oriented control, whereas flatter exponents reflect more flexible, exploratory processing modes. In the present study, we tested whether aperiodic EEG dynamics predict coping preferences in a large sample of Chinese university students. EEG was recorded during rest and under task-induced challenge, allowing us to assess both trait-like and dynamic changes in neural states. Structural equation modeling compared a resting-state model with a task-based model incorporating two neural indices: rest-to-task changes in the exponent and within-trial fluctuations. The task-based model provided superior fit and predictive power. Together, the two EEG measures loaded on a latent "metacontrol" factor, which negatively predicted assimilative coping (persistence-oriented) and positively predicted accommodative coping (flexibility-oriented). These findings demonstrate that aperiodic EEG exponents provide mechanistic biomarkers of metacontrol and coping styles. By linking cortical E/I balance to individual differences in adaptive behavior, the results highlight a neurophysiological substrate for coping strategies and suggest that dynamic neural markers can enrich cross-cultural research on resilience and inform personalized interventions.

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Late-Breaking Poster

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP030.17/LBP073

Topic: I.06. Social Cognition

Support: National Institute of Health, USA, Grant R01MH122611

Title: Intracranial neural correlates of social navigation in humans

Authors: ***P. JAIN**[1], G. TOSTAEVA[2], S. E. QASIM[3], D. SCHILLER[1], I. SAEZ[1];
[1]Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY; [2]Neuroscience, Icahn School of Medicine at Mount Sinai, New York City, NY; [3]Neurosurgery, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

Abstract: Social relationships can be represented in a low-dimensional space of affiliation, capturing the closeness of the dyad, and power, capturing the power dynamics of the dyad. Imaging studies using fMRI have found that these two-dimensional maps are represented in the hippocampus, tracking the affiliation and power dynamics of a relationship in a low-dimensional manifold. Here, we leveraged surgical intracranial interventions to study the neurophyiological basis of social dynamics, including unexplored spectrotemporal correlates of social navigation. Epilepsy patients undergoing stereo-EEG recording (n=19; mean age 37.52 Y; 11 M) played an interactive social navigation game. The game followed a fictional storyline where participants interacted with five main and one neutral character. Each interaction involved making a decision that either changed the closeness (affiliation) or the power dynamics (power) of the relationship. Through the game, characters moved from a neutral position to a position of more/less affiliation/power relative to the participant, effectively navigating the social power-affiliation plane through these repeated social interactions. We examined changes in the representation of the social map during the game in seven regions of interest: the hippocampus, amygdala, anterior cingulate cortex (ACC), orbitofrontal cortex (OFC), anterior and posterior insula, and the superior temporal sulcus (STS). These regions have been implicated in tracking relationships, decision-making, and representing others. We performed separate mixed-effect linear models over local field potentials' spectral power for each time point from 1.5 seconds before to 0.5 seconds after the decision. We found differences in theta power of affiliation and power decisions in the ACC, OFC, and the anterior and posterior insula. Decisions that changed the relationship along the affiliation dimension were more strongly associated with theta power modulation than decisions that changed the relationship along the power dimension. These differences were observed before and after the decision.Further, on the low-dimensional representation space, the social “angle” of the relationship relative to the self (the vector from the participant’s point of view to the character in each interaction) was tracked by hippocampal theta power during a window about a second before decision-making. These findings identify electrophysiological correlates of social navigation in the human brain similar to those of spatial navigation, demonstrating a social navigation signature in humans, providing a candidate signal for studying disorders that affect social abilities.

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Late-Breaking Poster

LBP031: I.07. Long-Term Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP031.01/LBP074

Topic: I.07. Long-Term Memory

Title: Memory Consolidation Processes of Emotionally Arousing Memories across a Stress Manipulation

Authors: *K. G. CLIVER, A. TOMPARY;
Psychological and Brain Sciences, Drexel University, Philadelphia, PA

Abstract: Memory is adaptable, allowing it to change and transform over time. To assess the extent to which a memory evolves through consolidation, researchers often examine the reactivation of previously encoded memory traces during retrieval. This process not only provides information about the content and fidelity of a memory but also how it is impacted by external factors such as acute stress. Our study investigates how memory reactivation can highlight the effects of both internal factors, like valence, and external factors, like stress, on memory. We conducted a two-day imaging experiment to replicate and extend on a previous behavioral study (Goldfarb et al., 2019), which found that stress influences item and associative memory. In this fMRI experiment, participants learned pairs of negative words and neutral objects while they rated their subjective arousal and valence for each pair. They then completed item and paired associative recognition tasks 24 hours later. We employed multivariate encoding-retrieval similarity analyses to look at how stress and valence impacted the reinstatement of specific memories over time. In preregistered analyses, we found that stress affected item recognition and paired associative retrieval differently: stress impaired item recognition relative to baseline, whereas associative memory retrieval remained unaffected. However, when associative memory was divided into specific-item memory and gist-item memory, we observed that participants consistently identified specific items more accurately than perceptually similar (gist) items across all conditions. Importantly, post-encoding stress reduced the magnitude of this difference. Our neuroimaging analyses showed that the match between encoding and retrieval patterns in the hippocampus was strongest in the no-stress condition, suggesting impaired memory reactivation under acute stress. In contrast, in the medial prefrontal cortex, we observed impaired memory reactivation for memories rated as highly arousing relative to neutral memories, regardless of stress condition. Together, these findings, alongside planned analyses of reactivation during awake rest, will help us to identify how stress during the memory cycle influences memory consolidation in the context of emotional memory.

Disclosures: K.G. Cliver: None. **A. Tompary:** None.

Late-Breaking Poster

LBP031: I.07. Long-Term Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP031.02/LBP075

Topic: I.07. Long-Term Memory

Support: GR-00017733

Title: Role of delta oscillations in the entorhinal cortex in memory integration

Authors: *S. GUNIN, J. HAAM;
Biological Sciences, Louisiana State University, Baton Rouge, LA

Abstract: Memory integration involves integrating new information into the existing memory representations. Anatomically, the temporoammonic (TA) pathway of the entorhinal cortex receives inputs from the neocortex, where remote memories are stored, and has direct projections to the CA1 of the hippocampus, where new memories are encoded and sent out to the cortical structures, suggesting its role in memory integration. While we have previously shown that delta oscillations in the TA pathway of the entorhinal cortex (EC) drive long-term memory formation, their role in memory integration remains unknown. We hypothesized that delta oscillation in the TA pathway mediates the integration of new memories into existing, related memory representations. We have previously shown that the TA pathway neurons generate delta oscillations via hyperpolarization-activated cyclic nucleotide-gated (HCN) channels, which are indispensable for long-term memory formation. As delta oscillations in the TA pathway are dependent on HCN channels, we investigated the effect of membrane potential modulation on the delta oscillations. We found that chemogenetic hyperpolarization and depolarization of glutamatergic neurons in the EC using the CaMKIIα promoter effectively alter the power of delta oscillations in the TA pathway. To understand the effect of chemogenetic modulation of delta oscillations in the TA pathway on memory integration, we developed a novel behavioral task called the remote memory update (RMU) task. The RMU task involved exposing C57BL/6 mice to a mild foot-shock in the presence of an odorant to form a contextual fear-memory. After a period of seven days, mice were placed in a two-chamber apparatus to test for chamber preference. This was followed by the remote memory retrieval and update session 24 hours later, with the fear-associated odorant present in one of the two chambers. Memory integration was tested 24 hours later by placing the mice in the apparatus without any odorant. We used the chemogenetic approach to selectively depolarize or hyperpolarize glutamatergic neurons in the superficial layers of EC and thereby modulate delta oscillations in TA pathway neurons, immediately after the memory retrieval and update session in the RMU task. Mice with chemogenetic depolarization showed diminished performance in the RMU task due to impaired delta oscillations. Mice with chemogenetic hyperpolarization performed similarly to the control group, showing intact memory integration. Thus, our findings elucidate the role of delta oscillations in the TA pathway neurons in memory integration.

Disclosures: S. Gunin: None. **J. Haam:** None.

Late-Breaking Poster

LBP031: I.07. Long-Term Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP031.03/LBP076

Topic: I.07. Long-Term Memory

Support: NIH Grant R01MH133732

Title: Memory for naturalistic conversations with sparse causal structure

Authors: *J. SEEWALD, J. CHEN;
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Abstract: In recall of movies, narratives, or other naturalistic stimuli, causal relationships between events can predict memory performance and structure. Causal structure guides memory so strongly that it dominates even when narratives are presented in scrambled order (Antony et al, 2024). In the brain, events with high causal centrality elicit increased default mode network (DMN) activation during spoken narrative recall (Lee and Chen, 2022). However, not all naturalistic experiences possess a strong causal network or chain, as commonly found in narratives. For example, long naturalistic conversations do not necessarily have a strong causal network, but instead are composed of clusters of semantically related events (conversation topics) with weak bridges between them. In this fMRI experiment, we presented participants (n = 9) with a series of videos of naturalistic conversations pulled from interviews and podcasts. Each video included two participants engaging in discussion of varying topics, ranging from retelling of past experiences to dating shows and building community post-pandemic. Participants were then prompted to perform unguided spoken recall of each conversation, also during scanning (recall length: $\bar{x}$ = 590 words, SD = 243 words). They were also asked to evaluate their personal opinions of the agents and conversation quality. To examine the degree to which our conversation stimuli showed modular event structure, we created event networks from sentence embeddings of the conversation transcripts, and compared modularity between the conversation event networks and movie event networks from a prior study (Lee and Chen, 2022). Modularity of conversations (average Q = 0.174) was significantly greater than that of movies (average Q = 0.009) ($p < 0.001$). We hypothesize that recall will be guided by causal structure within-cluster but that the macro-scale organization, i.e., the order of clusters (conversation topics) will be disrupted. Furthermore, we predict that DMN activity during recall will reflect the modular structure of the stimulus, with event cluster patterns being pushed further apart than would be predicted based on their semantics (text embeddings) alone. Overall, this data presents a new testbed for examining the influence of causal and semantic event network structure on episodic recall and brain systems.

Disclosures: J. Seewald: None. **J. Chen:** None.

Late-Breaking Poster

LBP031: I.07. Long-Term Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP031.04/LBP077

Topic: I.07. Long-Term Memory

Title: Distinct forms of pattern detection contribute to cellular memory in non-neural cells

Authors: *N. KUKUSHKIN[1], R. CARNEY[2], T. TABASSUM[2], T. J. CAREW[2];
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Abstract: Non-neural cells form long-term, CREB- and ERK-dependent transcriptional memory when treated with agonists of PKA and PKC (Kukushkin et al., Nat Comms 2024). This cellular memory is sensitive to various forms of input patterns. One such pattern is spaced repetition, whereby stimuli spaced in time produce a stronger memory than a single massed stimulus (the massed:spaced effect). Another pattern is coincidence, whereby simultaneous activation of PKA and PKC produces a synergistic, multiplicative long-term response. We show that these effects exist in parallel and are independent of each other, allowing non-neural cells to perform sophisticated temporal computations. We further show that short-term (minutes) stimulus patterning produces a long-term (days) imprint on transcription, translation, protein degradation, and autocrine protein secretion, indicating that cellular memory storage is distributed among multiple nodes of cellular signaling.

Disclosures: N. Kukushkin: None. **R. Carney:** None. **T. Tabassum:** None. **T.J. Carew:** None.

Late-Breaking Poster

LBP031: I.07. Long-Term Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP031.05/LBP078

Topic: I.07. Long-Term Memory

Support: University of Oklahoma Vice President for Research and Partnerships

Title: An Associative manipulation attenuates the other race effect in recognition memory without affecting perceptual effort, as measured using electroencephalography (EEG)

Authors: H. NOUH[1], M. C. ANTKOWIAK[2], S. F. NEWBOLDS[3], J. T. TOWNSEND[4], ***M. J. WENGER**[5];
[1]University of Oklahoma College of Medicine, Edmond, OK; [2]Psychology, The University of Oklahoma, Norman, OK; [3]Cellular and Behavioral Neurobiology, The University of Oklahoma, Norman, OK; [4]Psychological and Brain Sciences, Indiana University, Bloomington, IN; [5]Cellular and Behavioral Neurobiology, University of Oklahoma, Norman, OK

Abstract: The other race effect (ORE) in recognition memory refers to the higher levels of recognition accuracy that are observed for same relative to other race faces. The effect has been studied for more than 50 years and continues to be an active focus of research. Explanations for the effect include perceptual/cognitive, social, and computational perspectives. A prominent account of the effect is Tanaka's perceptual expertise hypothesis: specifically, that, although modern society is not legally segregated, the majority of our perceptual experience from birth is with faces of our own race, suggesting that lower perceptual experience with other race faces may place larger demands on perception than same race faces. Neural evidence consistent with this hypothesis comes from event related potential (ERP) studies. These studies have shown that

an early component, the N170, is larger in response to the presentation of other race relative to same race faces. This has been interpreted as reflecting greater perceptual demands for other race relative to same race faces. Separately, a number of studies have shown that an associative manipulation (associating a name with a face) is capable of attenuating or eliminating the ORE in behavioral data, but very little of this work has examined concurrent ERPs. In the present study, black and white participants performed a recognition memory task on days one and 10 of a 10-day study while concurrent EEG data were recorded. During the intervening eight days, participants repeatedly practiced associating names with faces. The behavioral data indicated that, as in preceding work, the ORE was attenuated. However, significantly, the N170 remained larger for other race relative to same race faces. This suggests that the studies that have attenuated the ORE using this associative manipulation are affecting mnemonic rather than perceptual abilities.

Disclosures: H. Nouh: None. **M.C. Antkowiak:** None. **S.F. Newbolds:** None. **J.T. Townsend:** None. **M.J. Wenger:** None.

Late-Breaking Poster

LBP031: I.07. Long-Term Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP031.06/LBP079

Topic: I.07. Long-Term Memory

Title: Faster memory encoding is linked to enhanced NREM sleep spindle activity

Authors: *P. BÜCHEL[1], J. KLINGSPOHR[2], M. S. KEHL[3], L. KUNZ[4], B. STARESINA[5]; [1]University of Bonn, Bonn, Germany; [2]University Hospital Hamburg Eppendorf, Hamburg, Germany; [3]Experimental Psychology, University of Bonn & Oxford, Bonn, Germany; [4]Department of Epileptology, University Hospital Bonn, Bonn, Germany; [5]University of Oxford, Oxford, United Kingdom

Abstract: Successful memory formation relies on intricate interactions between initial ‘online’ encoding and subsequent ‘offline’ consolidation processes. Importantly, encoding capacities and strategies vary across individuals, reflected in differences in learning speed. Subsequent consolidation is supported by sleep’s active role in stabilizing memories. Particularly sleep spindles, i.e., bursts of ~12 - 16 Hz oscillations emerging during non-REM (NREM) sleep, are considered to play a key role in sleep-dependent memory consolidation and have been linked both to memory retention and to interindividual differences in cognitive ability. Here we investigated whether differences in encoding speed and/or memory retention are linked to sleep spindle characteristics during NREM sleep. To test this, we devised a spatiotemporal image learning task (‘Memory Arena’) in which participants (n = 27) learned a sequence of 50 items across repeated exposure blocks to criterion. This was followed by a pre-sleep memory test, a two-hour nap opportunity and a final post-sleep memory test. We assessed participants’ encoding speed during the memory task, retention scores (post-sleep minus pre-sleep memory

performance) and extracted key characteristics of spindles detected during NREM sleep (density, amplitude, duration, frequency). Results show that memory encoding speed—but not retention—was associated with higher spindle density, amplitude, and duration, with effects strongest over parietal and temporal electrode sites. These findings suggest that individual differences in encoding speed are linked to spindle activity during subsequent sleep, highlighting that spindles may underpin not only consolidation processes but also interindividual differences in learning efficiency.

Disclosures: P. Büchel: None. **J. Klingspohr:** None. **M.S. Kehl:** None. **L. Kunz:** None. **B. Staresina:** None.

Late-Breaking Poster

LBP031: I.07. Long-Term Memory

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Program #/Poster #: LBP031.07/LBP080

Topic: I.07. Long-Term Memory

Support: NIH Grant R01 MH074692
NIH Grant F32 MH114536

Title: Dopaminergic processes predict temporal distortions in event memory

Authors: *E. E. MORROW[1], R. HUANG[2], D. V. CLEWETT[1];
[1]Psychology, University of California, Los Angeles, Los Angeles, CA; [2]University of California, Los Angeles, Los Angeles, CA

Abstract: Our memories do not simply keep time — they warp it, bending the past to fit the structure of our experiences. For example, people tend to remember items as occurring farther apart in time if they spanned a change in context, or 'event boundary,' compared to the same context. While these distortions could sacrifice precise timing, they might also serve to divide and organize information into distinct memories. In the current study, we combined functional magnetic resonance imaging (fMRI; $n = 32$) with eye-tracking ($n = 28$) to test whether activation of the dopaminergic system, known to influence encoding and time perception, predicts time dilation between adjacent events in memory. Participants encoded item sequences while listening to tones that mostly repeated over time, forming a stable auditory context, but occasionally switched, creating an event boundary. We found that boundaries predicted greater retrospective estimates of time between item pairs. Critically, tone switches significantly activated the ventral tegmental area (VTA), a key midbrain dopaminergic region, and these responses predicted greater time dilation between item pairs that spanned those switches. Boundaries furthermore predicted a momentary increase in blinks. Activation of the VTA predicted blinking in general, consistent with the idea that blink behavior is a potential marker of dopaminergic activity. On a larger timescale, higher blink counts predicted greater time dilation in memory, but only for boundary-spanning item pairs. Together, these findings suggest that dopaminergic processes are

sensitive to event structure and may drive temporal distortions that help to separate memories of distinct events.

Disclosures: E.E. Morrow: None. **R. Huang:** None. **D.V. Clewett:** None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP032.01/LBP081

Topic: I.08. Learning and Memory

Support: R01 EY017077
F31 EY035546

Title: Common mechanisms of rule learning across tasks in the prefrontal cortex

Authors: *R. JAFFE[1], W. DANG[2], C. CONSTANTINIDIS[2];
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Abstract: The lateral prefrontal cortex integrates information carried by reward circuits to effectuate learning for spatial working memory, but whether shared mechanisms apply to object memory is debated, as alternative hypotheses suggest a supervisory role instead. We examined prefrontal activity via chronic arrays in Rhesus monkeys (three male, one female) training in one spatial and two object memory tasks. All tasks required remembering the location or shape of a cue stimulus. Two tasks presented successive stimulus pairs, then prompted a saccade to one of two targets to indicate if stimuli matched. In a second shape task, the cue was followed by a stimulus pair, and a saccade to whichever matched the cue. We recorded 3863 neurons from 489 sessions over all tasks. Task paradigms discretized training via alternating trial blocks with different stimulus combinations. Blocks shortened until combinations were randomly interleaved, decreasing effectiveness of other strategies and requiring monkeys to learn how presented stimuli determined rewarded targets. Absence of rule learning would result in failure following a switch between stimulus combinations, causing a consistent drop in performance. We thus quantified learning by evaluating the progressive decrease in drop magnitude after a switch (linear regression; $p<E-4$ in all cases) classified into early/mid/late stages by the monotonic change around the point of maximum slope across sessions. Training effects did not exclusively cause monotonic increases in activity, and evoked saccade epoch firing rate decreased from early to late training in the first shape task, despite increasing in the second shape task, and remaining stable in the spatial task (Spatial task: $F(3,404) = 9.69$, $p = 0.19$. Shape task 1: $F(3,1656) = 33.83$, $p = 1.47E-17$. Shape task 2: $F(2,1792) = 5.84$, $p = 2.41E-3$). Nonmonotonic changes were also seen when decoding task factors. In the second shape task, saccade direction decoding decreased from early to mid training, without any changes from mid to late (mean early/mid/late decoding rates: 73.23%/64.56%/65.58%). Firing rate variance

unexplained by task factors between early and mid training also revealed transient increases in the spatial task, contrasted by transient decreases in both shape tasks (Spatial task: $F(2,265) = 14.94$, $p = 7.14E-07$. Shape task 1: $F(2,1407) = 10.06$, $p = 4.60E-05$. Shape task 2: $F(2,1410) = 41.04$, $p = 4.73E-18$). Our results demonstrate that nonmonotonic activity changes are evident during learning of both spatial and shape working memory tasks.

Disclosures: R. Jaffe: None. **W. Dang:** None. **C. Constantinidis:** None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP032.02/LBP082

Topic: I.08. Learning and Memory

Title: The Claustrum Supports Adaptation Of Frontal Cortex To Task Contingencies

Authors: *N. PERETZ-RIVLIN[1], Y. FATAL[1], S. LEVIN[1,2], K. PROFESORSKY[1], A. CITRI[1,3];
[1]The Edmond and Lily Safra Center for Brain Sciences, Hebrew University of Jerusalem Israel, Jerusalem, Israel; [2]Weizmann Institute of Science, Rehovot, Israel; [3]Program in Child and Brain Development, Canadian Institute for Advanced Research, Toronto, ON, Canada

Abstract: Adaptation to changing contingencies is essential for goal-directed behavior, a function in which the anterior cingulate cortex (ACC) has been widely implicated. The claustrum, a subcortical hub with extensive cortical connectivity, projects densely to the ACC and has been hypothesized to regulate attentional selection and impulse control. Here we investigated the causal role of claustral neurons projecting to the ACC (ACCp) in a sensory-guided decision task (ENGAGE) that requires withholding responses to a WAIT signal and responding selectively to a variable-intensity GO cue. Using viral strategies and optogenetic stimulation of ACCp neurons, combined with Neuropixels recordings in frontal cortex, we tested whether claustral activation modulates real-time task performance or rather enables learning across sessions. Acute stimulation of ACCp neurons robustly altered frontal cortical activity, but did not immediately change behavioral responses during the task. Instead, repeated stimulation disrupted adaptive improvements: whereas control mice developed selective response strategies, characterized by enhanced hit rates to salient cues, reduced premature errors, and faster reaction times, ChR2-expressing mice failed to adapt and maintained inefficient, impulsive policies. Electrophysiological analyses revealed corresponding alterations in frontal encoding, including attenuated representation of the GO cue, enhanced responses to the WAIT signal, delayed premotor activation, disrupted delta/theta oscillatory correlates of selectivity, and graded population state transitions. Together, these findings identify the claustrum-ACC pathway as critical not for immediate cue processing, but for the refinement of behavioral strategies and the emergence of efficient, selective policies. This work positions the claustrum as a key regulator of cognitive flexibility and inhibitory control.

Disclosures: N. Peretz-Rivlin: None. **Y. Fatal:** None. **S. Levin:** None. **K. Profesorsky:** None. **A. Citri:** None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP032.03/LBP083

Topic: I.08. Learning and Memory

Title: Task-optimized recurrent networks reveal distinct structures for spatial working memory across development

Authors: W. LIU[1], P. JIANG[2], Y. LIU[3,4,5], J. MA[1], S. XU[1], S. LI[6], *S. PU[7], V. CHAUDHARY[1];
[1]Computer and Data Sciences, Case Western Reserve University, Cleveland, OH; [2]Computer Science, New York University, New York, NY; [3]Center for Neural Science, New York University, New York, NY; [4]Department of Biomedical Engineering, Florida Atlantic University, Boca Raton, FL; [5]Stiles-Nicholson Brain Institute, Florida Atlantic University, Jupiter, FL; [6]University of Chicago, Woodridge, IL; [7]University of West Florida, Pensacola, FL

Abstract: Working memory (WM) is supported by distributed computations across prefrontal (PFC) and posterior parietal cortex (PPC), yet the algorithmic principles linking task demands to circuit dynamics remain unclear. We use task-optimized recurrent neural networks (RNNs; e.g., LSTM/GRU) trained to perform spatial WM and to capture population activity recorded from macaque PFC and PPC during visually guided memory tasks. Model-neural correspondence is assessed with standard decoding, representational analysis, temporal profiling, and dynamical-systems probes. This combined approach identifies candidate network motifs that account for key features of frontoparietal population activity and suggests complementary roles for PFC and PPC in WM without relying on a single mechanism. Training the same architectures on datasets spanning developmental stages further indicates that maturational changes can be reflected in the solutions learned by the models. Probing the fitted networks reveals multiple viable regimes—ranging from sustained to transient patterns—that can implement WM, offering a unifying framework that accommodates diverse empirical observations. Together, the work advances a general modeling strategy that links behavior, neural population structure, and circuit-level hypotheses for frontoparietal WM across development.

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Late-Breaking Poster

LBP032: I.08. Learning and Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP032.04/LBP084

Topic: I.08. Learning and Memory

Support: BNI Internal Funding

Title: Thalamic rhythms supporting emotional memories: intracranial study of the human pulvinar

Authors: *T. UMESH[1], P. K. PHATARAPHRUK[2], L. VARISA[3], E. NESTER[3], J. HONG[4], A. YANG[3];
[1]Neuromodulation, Barrow Neurological Institute, Phoenix, AZ; [2]School of Biological and Health Systems Engineering, Arizona State University, Peoria, AZ; [3]Barrow Neurological Institute, Phoenix, AZ; [4]Research-Neuromodulation, Barrow Neurological Institute, Tempe, AZ

Abstract: Emotions are a powerful, yet complex modulator of memory. Behavioral studies have consistently shown that whereas we often remember the gist of emotional stimuli, we forget the details. This is exemplified by the "weapon focus" effect, in which crime eye-witnesses remember the central emotional content of the experience (weapon used), but not the peripheral details (perpetrator's clothing). While research on emotional mnemonics remains focused on cortical structures and the amygdalo-hippocampal circuit, little is known about the role of the thalamus. Here, we focus on the pulvinar, a higher-order thalamic nucleus with extensive connectivity with structures involved in visual and emotional processing. Human lesion studies demonstrate a critical role in visual attention, particularly in the context of salient stimuli. However, physiologic investigations in humans have primarily utilized functional magnetic resonance imaging (fMRI), with limited resolution particularly for such small, deep brain structures. We leveraged exceedingly rare direct pulvinar recordings from human epilepsy patients undergoing invasive mapping for seizures with stereo-encephalography (sEEG). Subjects (N=6; 2-5 pulvinar electrodes per subject) viewed a series of images with variable emotional valence during the encoding block. During the retrieval block that followed a short distractor, subjects were tested on their ability to identify the same image presented during encoding (target) as old, and similar (lure) or novel (foil) images as new. We examined oscillatory activity in the local field potential (LFP) induced by images during encoding, stratified based on: (i) subsequent memory (i.e., correct vs incorrect response during retrieval); and (ii) memory for the gist (targets) vs. the details (lures). Statistical analysis performed at the group level using the Wilcoxon signed rank test; $p<0.05$ was considered significant. Successful target recognition was associated with increased theta-band (4-8 Hz) power that was sustained throughout the first second post-stimulus - an effect that was observed for negative but not neutral images. In contrast, successful lure discrimination was associated with decreased theta, which was again specific to negative stimuli. This provides first intracranial evidence implicating the human pulvinar in processing salience, specifically in this case, bottom-up salience driven by

emotional valence. Furthermore, findings suggest that pulvinar theta rhythms may be involved in neural processes underlying asymmetric emotion-induced mnemonic interference, enhancing memory for the gist, but impairing memory for the details.

Disclosures: T. Umesh: None. **P.K. Phataraphruk:** None. **L. Varisa:** None. **E. Nester:** None. **J. Hong:** None. **A. Yang:** None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

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Program #/Poster #: LBP032.05/LBP085

Topic: I.08. Learning and Memory

Support: The neural mechanism of basic sensory information binding 212610043

Title: Effective training for the auditory-to-visual delayed matching-to-sample task in macaques

Authors: *Y. ZHAO[1,2], M. LI[2];
[1]Beijing Normal University, Beijing, China; [2]Beijing Normal University, State Key Laboratory of Cognitive Neuroscience and Learning, Beijing, China

Abstract: Previous research indicates that the temporal lobe in primates is a critical substrate for storing visually-relevant cross-modal long-term memory (Parker et al., 2004). It can be investigated using the macaque cross-modal delayed matching-to-sample (DMS) task paradigm, which excludes interference from visual cue representation on visual imagery. However, compared with the unimodal visual DMS task, the cross-modal DMS task imposes a greater cognitive load on macaques, rendering the training process considerably more challenging. Therefore, the development of an effective training method is crucial. We trained two 10-year-old male macaques on an identical auditory-to-visual DMS task using distinct response formats: Monkey A responded via touchscreen, and Monkey B utilized oculomotor control. Monkeys were required to choose a visual object (an apple image or a gray circle) that matched a preceding auditory cue (an "apple" sound or a sine wave) after a 600-1000 ms delay. Notably, Monkey A received supplementary artificial training with multisensory stimulation (auditory, olfactory, visual, gustatory, and tactile). The training protocol was iteratively refined by systematically varying stimulus parameters (e.g., size, rotational position) and trial presentation structure (e.g., blocked vs. pseudorandom). Despite an initial tendency to rely on incidental visual cues, both subjects successfully learned the task. The daily behavioral correct rates stabilized above 80% (Monkey A: n = 10; Monkey B: n = 17), significantly higher than the 50% chance level (t-test, $p < 0.001$). Moreover, Monkey A, who received multisensory enrichment, achieved proficiency in fewer days than Monkey B (Monkey A: 91 days; Monkey B: 134 days). These results demonstrate that macaques can learn an auditory-to-visual DMS task with different response formats. Furthermore, richer multisensory stimulation during training facilitates the rapid association of specific sounds and objects. This study provides an efficient and

generalizable training methodology and establishes a foundation for future investigations into the neuronal mechanisms of cross-modal long-term memory in primates.

Disclosures: Y. Zhao: None. **M. Li:** None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP032.06/LBP086

Topic: I.08. Learning and Memory

Support: ASAP foundation
UCSF

Title: Overexpression of alpha synuclein in midbrain dopamine neurons causes cognitive deficits in a mouse model of Parkinson's Disease.

Authors: *K. ROMO[1], J. HERNÁNDEZ LÓPEZ[1], X. ZHUANG[2], B. COUTANT[1], A. B. NELSON[1];
[1]Neurology, UCSF, San Francisco, CA; [2]Neurology, University of California, San Francisco (UCSF), San Francisco, CA

Abstract: Cognitive decline in Parkinson's Disease (PD) is a difficult problem with few treatments, partly due to the lack of knowledge regarding its underlying mechanisms. While dementia is a frequent feature of advanced PD, cognitive changes are also commonly seen in early PD. These include loss of "executive" functions such as flexible decision-making. In PD, neuronal aggregates consisting of the presynaptic protein alpha-synuclein (αsyn) accumulate in multiple brain areas, including midbrain dopamine neurons. Much is still unknown about how αsyn accumulation contributes to executive dysfunction in PD. We hypothesized that αsyn accumulation in midbrain dopamine neurons would lead to progressive cognitive deficits in mice. To investigate this hypothesis, we used AAV to achieve cell type-specific αsyn overexpression in dopamine neurons and assessed the impact on instrumental and reversal learning. DAT-Cre mice were injected with AAV encoding Cre-dependent wild-type human αsyn and mCherry (αsyn group) or mCherry alone (control). In this model, we observe progressive αsyn pathology without cell loss, reduced striatal dopamine release, and mild motor deficits, including reduced open field movement velocity. Here we performed operant training, and tested animals' performance on instrumental and reversal learning at 3 and 8 weeks after viral injection. We used two approaches, either injecting AAVs first, then initiating operant training, or initiating operant training, then injecting AAVs. With the first approach, animals showed progressive difficulty with instrumental learning tasks at 3 and 8 weeks. This finding made additional reversal learning testing a challenge. Thus, we adopted the second approach. To date, we find that healthy mice quickly achieve consistent performance on the operant reversal task, which we are now comparing between the αsyn and control groups. We anticipate that at 8

weeks post-surgery we will uncover a selective deficit in reversal learning. From this work, we have shown that αsyn overexpression in dopamine neurons, even without cell loss, can drive functional deficits, including loss of synaptic dopamine release and deficits in cognitive performance. We hope our ongoing work will shed light on the mechanisms of cognitive dysfunction in PD, leading to new approaches for treatment.

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Late-Breaking Poster

LBP032: I.08. Learning and Memory

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Program #/Poster #: LBP032.07/LBP087

Topic: I.08. Learning and Memory

Support: NSF Award Number 2207350, Subaward 026450E

Title: fNIRS Evidence for Transitional Frontal-Parietal Connectivity in Early Symbolic Number Acquisition

Authors: *B. SHETTIGAR;
University of Iowa, IOWA CITY, IA

Abstract: In children, numerical cognition shifts from relying on non-symbolic representations (dot arrays) to symbolic processing (Arabic numerals). Literature shows non-symbolic processing recruits the right parietal cortex while symbolic processing shifts from frontal regions to the left parietal cortex as children become more proficient. This suggests connectivity between frontal and parietal regions may reflect transitional stages where children recruit additional frontal regions to support symbolic number processing until proficiency. We hypothesized greater frontal-parietal connectivity should predict better symbolic performance in preschoolers during this transition. We analyzed fNIRS data from 48 preschoolers ages 4-6 performing symbolic (numerical comparison) and non-symbolic (dot comparison) tasks. Accuracy on task was the performance measure, and math ability was measured using the Woodcock-Johnson Applied Problems subtest. fNIRS preprocessing included motion correction, physiological noise removal, and drift correction (conducted by Bhoomika). Task-based second-level analyses examined connectivity patterns, focusing on frontal-parietal cross-correlations. Linear mixed models were run with connectivity as DV and math performance (accuracy, applied problems score) as predictors, controlling for age. We found a main effect of applied problems raw score, $F(1, 59.4)=3.937$, $p=0.052$, and a significant effect of region of interest, $F(9,15792.0)=777.668$, $p<0.001$, plus a two-way interaction between applied problems scores and ROI, $F(9,15792.0)=8.462$, $p<0.001$. Post-hoc analyses showed applied problems scores related to cross-correlation in ROIs: Area1-3 ($p<0.001$), Area1-4 ($p=0.009$), Area2-3 ($p=0.018$), Area2-4 ($p=0.009$), Area3-4 ($p=0.002$). Area1=left frontal, Area2=right frontal, Area3=left parietal,

Area4=right parietal. Post-hoc results indicated parietal-frontal connectivity was negatively related to applied problems scores. Findings suggest greater frontal involvement reflects a transitional stage of symbolic number acquisition, in which children rely on executive resources to support numerical representations. As symbolic processing becomes efficient, reliance shifts to the left parietal cortex, consistent with adult-like processing. This trajectory underscores the importance of connectivity dynamics in acquiring symbolic numerical skills.

Disclosures: B. Shettigar: None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP032.08/LBP088

Topic: I.08. Learning and Memory

Support: NIH R00MH121563

Title: Valence and behavior encoding in the dorsal striatum during fear learning

Authors: *K. J. LEE[1], N. POLL[1], D. P. LEMMON[1], F. BUSHRA[2], C. R. HEYMAN[1], M. MAUGHAN[1], A. DILIBERTO[1], F. MILLS[1];
[1]Neurobiology, University of Utah, Salt Lake City, UT; [2]Computer Science, University of Utah, Salt Lake City, UT

Abstract: The dorsal striatum (DS) has been extensively studied as a critical site for learning, decision-making, and motor output. However, investigations of the striatum's function have overwhelmingly focused on responses to rewards or reward omission, and despite decades of research comparatively little is known about its role in fear responses to aversive stimuli. In the present study, we examine the neural representations of valence and behavior in dorsal striatum neurons during a multi-stage fear learning task, where mice learn to discriminate between reward-predicting, punishment-predicting and neutral cues. Using *in vivo* calcium imaging (GCaMP8m) in freely-moving mice (n= 20 mice; 10 male, 10 female, 717 D2+ neurons), we find that approximately 22% of DS neurons expressing the dopamine D2 receptor (D2+ MSNs) show conditioned responses to a shock-predicting cue following Pavlovian fear conditioning. The responses observed in these neurons were significantly distinct from responses to both reward-predicting and neutral cues, consistent with valence selectivity rather than salience responses or sensitization (One-way ANOVA, $F(2, 327) = 143.4$, $p < 0.0001$). We also quantify subsecond defensive behavioral motifs during these recordings to disentangle the contribution of motor effects to the responses observed, and identify both valence-encoding and action-encoding subpopulations of D2+ MSNs. These represent, to our knowledge, the first single-cell resolution recordings examining the dorsal striatum during fear learning, providing new insight into the breadth of striatal circuits involved in orchestrating defensive responses to threats.

Disclosures: K.J. Lee: None. **N. Poll:** None. **D.P. Lemmon:** None. **F. Bushra:** None. **C.R. Heyman:** None. **M. Maughan:** None. **A. DiLiberto:** None. **F. Mills:** None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

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Program #/Poster #: LBP032.09/LBP089

Topic: B.07. Network Interactions

Support: NIH grant NS121106

Title: Inhibitory dynamics during sharp wave-ripples in the hippocampus

Authors: *G. G. SZABO[1], J. S. FARRELL[2], B. DUDOK[1], C. VARGA[3], B. VARGA[1], T. GSCHWIND[1], I. SOLTESZ[1];
[1]Stanford University, Stanford, CA; [2]Neuroscience, Stanford University, Stanford, CA; [3]Physiology, University of Pecs, Pecs, Hungary

Abstract: Short, high-frequency electrographic events, called sharp wave-ripples (SPW-Rs) can be recorded during the resting states of the brain and are critically involved in learning and memory. In the hippocampus, where SPW-Rs are generated, distinct types of interneurons show diverse activity dynamics during these oscillations. One characteristic behaviour is displayed by the recently described TORO (theta-OFF/ripple-ON) cells, such GABAergic neurons that show particularly robust spiking activity during SPW-Rs but reduced firing during theta activity. We previously showed that TORO cells preferentially target other GABAergic neurons, predicting the occurrance of interneurons with activity patterns opposite to TORO. To test this hypothesis, using high-throughput two-photon imaging, we scanned through interneuronal activity in all layers of the CA1 region. We found that interneurons displaying reduced activity during SPW-Rs but increased activation during running-associated theta periods are particularly abundant in proximity to the radiatum/lacunosum-moleculare border. To further characterize these cells we performed two-photon imaging and juxtacellular recordings in awake mice and identified a GABAergic cell population that belongs to the cannabinoid receptor type-1 (CB1R) - expressing subfamily of interneurons and targets layer-specific dendritic compartments of CA1 pyramidal cells. In addition, we find that such CB1R-expressing interneurons receive strong inhibition from muscarinic type 2-expressing neurons, a cell population that includes TORO cells. Our findings outline a functional circuit element ideally positioned to permit CA3 inputs to feed onto CA1 dendrites via Schaffer collaterals during SPW-Rs and thus to play an important role in SPW-R mediated learning and memory mechanisms.

Disclosures: G.G. Szabo: None. **J.S. Farrell:** None. **B. Dudok:** None. **C. Varga:** None. **B. Varga:** None. **T. Gschwind:** None. **I. Soltesz:** None.

Late-Breaking Poster

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Program #/Poster #: LBP032.10/LBP090

Topic: I.08. Learning and Memory

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Sloan Research Fellowship
Whitehall Three Year Research Grant
IES Brain Research Foundation Monique C. & George L. Braude Summer Fellowship in Neuroscience

Title: Role of LEC Glutamatergic and GABAergic projections to Hippocampal area CA1 in learning and memory

Authors: *J. TAI[1,2], M. HERNANDEZ FRAUSTO[3], C. JOHNSON[4], J. BASU[5];
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Abstract: The neural circuitry connecting the hippocampus (HC) and entorhinal cortex (EC) gives rise to critical learning and memory processes, including spatial navigation and episodic memory processing. The integration of multisensory inputs from the lateral entorhinal cortex (LEC) and spatial inputs from the medial entorhinal cortex (MEC) by hippocampal pyramidal neurons allows association of incoming spatio-sensory input with prior experience that contextualizes the current environment. This interaction is critical for generating adaptive learned behaviors, but we know little about the organization and function of the diverse axonal projections that facilitate this long-range signaling and how this circuitry enables both stable internal representations and adaptive responses to a changing external environment. We and the Monyer lab recently found that in addition to the canonical excitatory projections, LEC and MEC both send direct, long-range inhibitory projections to CA1 that predominantly target local interneurons (INs). Our recent study (Basu et al., Science 2016) established a critical role of GABAergic LEC to CA1 inputs in modulating dendritic spikes, long-term plasticity, and contextual- and novelty- related learned behavior, whereas inputs to CA3 modulate somatic spikes to increase recurrent circuit activity and learning-driven place map stability (Robert et al, Science 2025). Here, we are parsing out the organization and functional role of the GABAergic

neuron subtypes with viral neuronal tracing, fiber photometry recordings of GABAergic LRIPs during freely moving behavior, and two-photon imaging of hippocampal pyramidal neurons with optogenetic silencing of LEC inputs during a goal-oriented learning task. Our preliminary data suggest that the long-range projections from the EC to HC are largely heterogenous in their molecular build, functional features, and innervation patterns across hippocampus.

Disclosures: J. Tai: None. **M. Hernandez Frausto:** None. **C. Johnson:** None. **J. Basu:** None.

Late-Breaking Poster

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Program #/Poster #: LBP032.11/Web Only

Topic: I.08. Learning and Memory

Support: NSERC-DG: RGPIN-2020-06929
NSERC Alliance-Alberta Innovates Advance

Title: Circadian disruption selectively impairs long-term stability of hippocampal place cell representations

Authors: Y. KAUSHIK[1], D. R. ROBERTSON[1], A. HUBER[1], I. ESTEVES[1], H. CHANG[1], N. S. HONG[1], M. H. MOHAJERANI[2], B. L. MCNAUGHTON[3], *R. J. MCDONALD[1];
[1]Univ Lethbridge, Lethbridge, AB, Canada; [2]Psychiatry, McGill University, Montréal, QC, Canada; [3]Department of Neuroscience, The University of California Irvine, Irvine, CA

Abstract: Circadian rhythms regulate numerous physiological and cognitive processes, including memory formation and retrieval. Disruption of these rhythms, due to shift work, jet lag, irregular sleep, etc., has been linked to impaired memory performance, yet the neural mechanisms remain unclear. In this study, we investigated how photoperiod shifting affects the formation and long-term stability of spatial memory representations in the hippocampus. We conducted longitudinal 2-photon calcium imaging in the hippocampus of eight male Thy1-GCaMP6s mice, split into control and experimental groups (n = 4 each). The experimental group underwent a 3-hr daily phase advance of their light schedule (T21) for seven consecutive days, which started one day prior to behavioral training, followed by a return to a stable light-dark cycle. Both groups were trained on a head-fixed spatial foraging task with sucrose water rewards and imaged over 10 consecutive days. Two additional imaging sessions assessed retention: one conducted 7 days post-training (Retention 1), and another 16 days later (Retention 2), both under stable lighting conditions. The results showed that during acquisition, both groups developed robust spatial representations by Day 6, as shown by activity maps, spatial tuning metrics (sparsity, spatial information, field width), population vector correlations, and trial-wise tuning stability. These metrics revealed no differences between groups, indicating both developed stable, well-defined place fields. However, during retention, the experimental group showed reduced place cell stability. Moreover, trial-by-trial tuning reliability, population vector

similarity, and place field persistence were all lower compared to controls. Although control mice retained some spatial coding, their maps were also not fully preserved, reflecting natural decay in stability over time. These findings suggest that while hippocampal spatial encoding is maintained during circadian disruption, long-term memory retention is impaired, likely due to disrupted consolidation and recall. This aligns with our prior findings using the Morris water task (2001), where spatial learning remained intact, but retention was impaired following the same phase-shift protocol.

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Late-Breaking Poster

LBP032: I.08. Learning and Memory

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP032.12/LBP091

Topic: I.08. Learning and Memory

Title: Functional ultrasound mapping of medial septal nucleus deep brain stimulation in NMDA receptor hypofunction schizophrenia model

Authors: *H. PARK[1], R. AFSAHI[2], D. J. LEE[3];
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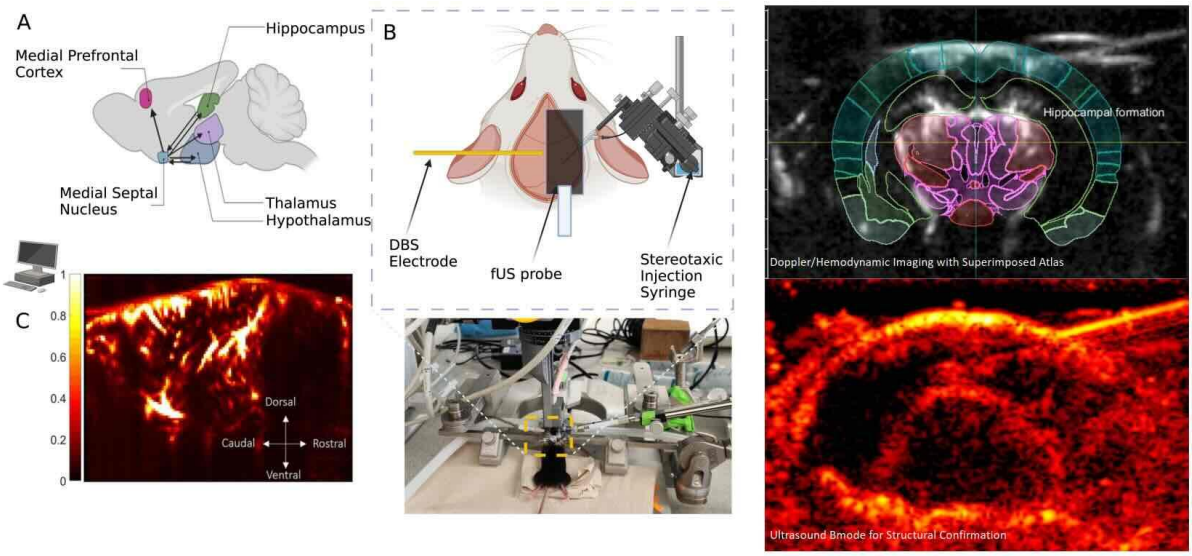
Abstract: Schizophrenia is marked by disrupted septohippocampal network communication, contributing to cognitive and behavioral deficits. NMDA receptor (NMDAR) hypofunction, especially in the hippocampus, impairs oscillatory coordination and information processing. The medial septal nucleus (MSN), which provides theta and gamma rhythmic drive to the hippocampus, may modulate these networks, yet its cerebrovascular impact under NMDAR blockade remains unclear. Here, we used high-resolution functional ultrasound imaging (fUSI) to assess cerebral blood volume (CBV) changes following neuromodulation in a mouse model of NMDAR hypofunction. Adult mice received unilateral right-side intrahippocampal injections of either saline (n = 32) or MK-801 (n = 36), followed by MSN stimulation at either 7.7 Hz (theta) or 100 Hz (gamma) for 5 minutes via implanted electrodes. Six right-hemisphere regions of interest (ROIs)—hippocampus, striatum, pallidum, thalamus, hypothalamus, and medial prefrontal cortex (mPFC)—were analyzed relative to a 5-minute pre-stimulation baseline. Mice were included based on predefined Z-score criteria for CBV stability and response magnitude. MK-801-treated mice exhibited significantly greater CBV decrease across all ROIs compared to saline. In saline-injected mice, gamma stimulation elicited focal CBV increases in hippocampus, thalamus, and mPFC, while theta stimulation produced broader but attenuated responses. In MK-801 mice, gamma stimulation partially attenuated CBV decreases in the thalamus, hypothalamus, and pallidum, while hippocampal CBV increased modestly relative to non-stimulated controls.

Theta stimulation showed strong attenuations to CBV decrease in hippocampus and mPFC, whereas attenuation in other regions demonstrated weaker responses. These results indicate that MSN stimulation can attenuate cerebrovascular flow and ROI function for certain ROIs, which depend on the stimulation paradigm. fUSI offers a robust platform to map neuromodulatory responses in neuropsychiatric disease models.



Disclosures: H. Park: None. **R. Afsahi:** None. **D.J. Lee:** None.

Late-Breaking Poster

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Title: Connectomic reconstruction from hippocampal CA3 reveals spatially graded mossy fiber inputs and selective feedforward inhibition to pyramidal cells

Authors: *Z. ZHENG[1], C. PARK[2], E. HAMMERSCHMITH[3], R. LU[1], S.-C. YU[4], M. SOREK[5], A. STERLING[6], W. SILVERSMITH[7], F. C. COLLMAN[8], H. SEUNG[7], D. W. TANK[1]; [1]Princeton University, Princeton, NJ; [2]Princeton Univeristy, Princeton, NJ; [3]Neuroscience, Princeton Neuroscience Institute, Princeton, NJ; [4]Princeton Neuroscience Institute, Princeton, NJ; [5]Princeton Neuroscience Institute, Princeton University, Norwood, MA; [6]Princeton University, Somerville, MA; [7]Princeton Neuroscience Institute, Princeton University, Princeton, NJ; [8]Allen Inst. For Brain Science, Seattle, WA

Abstract: The mossy fiber (MF) connections to pyramidal cells in hippocampal CA3 are hypothesized to participate in pattern separation and memory encoding, yet no large-scale neuronal wiring diagram exists for these connections. We assembled a 3D electron microscopy volume (~1x1x0.1mm^3) from mouse hippocampal CA3. By proofreading and automated segmentation, we reconstructed and classified all soma-containing neurons—including 1,815 pyramidal cells and 229 inhibitory cells—and over 55,000 MFs. Pyramidal cells receive more numerous MF inputs along a proximodistal gradient. Some distal cells show surprisingly high convergence via relatively small terminals with fewer vesicles. Pyramidal cells share significantly more MF inputs than networks randomized by degree-preserving swap, and are better approximated by networks randomized by proximity-preserving swap. We identify a feedforward inhibitory circuit from MFs via perisomatic interneurons that selectively target a pyramidal subtype. We demonstrated large-scale mapping across levels in the hippocampus—from circuits to cell types to vesicles. The dataset is shared through Pyr.ai, an online platform for hippocampal connectomics.

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Late-Breaking Poster

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Program #/Poster #: LBP032.14/LBP093

Topic: I.08. Learning and Memory

Support: Irish Research Council
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Research Ireland

Title: Microglial plasticity across development mediates infantile amnesia

Authors: *E. STEWART[1,2,3], L. ZIELKE[4], A. R. DE BOER[4], S. D. POWER[5], T. J. RYAN[4,6,7]; [1]Columbia University Irving Medical Centre, New York, NY; [2]School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Dublin, Ireland; [3]Trinity College Institute for Neuroscience, Dublin, Ireland; [4]Trinity Biomedical Sciences Institute, Dublin, Ireland; [5]Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany; [6]Child & Brain Development Program, Canadian Institute for Advanced Research (CIFAR), Toronto, ON, Canada; [7]Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Abstract: Infantile amnesia describes the inability to recall memories formed during a critical period of development in infancy and early childhood and is a hallmark of postnatal development. Yet, the neurobiology of this highly conserved phenomenon remains poorly understood. Our previous work has demonstrated that an immune challenge during pregnancy, maternal immune activation (MIA), prevents infantile amnesia in male offspring, suggesting an important role of immune cells and signalling in the neurobiology of this phenomenon. This work aimed to gain a better mechanistic understanding of infantile amnesia. Here, we characterized the relationship between infantile amnesia and neuro-immune signalling with a focus on microglial cells. Microglia, specialized macrophages of the central nervous system, are known to play an important role in synaptic refinement during postnatal development and have recently been implicated in memory related functions. Through histological analysis we profiled dynamic changes in microglial morphology across the postnatal window that parallelled the onset of infantile forgetting. We investigated the role of microglial activity in infant memory retention and found that pharmacological inhibition of microglial activity during a specific postnatal window prevents infantile amnesia for a contextual fear memory. Using activity-dependent tagging of infant encoded engram cells, we demonstrated that microglial inhibition alters engram size and engram reactivation in the amygdala and results in changes in microglia-engram cell interactions. Our results suggest that microglial activity during postnatal development may affect engram plasticity and memory accessibility. Finally, we characterised a relationship between the lack of infantile amnesia in MIA offspring and microglial activity. Our results identify microglia as key regulators of memory accessibility in infancy.

Disclosures: E. Stewart: None. **L. Zielke:** None. **A.R. de Boer:** None. **S.D. Power:** None. **T.J. Ryan:** None.

Late-Breaking Poster

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Program #/Poster #: LBP032.15/LBP094

Topic: I.08. Learning and Memory

Support: STI2030-Major Projects 2021ZD0203501

Title: Neuronal dynamics of Dentate Gyrus engram cells during natural and artificial recall of fear memory

Authors: *J. XU[1,2], L. LIN[3,2];
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Abstract: Memory engrams are physical traces of memory in the brain. These neuronal ensembles are activated during learning and can be reactivated by sensory cues (or partial cues) during memory retrieval to trigger behavioral expression. While many studies have used immediate early gene (IEG)-based strategies to identify and manipulate engram cells, and optogenetic activation of hippocampal engrams has been shown to induce freezing behavior, the in vivo spiking dynamics of engram cells during memory retrieval remain unclear. Here, we combined TRAP2-based genetic labeling, in vivo multichannel electrophysiology and optogenetic tagging, to characterize dentate gyrus (DG) engram cell activity during three types of fear memory retrieval: auditory-cued, contextual, and artificial (opto-retrieval). We found that most engram cells were strongly activated by tone pips during cued recall, but their firing rates were suppressed during freezing. Similarly, during contextual recall, most engram cells showed reduced activity during freezing. Optogenetic stimulation of DG engram cells led to transient activation followed by decreased firing during freezing behavior. Notably, engram cells overlapped substantially with tone-responsive and freezing-modulated neurons and tended to form co-active neuronal ensembles. These findings suggest that artificial engram activation may recruit broader memory-related ensembles to drive behavioral retrieval. This study provides the first in vivo electrophysiological evidence of how DG engram neurons contribute to memory retrieval dynamics.

Disclosures: J. Xu: None. **L. Lin:** None.

Late-Breaking Poster

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Topic: I.08. Learning and Memory

Title: Time-of-day variation in hippocampal Arc expression across the sleep-wake cycle

Authors: *C. MYRUM, A. SOCARRAS, Z. REHMAN;
Loyola University Maryland, Baltimore, MD

Abstract: *Activity-regulated cytoskeleton-associated protein* (Arc) is a gene critical for synaptic plasticity, learning, and memory consolidation. Sleep is also essential for long-term memory consolidation, which relies heavily on the hippocampus—a brain region central to this process. While Arc is known to play a key role in experience-dependent plasticity, existing literature presents conflicting findings on whether Arc expression increases or decreases during sleep. Even less clear is how Arc expression varies across hippocampal subregions and under different behavioral conditions. To begin addressing these questions, we examined Arc expression under

naïve conditions (i.e., in the absence of behavioral manipulation) across four timepoints in the sleep-wake cycle: 3 and 8 hours into both the light (sleep) and dark (wake) phases. We used male and female F344 rats (~3 months old) and video recorded animals for 3 hours prior to sacrifice to confirm predominant behavioral state (sleep or wake). Using immunocytochemistry, we assessed Arc+ cell density in the dentate gyrus of the hippocampus (N = 9-12 animals/group; 2-6 sections/animal). While the overall ANOVA was not statistically significant, we observed a trend toward higher Arc+ cell density during the dark (wake) phase compared to the light (sleep) phase. These preliminary data suggest a potential modulation of Arc expression by behavioral state, consistent with increased neuronal activity during wakefulness. Ongoing work aims to increase sample size, quantify additional hippocampal sections, and examine other hippocampal subregions to further investigate region- and state-specific dynamics of Arc expression across the sleep-wake cycle.

Disclosures: C. Myrum: None. **A. Socarras:** None. **Z. Rehman:** None.

Late-Breaking Poster

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NJCCR (COCR26PDF037)

Title: Novel therapeutic approaches for chemotherapy-related cognitive impairment

Authors: M. JANG[1], *S. KIM[2], W.-H. CHO[3], **A. MOON**[1], S. LEE[1], J. LEE[4], Y.-S. KIM[5]; [1]Neurosurgery, Robert Wood Johnson Medical School, Rutgers University, Piscataway, NJ; [2]Neurosurgery, Robert Wood Johnson, Piscataway, NJ; [3]RWJMS, Robert Wood Johnson Medical School, Rutgers University, Piscataway, NJ; [4]Robert Wood Johnson Medical School, Rutgers University, Piscataway, NJ; [5]Neurology, Robert Wood Johnson Medical School, Rutgers University, Piscataway, NJ

Abstract: Chemotherapy-induced cognitive impairment (commonly known as “chemobrain”) significantly reduces the quality of life in both childhood and adult cancer survivors, and has emerged as an important medical concern. Despite the growing number of cancer survivors, there is currently no proven medication to effectively alleviate chemotherapy-related sequelae, highlighting the urgent need for novel therapeutic approaches.
Exercise physical therapy has been shown to be a safe and effective intervention for cancer

patients, alleviating many adverse effects of chemotherapy. However, physical activity may not always be feasible for patients suffering from cancer-related pain, movement difficulties, or other comorbidities. Alternative approaches are therefore required. The primary goal of my proposed work is to identify downstream molecular mechanisms of exercise that can be mimicked pharmacologically to alleviate chemobrain.
In my preliminary studies, chemotherapy agents such as cisplatin and doxorubicin induced sleep disturbances, significant weight loss, prolonged memory decline, and increased anxiety symptoms commonly observed in patients undergoing chemotherapy. Bulk and scRNA sequencing revealed widespread molecular alterations associated with these behavioral phenotypes. From this analysis, several key molecular candidates were identified, which were subsequently prioritized using an AI-based screening platform to search among FDA-approved drugs. This approach enabled the rapid identification of potential therapeutic compounds capable of mimicking the beneficial effects of exercise.
Together, these studies aim to uncover druggable molecular targets and repurpose FDA-approved therapeutics, providing a pathway toward safe, effective, and clinically translatable interventions for chemobrain.

Disclosures: M. Jang: None. **S. Kim:** None. **W. Cho:** None. **A. Moon:** None. **S. Lee:** None. **J. Lee:** None. **Y. Kim:** None.

Late-Breaking Poster

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Program #/Poster #: LBP032.18/LBP097

Topic: I.08. Learning and Memory

Support: NIH Grant MH124997

Title: Hippocampal cell and circuit specific differences in mitochondrial form and function

Authors: *S. FARRIS, M. ALSALMAN, L. TURNER, S. A. SWANGER;
Virginia Tech, Roanoke, VA

Abstract: The localization of mitochondria to dendrites provides the energy and metabolites essential for synaptic function. Emerging evidence indicates that dendritic mitochondria can be molecularly and structurally distinct, however, the functional significance of these differences is unclear. We previously reported that hippocampal CA2 neurons are enriched for transcripts encoding mitochondrial proteins compared to neighboring hippocampal CA1 neurons. This suggests that mitochondria may function differently in CA2. Because mitochondrial function is closely tied to its morphology, we hypothesized that mitochondria would be larger in CA2 dendrites relative to CA1 dendrites. To test this, we infused AAV-cre into heterozygous tdtomato;mitotag mice to sparsely label CA1 and CA2 neurons and mitochondria. We compared mitochondrial area and % dendrite occupancy across cell types and dendritic layers. We found

CA2 dendrites harbor larger mitochondria than CA1 dendrites and take up a greater % dendrite occupancy. As previously reported, both subregions have larger mitochondria in distal dendrites compared to their proximal dendrites. Immunostaining for fission and fusion factors revealed an enrichment of fusion factor OPA1 in CA1 distal dendrites that explains the layer-specific increase in mitochondrial size there, but not the difference compared with CA2.
To test whether mitochondria are functionally different, we monitored mitochondrial and cytosolic calcium levels using targeted calcium indicators in live slices. Consistent with the enrichment of the mitochondrial calcium uniporter expression in CA2 distal dendrites, mitochondria had elevated basal calcium levels in CA2 distal dendrites relative to CA2 proximal dendrites. In contrast, there was only a slight elevation of basal mitochondrial calcium in CA1 distal dendrites relative to CA1 proximal dendrites, consistent with the smaller layer-specific differences in mitochondrial morphology. Upon depolarization with KCl, cytosolic and mitochondrial calcium signals increased throughout CA1 and CA2 dendrites. No differences were observed in cytosolic calcium levels that would explain the layer-specific differences in mitochondrial calcium levels. Taken together, our data indicate that cell intrinsic and input-specific mechanisms contribute to the morphological and functional differences in dendritic mitochondria across hippocampal circuits. Mitochondrial heterogeneity likely supports the diversity of synaptic functions and connectivity patterns of different brain regions. It may also contribute to differential circuit susceptibility to brain disorders.

Disclosures: S. Farris: None. **M. Alsalman:** None. **L. Turner:** None. **S.A. Swanger:** None.

Late-Breaking Poster

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Program #/Poster #: LBP032.19/LBP098

Topic: I.08. Learning and Memory

Support: DARPA W911NF2420108

Title: Electrophysiological characterization of the novel general anesthetic KSEB 01-1 on $GABA_{A,\ fast}$currents in hippocampal CA1 pyramidal neurons

Authors: *K. A. BARTOL[1], B. MACIVER[2], M. DAVIES[2], E. J. BERTACCINI[3], R. A. PEARCE[4];
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Abstract: Many GABAergic general anesthetics, including barbiturates and propofol, produce undesired hemodynamic and respiratory depression. KSEB 01-1, a recently developed general anesthetic that is based on a novel chemical core, produces anesthesia without causing

hemodynamic instability or respiratory depression. It is hypothesized to do so through selective enhancement of the slow subtype of γ-aminobutyric acid type A receptor mediated inhibition ($GABA_{A,slow}$), as inferred by extracellular recordings of population spikes in the hippocampal CA1 region and direct recordings of evoked $GABA_{A,slow}$ responses. However, electrophysiological characterization of the effects of KSEB compounds on $GABA_{A,fast}$ and $GABA_{A,tonic}$ currents at the cellular level was not performed. Therefore, we conducted whole-cell patch clamp electrophysiological recordings from CA1 hippocampal pyramidal neurons in mouse brain slices (n=8) and assessed the characteristics of spontaneous IPSCs during one-minute recordings in the absence or presence of 10 μM KSEB 01-1. Under both conditions, the great majority of IPSCs (n=1070) had characteristics typical of $GABA_{A,fast}$ IPSCs, with rise times < 3 ms and decay rates < 40 ms. These fast decay rates were well fit by lognormal distributions, with geometric mean (median) and SD values of 8.0 ± 1.9 ms (control) and 11.0 ± 1.8 ms (KSEB). A Likelihood Ratio Test based on pooled data indicated that these distributions differed significantly ($p<0.001$). These findings thus indicate that 10 μM KSEB 01-1 produces a statistically significant but modest slowing of fast IPSC decay. Additional studies are needed to compare relative changes in slow and tonic $GABA_A$ currents at this drug concentration.

Disclosures: K.A. Bartol: None. **B. MacIver:** None. **M. Davies:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on the patent for the KSEB drug class. **E.J. Bertaccini:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-inventor on the patent for the KSEB drug class. **R.A. Pearce:** None.

Late-Breaking Poster

LBP032: I.08. Learning and Memory

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Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

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Title: Sequential development of representations in the hippocampal-prefrontal network during initial learning and subsequent generalization

Authors: *S.-Y. TSENG[1,2], J. A. GUIDERA[3], D. GRAMLING[1], P. THOMPSON[4], J. HERNANDEZ[4], A. M. YORITA[4], R.-U. HAQUE[4], L. M. FRANK[1,5,2];

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Abstract: Learning complex tasks typically progresses through multiple stages: the brain first encodes concrete environmental features, then infers abstract, hidden structures such as latent states and task rules, and finally develops pragmatic behavioral policies based on those states and rules. Inferences about states, rules, and policies can then be transferred to new contexts to accelerate adaptation and learning. The hippocampal-prefrontal network is critical for these processes, but the precise neural mechanisms that support the progression from concrete to more abstract representations are not fully understood. To investigate how hippocampus (HPC) and medial prefrontal cortex (mPFC) evolve and coordinate during such staged learning, we trained rats to perform a series of spatial navigation tasks across distinct mazes with shared geometric structures while simultaneously recording from HPC and mPFC. During initial learning, neural representations for spatial location, task features, and actions emerged sequentially in both regions, with task and action representations developing as behavioral performance increased. When animals were introduced to new mazes, this same sequence of representational development was engaged, but in an accelerated manner, mirroring the faster learning rate for familiar tasks in new environments. Importantly, HPC and mPFC exhibited distinct representational dynamics. HPC encodings of different variables plateaued and stabilized once animals reached expert-level performance. In contrast, mPFC activity gradually transitioned from an early phase dominated by spatial encoding to a later phase dominated by task feature and action encoding, where the prevalence of these representations continued to increase across days of task switching and stable performance. Further, while HPC representations of task features and actions were environment-specific, mPFC representations generalized across environments. Communication subspace analysis further revealed stronger HPC to mPFC influence during early learning, suggesting that HPC inputs scaffold the initial spatial representations in mPFC. Together, these results reveal a coordinated, staged construction of concrete, abstract, and pragmatic representations across the HPC-mPFC network. They further highlight a division of labor, with HPC anchoring context-specific details and mPFC undergoing continual reconfiguration toward abstract, generalizable codes that reflect algorithmic compositionality and enable efficient task generalization.

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Late-Breaking Poster

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Topic: I.08. Learning and Memory

Support: NIH Grant R01MH130064
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Title: Brain-wide neural dynamics for olfactory learning in C. elegans

Authors: *J. LIANG[1], S. MOON[2], S. MOZA[1], H. LEE[2], P. ELEFTHERIADIS[1], J. CHEN[1], T. WU[1], H. LIU[1], H. LU[2], Y. ZHANG[1];
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Abstract: Learning and memory involve dynamic changes in neuronal excitability and connectivity, but how distributed circuits flexibly encode experience remains unknown. To systematically investigate olfactory aversive learning in *C. elegans*, we performed brain-wide calcium imaging using multicellular promoters to label ~70% of head neurons, enabling stable single-cell resolution of cytoplasmic GCaMP6 signals over learning.
Naïve animals prefer odorants of the pathogenic *Pseudomonas aeruginosa* PA14 over the food source *Escherichia coli* OP50, but after 4-6 hr of PA14 feeding they reduce this preference, similar to the mammalian associative learning paradigm called conditioned olfactory aversion. We recorded neuronal responses to alternating odor stimuli (OP50/PA14, PA14/Buffer, Buffer/Buffer) in naïve and trained worms. Learning induced widespread changes across sensory, interneuron, and motor neurons (14/68 neuron classes) under the OP50/PA14 regime but not under PA14/Buffer, demonstrating context-gated modulation of neural activity.
To model functional connectivity, we fitted convolutional kernels between sensory and inter/motor activity. Kernels trained on naïve data performed poorly on trained responses, indicating that changes in inter/motor dynamics cannot be explained by altered sensory activity alone. Tucker decomposition revealed learning-dependent modulation across the first three temporal components (~90% variance explained), corresponding to primary sensory responses, asymmetric odor activation, and history-dependent suppression. These components aligned with first three principal components of body posture dynamics, indicating that components encode specific sensorimotor responses. By analyzing trajectories of neural activities projected to the low-dimensional neural state space, we find that training reconfigured network level activity patterns. Using the interactions between neural and temporal components produced by Tucker decomposition, we characterized different roles of neurons in generating context-gated expression of learning.
Network analysis further showed increased modularity of sensory neuron recruitment under OP50/PA14 after learning, reflecting more stable ensemble activation. Finally, linear dynamical system modeling revealed stimulus-specific fixed points, with PA14 representations shifting toward Buffer after learning, suggesting reuse of existing representations.
Together, these results show that aversive learning globally reshapes distributed neural dynamics in *C. elegans*, linking sensory, network, and circuit computations to the flexible encoding of experience.

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Program #/Poster #: LBP032.22/LBP101

Topic: I.08. Learning and Memory

Title: Broadly distributed decay constants enable intrinsic temporal coding in CA1

Authors: *S. ZOMORODI[1], B. KNAUER[2], Y. BRAHIMI[3,4,5], A. REBOREDA[3,4], M. YOSHIDA[3,4,6], Z. TIGANJ[1,7];
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Abstract: Temporal relationships are essential for learning and episodic memory, yet it is unclear whether single neurons in the hippocampus can intrinsically sustain time-varying activity on behavioral timescales without network input. Using whole-cell recordings in rat CA1 slices under synaptic blockade and cholinergic activation (carbachol), we delivered a brief depolarizing pulse and quantified post-stimulus firing. Across recorded neurons, many exhibited stimulus-evoked persistent activity that changed gradually over extended intervals. Model comparisons indicated that an exponentially decaying profile was the most common response, with a smaller subset better described by linear decay and others showing non-monotonic or biphasic structure. Exponential time constants spanned ~1-50 s, yielding a broad coverage of behaviorally relevant delays. A model-based time readout, obtained by inverting the fitted dynamics, produced time estimates whose uncertainty scaled with the interval, consistent with scalar timing. These findings provide direct evidence that individual CA1 neurons possess intrinsic mechanisms that generate a spectrum of exponential decays over tens of seconds, supporting cellular-level codes for "time since event". Such multi-timescale firing profiles could serve as temporal context signals and supply building blocks for time cells, place cells, and distributional value representations assumed in memory and reinforcement learning models.

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Late-Breaking Poster

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Title: The dynamics of episodic recall

Authors: *N. MIZRACHI[1], E. AHISSAR[2];
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Abstract: The mechanistic understanding of memory recall, a process long known to be influenced by environmental context, has posed a persistent challenge to neuron-centric models. In this study, we approached recall by shifting the focus from internal neuronal representations to brain-environment interactions, employing precise tracking of gaze dynamics within a well-controlled virtual reality (VR) setting. We found that each verbal report of recalled event was consistently preceded by a gradual process of brain-environment coupling: fixational pauses became progressively longer, while gaze direction slowly converged on a specific spatial location associated with the memorized object—a recall-specific location (RSL). Upon the initiation of the verbal report, gaze rapidly diverged from the RSL. Chunked verbal reports were associated with convergence onto shared or spatially clustered RSLs. Moreover, when recall occurred in the same spatial context as encoding, participants recalled objects in the order they were encountered and RSLs were more correlated with gaze locations during encoding. These findings reveal a direct mechanistic dependence of memory recall on the environment and support the view that the environment is not merely a context for memory, but an integral component of the memory itself.
Transparency, rigor, and reproducibility in this research: Information regarding this work's experimental design, analytical methods, controls, sex of experimental subjects, a priori sample size estimation, and all statistical analyses can be found in the following preprint: https://www.biorxiv.org/content/10.1101/2025.08.27.671980v1 **The collected data, custom code, and the virtual reality experimental setup are freely available at the following link:** https://zenodo.org/records/16901726

Disclosures: N. Mizrachi: None. **E. Ahissar:** None.

Late-Breaking Poster

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Program #/Poster #: LBP032.24/LBP103

Topic: I.08. Learning and Memory

Title: Donepezil prevents scopolamine-induced memory deficits in the Barnes maze without improving impaired EEG biomarkers of cognition: Relevance for cognitive enhancer drug development

Authors: *K. CARVALHO, F. ADRAOUI, C. DRIEU LA ROCHELLE;
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Abstract: Cognitive symptoms are found in most CNS disorders, from schizophrenia to Alzheimer's disease (AD). AD is notably characterized by a loss of acetylcholine in the brain, responsible for early cognitive symptoms. Thus, the acetylcholine esterase inhibitor donepezil has consistently been used as standard of care for AD. Yet, there is a need for more effective drugs that target the underlying neurobiology of the disease. While behavioral testing has consistently been used to assess cognition, electroencephalography (EEG) approaches have recently been suggested as additional endpoints to better evaluate the effects of drugs on neural circuits relevant to cognitive deficits, thereby increasing the translational value of preclinical results.
In this study, we used a pharmacological model of Alzheimer's disease induced by scopolamine (0.3 and 1 mg/kg, sc), an acetylcholine muscarinic receptor antagonist, to reproduce impaired learning and memory in Sprague-Dawley rats. In the Barnes maze, a spatial memory test, scopolamine-treated rats displayed impaired learning during the training phase and poor memory performance in the probe phase compared to vehicle. Co-treatment with donepezil (10 mg/kg, po) improved learning performance and completely prevented memory alteration during the probe phase. To gain further insights, we used freely moving EEG-implanted rats to study the effect of scopolamine and donepezil co-treatment on EEG biomarkers of cognitive capacities. Spontaneous oscillations as well as event-related potentials were therefore recorded after dosing. Scopolamine markedly impacted spontaneous brain activity, increasing theta and gamma waves while decreasing delta and alpha waves. Additionally, scopolamine also impaired auditory steady-state response (ASSR), mismatch negativity (MMN) and auditory gating. Strikingly, donepezil failed to reverse any of these electrophysiological deficits.
These results may suggest that new cognitive enhancers improving both behavior readouts and EEG biomarkers would have better outcomes in clinical studies. Moreover, such results clearly underline the importance of combining behavioral and electrophysiological approaches when evaluating new cognitive enhancers in preclinical development.

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PHARMACOLOGY. **C. Drieu La Rochelle:** A. Employment/Salary (full or part-time); BIOTRIAL PHARMACOLOGY.

Late-Breaking Poster

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Title: Oscillatory dynamics underpinning temporal coding in the developing hippocampus

Authors: *J. SWANN, R. PEDROSA, L. MUESSIG, F. CACUCCI, T. WILLS;
University College London, London, United Kingdom

Abstract: Hippocampal neurons encode spatial and mnemonic information by a rate code that signals current location as well as a temporal code whereby spikes of individual pyramidal neurons occur at progressively earlier phases of the ongoing theta oscillation while an animal traverses a 'place field' of a given neuron ('phase precession'). On the network level the activity of ensembles of pyramidal cells forms ordered sequences of hippocampal place cell firing that are nested within each theta cycle and reproduce, at compressed timescales, the spatial organization of place fields in the environment ('theta sequences'). In adult rodents both phase precession and theta sequences are primarily properties of pyramidal cells in field CA1, and are known to be shaped by inputs from other field CA3, and entorhinal cortical input, and are associated with local gamma oscillations. However, it remains unclear how these patterns emerge during early life and what changes in the hippocampal network activity might drive their maturation. Here, we performed high-density tetrode and silicon probe electrophysiological recordings from the CA1 area of the hippocampus in developing (postnatal days 17-35) and adult Lister Hooded rats of both sexes (n=33) while animals spontaneously foraged in either open field or linear environments. We found that both phase precession and theta sequences emerged progressively over age, becoming stronger and more distinct. We found that medium gamma power, which preferentially represents entorhinal input, increases across development relative to slow gamma, which preferentially reflects input from CA3. The preferred theta phases at which slow and medium gamma are strongest shift through development. Consequently, the overall preferred theta phase at which CA1 pyramidal neurons fire action potentials shifts concurrently and becomes less variable. Notably, only theta sequences were significantly associated with this increase in medium gamma proportion, while theta phase precession was not. Phase precession and theta sequences therefore follow different developmental trajectories, suggesting that their underlying mechanisms may diverge, with theta sequences more tightly linked to the maturation

of entorhinal-CA1 communication. These results supports an emerging consensus that phase precession and theta sequences are dissociable phenomena, and not that theta sequences are simply an emergent property of a population of phase precessing cells, as initially proposed following the processes' discovery.

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Late-Breaking Poster

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Title: Reward-referenced navigational encoding in the mouse subiculum

Authors: *L. K. WILMERDING, K. GOURIANOVA, Z. MALONE, C. GRIENBERGER; Biology, Brandeis University, Waltham, MA

Abstract: To support flexible behavior, the hippocampus maintains population-level representations of space related to two reference frames - the environmental boundaries and reward delivery. The subiculum serves as a major output hub of the hippocampal formation, transmitting a robust conjunctive code for diverse navigational information to a wide range of cortical and subcortical targets. It is still unclear how the subiculum integrates competing navigational reference frames during learning. To address this question, we used Neuropixels probes to record single-unit activity in the subiculum from head-fixed mice running on a linear treadmill for a reward delivered on each lap. The treadmill belt was marked with three distinct tactile cue zones to create stable environmental boundaries. We first delivered the reward at a familiar site and then shifted it by 90 cm to a novel location halfway across the belt. Similar to prior work, we observed many cells with significant spatial information, as well as conjunctive coding for other variables, such as velocity. In contrast to recent studies reporting roughly equal CA1 populations tuned to track-relative and reward-relative reference frames, we found that subiculum units predominantly remapped their fields relative to the reward rather than to the stable tactile cues. We took a population vector (PV) approach to examine the population-level representation before and after the reward zone shift. Over the course of the first 10-20 trials after the shift, the subiculum PV gradually decorrelated from the familiar representation towards a new stable representation. We confirmed the bias toward the reward-relative reference frame at the population level by comparing the strength of the PV correlations before and after the shift. We found a larger proportion of reward-referenced units in the distal subiculum. Together, our

results suggest that the subiculum does not act as a simple relay station for the environmental and reward-related information from CA1 but instead biases hippocampal outputs to the rest of the brain toward behaviorally salient features of the environment, such as the reward.

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Late-Breaking Poster

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Title: Optical recordings of unitary synaptic connections reveal high and random local connectivity between CA3 pyramidal cells

Authors: A. MIKE[1], J. BRUNNER[1], ***J. SZABADICS**[2];
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Abstract: The hippocampal CA3 region is thought to play crucial roles in episodic memory functions because of the extensive recurrent connections between CA3 pyramidal cells (CA3PCs). However, different methods provided contradicting observations about the synaptic connectivity between CA3PCs. Therefore, we estimated the connectivity rate between individual CA3PCs using a new approach that is not affected by the confounds of conventional methods. Specifically, we used voltage imaging with the Voltron sensor in acute slices from rats to test CA3PC connections by detecting spontaneous spiking and subthreshold synaptic responses in anatomically identified neurons. We detected 164 monosynaptic excitatory connections in 3078 tested CA3PC-CA3PC pairs. We verified that the imaged excitatory connections were mediated by AMPA receptors. Our results also showed that the recurrent connections did not enrich into preferred connectivity motifs and followed a distribution that was consistent with random connectivity in general. Moreover, voltage imaging revealed CA3PCs with distinct firing properties and somatic locations corresponding to previously established heterogeneity and showed that specific connectivity rules create preferred information routes among these subpopulations. Altogether, our results obtained with a new voltage imaging approach argue for high local connectivity rates between CA3PCs.

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Late-Breaking Poster

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Title: Goal-directed hippocampal theta sweeps during memory-guided navigation

Authors: *W. TANG, X. MEI, R. E. HARVEY, E. CARBAJAL LEON, T. NETZER, H. CHANG, A. OLIVA, A. FERNANDEZ-RUIZ;
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Abstract: During navigation, animals must continuously sample their environment and plan routes to distant goals. The hippocampal-entorhinal circuit contains diverse spatially tuned neurons, such as place cells and grid cells, that contribute to the formation of internal spatial maps. However, flexible navigation also requires neural dynamics capable of rapidly deploying task-relevant information to guide behavior. Theta sequences, temporally compressed spiking patterns within theta cycles that sweep along spatial trajectories ahead of the animal, are a candidate substrate for such dynamics. Previous work identified experience-independent, left-right alternating theta sweeps as a mechanism for local spatial sampling. Yet whether theta sweeps also support trajectory evaluation toward distant, remembered goals remains unclear. Using large-scale recordings from freely moving rats performing goal-directed tasks in an open arena, we identified a distinct form of learning-dependent theta sequences that predicted upcoming goal-directed trajectories and co-occurred with left-right sweeps. These sequences coordinated with prefrontal cortical activity and were preferentially replayed during sharp-wave ripples, suggesting roles in both online planning and offline memory processing. We further demonstrate a circuit mechanism in which a subpopulation of CA1 neurons encodes egocentric goal direction, coupled with reduced feedback inhibition, to facilitate the generation of these goal-directed theta sweeps. Crucially, when animals learned distinct reward configurations within the same arena, theta sweeps were not restricted to a single, static spatial map. Instead, they selectively sampled discrete, configuration-specific "latent" maps of the same physical environment and flexibly switched between them as task demands changed. These findings suggest that theta sweeps support navigation through both physical and internal task space,

enabling flexible behavior. Their experience-dependent, goal-directed nature reveals a hippocampal mechanism for prioritizing relevant trajectories alongside general environmental sampling—a dual coding strategy for adaptive navigation in complex environments.

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Late-Breaking Poster

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Program #/Poster #: LBP033.05/LBP108

Topic: I.09. Spatial Navigation

Title: Maturation of the head-direction system in the vertebrate brain

Authors: *M. CARRIÈRE, G. DEBREGEAS, V. BORMUTH;
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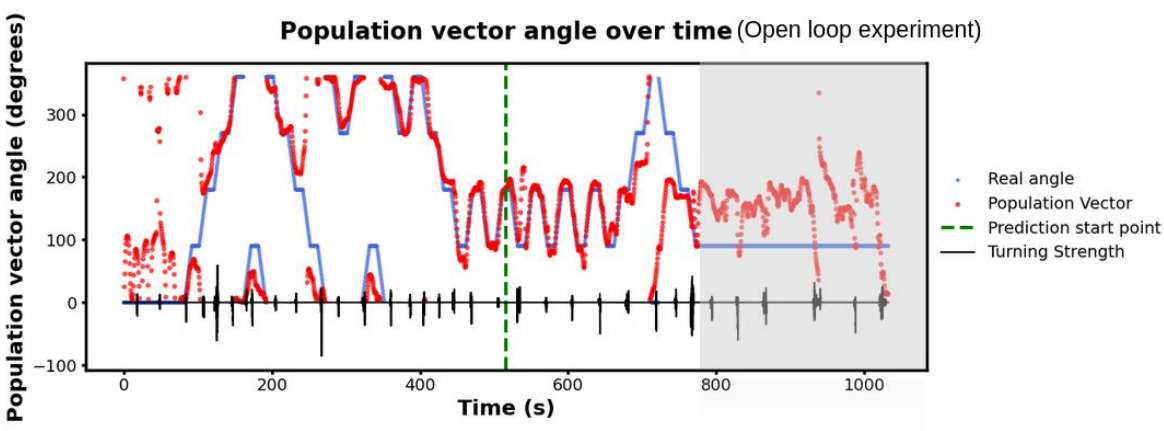
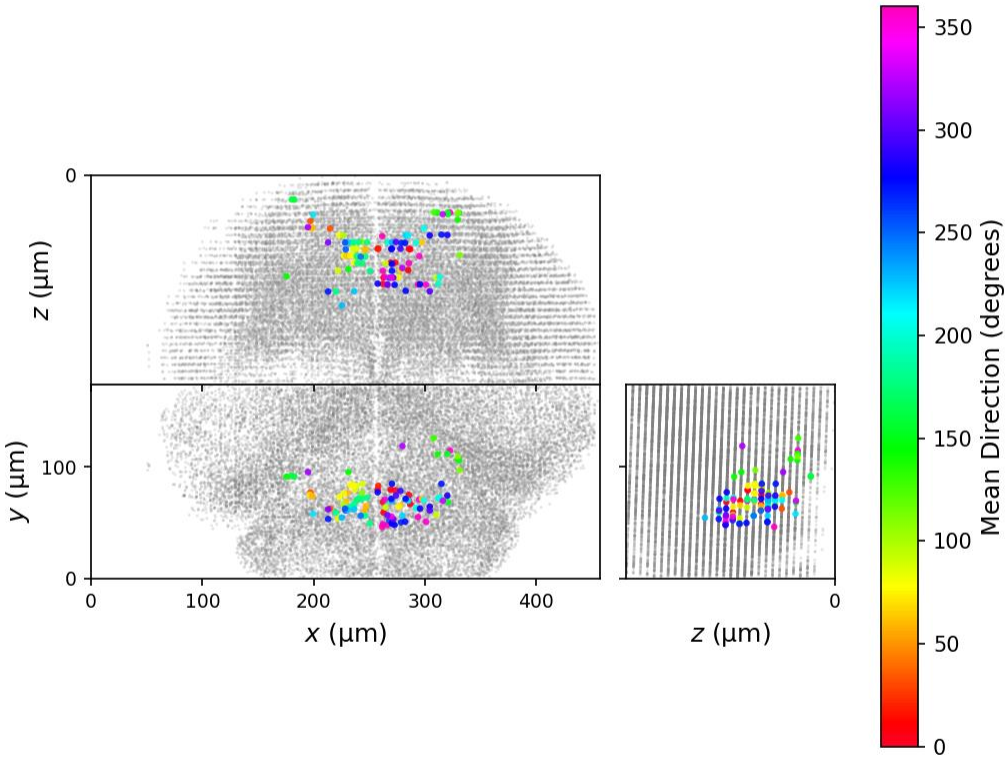
Abstract: Head direction (HD) cells encode an animal's facing direction, forming a neural compass essential for spatial navigation. First identified in rodents, HD cells were only recently discovered in zebrafish larvae, enabling brain-wide imaging. However, zebrafish lose transparency with age, limiting longitudinal studies. Here, we investigate HD circuit emergence in *Danionella cerebrum* (DC), a newly introduced transparent vertebrate model that allows whole-brain calcium imaging across development. Using a virtual reality setup, we recorded neural activity at cellular resolution in 1-2 week-old DC larvae exposed to controlled heading cues. Candidate HD cells were identified based on tuning curves selective for specific heading angles, and population decoding showed reliable direction encoding. To verify HD cell properties, we are conducting visual perturbation tests assessing tuning stability in darkness and remapping across environments. Our results show that HD circuits in DC mature early, forming stable and specific directional representations. DC's lifelong transparency and compatibility with behavioral assays make it an ideal system for longitudinal studies of spatial coding. This work bridges systems neuroscience and computational modelling by providing experimentally validated data on attractor-like networks. It opens avenues for investigating how neural circuits self-organize and adapt to multisensory environments.





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Title: Changes in hippocampal population activity during a reward down-shift task

Authors: *M. DONAHUE[1], N. MASALA[1], B. L. BOUBLIL[1], M. SABARIEGO[2], L. A. EWELL[1];
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Abstract: The activity of the hippocampus is believed to support memory-guided decision making through the activity of spatially-modulated neurons called “place cells”. Hippocampal place cells are able to dynamically represent reward locations and will change their firing patterns after rewards are removed; however, how place cell activity changes in response to a decrease in reward value is not well understood. In our study, mice (n = 9 mice, 5 males, 4 females) completed a figure-8 task where one arm contained a large reward (30 µL sucrose) while the other arm contained a smaller reward (5 µL sucrose). Mice performed 20 free choice trials to establish their preference for the large reward arm and 20 forced choice trials, where they are required to visit each arm for 10 trials, per day. After mice displayed a preference for the large reward (>70% large reward for two days), the large reward was down-shifted in magnitude to match the smaller reward (5 µL sucrose). To assess neural mechanisms of adjustment to reward devaluation, we performed one-photon calcium imaging of the CA1 subregion of the hippocampus. We found that during the initial preference phase of the task, the normalized firing rate of hippocampal population activity was higher when mice were forced to visit the large reward compared to the small reward (generalized linear mixed model, $p = 0.0032$). On the day that the reward was down-shifted, this difference normalized between the two reward arms (generalized linear mixed model, $p = 0.3022$). As mice lost their preference for the previously large rewarded arm, this effect eventually reversed; hippocampal population activity was higher when mice were forced to visit the stable reward arm compared to the down-shifted reward arm (generalized linear mixed model, $p < 0.001$). Interestingly, this effect was not driven by an overrepresentation of place cells at the large reward, but instead by out-of-field firing at the reward location by place cells with fields elsewhere on the maze. This study offers new insights into how reward is dynamically coded within the hippocampus.

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Late-Breaking Poster

LBP033: I.09. Spatial Navigation

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP033.07/LBP110

Topic: I.09. Spatial Navigation

Support: SFARI Grant 903332

Title: Path integration in a rat model of Fragile X Syndrome

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Abstract: Fragile X Syndrome (FXS) is a common inherited form of intellectual disability. FXS frequently co-occurs with autism spectrum disorder (ASD), a neurodevelopmental condition associated with sensory hypersensitivity and altered multisensory integration - features that remain poorly understood. The mammalian brain relies on multisensory integration for efficient navigation. A key example is the head-direction (HD) circuit, in which HD cells fire selectively when the animal faces a particular direction. To maintain a stable reference frame, this circuit relies on weighted integration of vestibular inputs conveying self-motion information with visual inputs relaying information about stable visual landmarks. We recently showed that the HD system in *Fmr1*$^{-/y}$ rats, a model of FXS, fails to integrate visual and self-motion cues during reorientation, instead relying solely on visual inputs, recapitulating a common feature of ASD in humans. This predicts impaired performance on navigation tasks requiring path integration (PI), which depends on self-motion cues alone. Surprisingly, our present study reveals that *Fmr1*$^{-/y}$ rats are not generally impaired at PI, but that the presence of visual input specifically disrupts their ability to use self-motion cues. We tested *Fmr1*$^{-/y}$ rats on a PI task using a homing paradigm (Najafian et al., Nat Commun 14:7373, 2023). The apparatus consisted of a large circular arena surrounded by a curtain that blocked polarising visual landmarks, with eight goal boxes positioned around the perimeter. At the beginning of each session, one of the goal boxes was designated as a 'home' box. Reward delivery in the home box was triggered by a lever on a remotely controlled car (a 'robot'), positioned in a randomized location on the arena. During each trial the rat thus had to find the robot, press the lever, and use PI to return to the home box to receive reward, upon which the robot moved to a new location. After extensive training, *Fmr1*$^{-/y}$ rats (n = 12) and their WT littermates (n = 10) were tested in two conditions: in light and in darkness. In light, *Fmr1*$^{-/y}$ rats took longer and less efficient homing paths and were more likely to make an error on their approach to arena periphery. However, they performed on par with WT rats in darkness. These results suggest that *Fmr1*$^{-/y}$ rats are not impaired in PI per se, but that

visual input disrupts their ability to use PI. We are currently recording HD cells during the task to determine whether the impaired navigation of *Fmr1*$^{-/y}$ rats in light reflects a corresponding loss of accuracy in their HD system.

Disclosures: A. Vadher: None. **A. Duszkiewicz:** None. **J. Sebastian:** None. **A. Peyrache:** None. **E.R. Wood:** None. **P.A. Dudchenko:** None.

Late-Breaking Poster

LBP033: I.09. Spatial Navigation

Location: SDCC Hall B

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National Institute of Mental Health, R01MH125916
National Institute of Neurological Disorders and Stroke, R01NS138075

Title: Affordance-Based Parcellation: How Anterior Cingulate Cortex Categorizes Egocentric Space

Authors: *I. R. NAIR[1], K. RAMESH[1], K. GAWF[1], S. K. OGAWA[1,2], T. KITAMURA[1,2,3]; [1]Department of Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX; [2]Peter O'Donnell Jr. Brain Institute, University of Texas Southwestern Medical Center, Dallas, TX; [3]Department of Neuroscience, University of Texas Southwestern Medical Center, Dallas, TX

Abstract: Navigation relies on the transformation of allocentric maps into egocentric representations, enabling motor control. Although the Retrosplenial cortex mediates this transformation, the organization of egocentric space according to behavioral affordances remains unresolved. Environmental features provide distinct action possibilities based on their geometry: boundaries support wall-following, corners facilitate turning, and objects enable approach, investigation, and interaction. This necessitates categorizing space by its action possibilities. The present study hypothesizes that the anterior cingulate cortex (ACC), situated between the spatial and motor systems, categorizes space according to affordances. Using calcium imaging in freely navigating mice (AAV-Syn-GCaMP6f), we employed one-photon miniscope recordings and, in a separate group of mice, two-photon tracking of individual cells across multiple days in arenas with different geometric features. UMAP dimensionality reduction revealed population organization, while two-photon assessed stability. ACC neurons exhibited categorical responses to environmental features, with around 20% encoding boundaries, 15% encoding corners, 24% encoding objects, and 12% encoding corridors. The Gaussian Mixture Model reveals that the ACC is organized into 7-8 discrete manifold states, representing feature combinations from the animal's egocentric perspective. States exhibit a specific egocentric orientation with respect to the object. State sequences during navigation reflected affordance-based organization—distinct

states for wall-following versus object approach. Two-photon imaging revealed remarkable stability, as cells maintained their categorical identity across days, with 85% preserving their feature preferences. When exploring
different arenas, most cells retained egocentric tuning, while only a few remapped, suggesting stable affordance detection with contextual flexibility. The results demonstrate that the ACC implements affordance-based parcellation of egocentric space using stable categorical representations. Rather than continuous spatial coding, the ACC divides the environment into discrete categories defined by available actions. This organizational structure links perception to action and facilitates rapid behavioral decisions by detecting affordances.

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Late-Breaking Poster

LBP033: I.09. Spatial Navigation

Location: SDCC Hall B

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Program #/Poster #: LBP033.09/LBP112

Topic: I.09. Spatial Navigation

Support: NIH - NIA Grant R01AG073157

Title: Fall-related ruminations are linked to spatial orientation and processing efficiency

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Abstract: Walking and wayfinding rely on multiple cognitive processes, including spatial orientation and path planning. Humans must therefore attend to their environment and their own position and movement in space, including balance, stepping, and situational demands. Previous research indicates that walking-related anxiety can hinder gait-related activities by diverting attention toward concerns about past and future falls, which can lead to inefficiencies in information processing. In this study we hypothesized that the link between gait-specific attention and cognitive processes key to navigation persists independent of walking. In a pen-and-paper format, we administered the Perspective taking Spatial Orientation (PSOT) and Trail Making Tasks (TMT) and the Gait-Specific Attentional Profile (G-SAP) to 49 adults (26F, 44.2±20 y.o.). Among the G-SAP subscales (anxiety, conscious movement processing, fall-related ruminations, and processing inefficiency), we found significant correlations for both the PSOT and TMT (part A) tasks with the ruminations subscale (PSOT: ρ=0.35, p=0.021; TMTa: ρ=0.34, p=0.019) and a significant correlation between TMT part A and processing inefficiency (ρ=0.30, p=0.038). During walking, ruminations about falling can affect path planning and movement coordination. Our findings suggest an important relationship between increased fall-

related ruminations and reduced basic spatial cognition abilities, even when there is no walking taking place. One possible explanation is that ruminating on falls leads to inefficient processing of spatial and motor information, as revealed by TMT Part A, which measures processing speed. The relationship between ruminations and PSOT suggests that spatial orientation is key to how movement planning may be compromised by excessive rumination. The TMT Part A relies on visual path scanning and tracking abilities, in addition to cognitive processes like attention, and speed; the observed link to processing inefficiencies may therefore indicate poor movement planning during walking. Together, we propose that these attentional mechanisms may affect gait through fundamental changes to how (and how quickly) spatial information is processed by the walker. This interpretation is consistent with prior findings showing that, among the four G-SAP subscales, only conscious movement processing directly affected gait performance, while the other three were hypothesized to influence walking more indirectly, via cognitive processes. Here, we identify spatial orientation and processing speed/tracking as pathways to explore further.

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Late-Breaking Poster

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Topic: I.09. Spatial Navigation

Support: NSF Grant (IIS-2024663, NCS-FO)

Title: Correlates of trait autism and spatial navigation in a healthy young adult population

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Abstract: Recent nationwide research has found that Autism Spectrum Disorder (ASD) is associated with elevated dementia risk, with ASD adults under 65 more than twice as likely to develop Alzheimer's Disease (AD) compared to neurotypical individuals. The role of spatial navigation, a cognitive domain implicated in both ASD and AD, remains underexplored in both conditions. Typically, clinical populations have been compared to healthy controls, but the relationship between ASD traits and spatial abilities within the healthy population has not been tested. In this study, we aim to explore whether spatial navigation abilities are correlated with the Autism Spectrum Quotient (AQ) and whether these relationships differ by biological sex. We analyzed data from a subset of 153 neurotypical young adults (N = 64 males, N = 89 females; ages 18 - 35) drawn from a larger study on individual differences in navigation abilities. From the 40 tasks included in the larger project, we analyzed a subset of eight to assess relationships

between autism traits, spatial abilities, and cognitive performance. These included the AQ10 screening survey, one immersive virtual reality viewpoint transformation task (iVTT), four desktop-based spatial tasks - spatial orientation (SOT), road map (RMT), and both Shepard-Metzler (SM) and Vandenberg-Kuse (VK) versions of mental rotation (MRT) - the Santa Barbara Sense of Direction (SBSOD) scale, and Raven's Progressive Matrices (RPM) as a measure of fluid intelligence. We assessed associations between visuospatial performance and trait autism through partial correlations controlling for age and sex, conducted the correlations stratified by sex, and performed independent-sample t-tests to evaluate sex differences. Results from the partial correlation matrices conducted on females revealed a significant positive correlation between MRT VK and the AQ10, while no association emerged for males. Additionally, males significantly outperformed females on MRT VK and other spatial tasks (iVTT, RMT, SBSOD, MRT SM) despite no sex differences being observed in the AQ10 scores. These findings suggest that spatial mental rotation abilities in females have overlapping cognitive measures that may share brain circuitry linked to autism traits. Future studies will aim to integrate neuroimaging and longitudinal designs to conduct confirmatory analyses and inform targeted intervention strategies for the clinical populations.

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Late-Breaking Poster

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Topic: I.09. Spatial Navigation

Support: NIA R03AG087366
Alzheimer's Association AARF-22-926755

Title: The virtual grocery store: a new method for assessing ecological spatial behavior

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Abstract: Studies of nonhuman mammals exploring physical mazes have been foundational for neurobiological models of hippocampal-mediated spatial memory and navigation. In recent years these paradigms have been adapted for humans using virtual reality (VR) technology. These tasks typically require participants to learn and recall locations within 2D generated environments using a mouse or joystick to navigate. However, stationary VR paradigms rely on visual input, limit assessment of more naturalistic multisensory integration (e.g., vestibular and proprioceptive cues), and often lack ecological validity. To address these gaps, we developed the VR Grocery Store (VGS) to test spatial memory in a fully immersive, ambulatory, and ecologically valid VR environment. By enabling naturalistic walking cues and head/body turns, the VGS allows participants to experience enriched vestibular and proprioceptive feedback while

simulating the real-world experience of locating items in a virtual store. In a proof-of-concept pilot study, 13 young and 3 older adults performed a spatial memory task that required learning and retrieving the locations of common grocery items over the course of two experimental sessions. On Day 1, participants completed three shopping-restocking cycles in a virtual environment. Each cycle used a new 20-item list (no overlap) to encourage exploration of the entire store. After shopping, shelves were cleared, and participants replaced each item in its original location. Cycles continued until they placed ≥18/20 items correctly, ensuring familiarity with the starting store. On Day 2 (24-48 h later), participants completed one cycle with a new, non-overlapping list to simulate navigating an unfamiliar store, then returned to the familiar store for one final cycle to assess effects of environmental familiarity. This design was meant to examine the effect of environmental familiarity on memory performance, given prior evidence that age differences in spatial memory are reliably attenuated in familiar vs. novel real-world contexts. The number of trials required to reach criterion on Day 1 did not differ between young (3.9 trials) and older (4 trials) adults. Older adults performed worse than young adults on Day 2, but the magnitude of this age difference was notably smaller in the well-learned, familiar store. These findings support the feasibility and construct validity of the VGS for assessing naturalistic spatial memory in aging populations.

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Late-Breaking Poster

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Topic: I.09. Spatial Navigation

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California Nanosystems Institute
Aging and Alzheimer's Disease NIA Training Grant (T32 AG00096)
Faculty Mentor Program Fellowship

Title: Multimodal neuroimaging reveals distinct brain structures underlying path integration in young and midlife adults

Authors: *D. COSSIO[1], N. KROHN[1], M. HEGARTY[2], E. G. JACOBS[3], E. R. CHRASTIL[4]; [1]University of California, Irvine, Irvine, CA; [2]University of California, Santa Barbara, Santa Barbara, CA; [3]UC Santa Barbara, Santa Barbara, CA; [4]Neurobiology & Behavior, University of California, Irvine, Irvine, CA

Abstract: The ability to navigate is an essential behavior for daily life. Navigation is sensitive to aging, and the regions supporting navigation are impaired early in AD. Path integration is a component of human spatial navigation that involves the continuous updating of position and

orientation during movement. In humans, age-related impairments in path integration have been well documented, with older adults performing worse than young adults and these impairments are linked to hippocampal dysfunction. Despite its important role in daily life, and documented impairments in older adults, little is known about path integration abilities in midlife adults. Further, the extent to which brain structure contributes to path integration performance across the lifespan remains unclear. To address these question, we analyzed white matter integrity, total hippocampal volume, hippocampal subfield volumes, and whole brain cortical thickness to examine the relationship between brain structure and path integration performance on the LOOP task, a measure of path integration ability, in young (ages 18-35, n = 23 and midlife (ages 45-55, n = 43) adults. Briefly, participants were guided in a circle, providing them with proprioception and visual optic flow but no landmarks, and had to indicate when they returned to the start of the circle. Our previous behavioral findings suggest that there are negligible effects of early aging on the LOOP task. Men and women made similar errors during path integration but relied on different strategies: women overshot the target, and men undershot. Examining the neuroimaging data here, we found that total hippocampus and subfield volumes were associated with strategy preference (overshooting or undershooting) in midlife adults, but not overall accuracy during path integration. In contrast, young adults' hippocampal volume was associated with accuracy but not strategy. In midlife, white matter integrity in the fornix - a major output tract of the hippocampus - correlated to both path integration accuracy and strategy use, but this relationship differed between men and women. In young adults, white matter integrity in the fornix correlated to better accuracy overall but was not related to strategy. These contrasting findings suggest that brain structure corresponds to path integration abilities, but that this relationship changes during midlife and may be influenced by sex. Investigating the neural underpinnings of path integration performance in midlife adults provides us with a greater understanding of human spatial navigation across the lifespan and may lead to improved early biomarkers of AD and insights into cognitive aging.

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Late-Breaking Poster

LBP033: I.09. Spatial Navigation

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Topic: I.09. Spatial Navigation

Support: CONAHCYT CVU 409838 scholarship to Cindy Oceánida Zurita Bautista

Title: Slow and fast EEG frequency Absolute Power during Eyes Closed as Predictors of Landmark speed codification and recall accuracy in 6 to 11 year old children.

Authors: *C. O. ZURITA BAUTISTA[1], I. G. GALÁN[2], Y. DEL RÍO-PORTILLA[3];
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Abstract: Pu et al. (2017) reported an association between landmark encoding and fast theta rhythm in healthy adult men. They observed greater fast theta power (4–8 Hz) in the right hippocampal and parahippocampal cortices during encoding in training trials, followed by a decrease once learning was established. They also found a positive relationship between theta power in these regions and better performance in landmark recall. This agrees with Werweg and Kahana's (2018) review, which noted that fast theta frequency (4–8 Hz) has been functionally linked to the retrieval of spatial information, although it has also been associated with impaired navigation performance. Other studies suggest that humans require consideration of a broader low-frequency spectrum. Jacobs (2014) proposed that the larger size of the human hippocampus may explain why theta oscillations occur at lower frequencies. Indeed, peaks of power in the 2–4 Hz range, or low-frequency theta, have been associated with the coordination of sensory and motor areas as well as with landmark encoding (Pu et al., 2017; Werweg & Kahana, 2018).In the present study, we examined scalp EEG activity in 49 children aged 6–11 years. Nineteen electrodes were positioned according to the international 10–20 system. EEG recordings were obtained while participants navigated through a virtual arena under four conditions: eyes open (EO), eyes closed (EC), resting baseline (B), and landmark encoding (C). Multiple linear regressions were computed to identify EEG absolute power predictors —delta (1–3 Hz), theta (4–7 Hz), alpha1 (8–10 Hz), alpha2 (10–12 Hz), beta1 (13–19 Hz), beta2 (20–30 Hz), and gamma (31–50 Hz)— of behavioral performance measures (landmark encoding speed and recall accuracy).Results showed that landmark encoding speed was predicted by EC beta1, beta2, and gamma power, $F(3, 45) = 7.01$, $p < .001$, explaining 31.9% of the variance ($R^2 = .319$, adjusted $R^2 = .273$). Specifically, EC beta2 positively correlated encoding speed ($B = 2.94$, $p < .001$), while EC gamma ($B = –1.41$, $p = .017$) and EC beta1 ($B = –0.93$, $p = .022$) negative correlated. Landmark recall accuracy was predicted by EC delta power, $F(1, 47) = 5.66$, $p = .021$, explaining 10.7% of the variance ($R^2 = .107$, adjusted $R^2 = .088$; Durbin–Watson = 2.11).These findings indicate that increased EC beta2 power is associated with slower landmark encoding, whereas higher EC beta1 and gamma power are linked to faster encoding. In contrast, increased EC delta power predicts lower recall accuracy. Together, these results highlight distinct roles of slow and fast EEG oscillations in children's spatial learning and memory.

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Late-Breaking Poster

LBP033: I.09. Spatial Navigation

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Program #/Poster #: LBP033.14/LBP116

Topic: I.09. Spatial Navigation

Title: Decoding hidden goal-directed navigational states and their neuronal representations using a novel labyrinth paradigm and probabilistic modeling framework

Authors: *P. S. HONMA[1], S. BANGERA[2], R. THOMAS[2], D. XIA[3], J. J. PALOP[4]; [1]Gladstone Institutes and UCSF, San Francisco, CA; [2]Gladstone Institutes, San Francisco, CA; [3]Denali Therapeutics, South San Francisco, CA; [4]Gladstone Institutes & UCSF, San Francisco, CA

Abstract: Goal-directed navigation involves a sequence of planned actions aimed at achieving long-term goals through reinforcement, but detecting hidden behavioral states that support this process and their neuronal substrates remains a fundamental challenge. To address this, we developed a novel hierarchical probabilistic modeling framework, Cognitive Mapping of Planned Actions with State Spaces (CoMPASS), which infers a nested state structure comprising short-term surveillance-ambulation states (Level 1) and long-term goal-oriented navigational states (Level 2). We paired this computational framework with a complex labyrinth maze that mimics a naturalistic foraging environment and promotes rewarded goal-directed navigation. Both wild-type (WT) and the humanized *App*^{SAA} mouse model of Alzheimer's disease (AD) were able to learn the task during a single 13-hour overnight trial, showing increased reward path exploitation and non-random decision-making at decision nodes as compared to simulated agents. CoMPASS revealed that successful navigation in wild-type mice (n=13, 22 mo.) is marked by increased recruitment of both surveillance and goal-oriented states specifically at decision nodes, demonstrating how sequential behavioral decisions culminate in long-term goals. In contrast, *App*^{SAA} mice (n=19, 22 mo.) exhibited impairments in these hidden states that were associated with deficits in navigational performance. To identify the neuronal mechanisms underlying these behavioral states of goal-directed navigation, we recorded wireless EEG from the posterior parietal cortex (PPC) in WT mice (n=5, 5 mo.), a region involved in spatial navigation planning. Gamma oscillations in PPC differentiated key elements of goal-directed navigation captured by the CoMPASS states, including motor planning and binding of spatial context with long-term reward information. Our findings establish behavior-centered state space modeling as a powerful approach for revealing latent goal-directed navigation processes and identify PPC gamma oscillations as a critical neural mechanism of navigational planning, with broad implications for understanding cognitive decline in Alzheimer's disease.

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Late-Breaking Poster

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Title: Cognitive maps facilitate spatial navigation in a model of hippocampal-striatal interaction

Authors: *A. EFREMOV[1], D. LEVENSTEIN[2], A. PEYRACHE[3], B. A. RICHARDS[2];
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Abstract: Early experiments on mammals' navigation led to a distinction between the hippocampus (HPC)-dependent "cognitive map" strategy and the striatum-dependent "stimulus-response" strategy. These two types of behavior were believed to be independent, but more recent experiments show a significant interplay between the two regions. However, the nature of the information they exchange and its processing is unknown. To investigate this, we developed a model that integrates the functionalities of two regions. HPC is simulated with a predictive recurrent neural network (pRNN) that learns to predict sequences of sensory observations and develops a cognitive map that captures the environment geometry. However, it remains unknown whether the information contained in the cognitive map is sufficient for solving navigational tasks, and what aspects of the cognitive map provide for efficient learning of such tasks. To model the interaction between the hippocampus and the striatum, we have combined pRNN with an actor-critic reinforcement learning algorithm, which takes the pRNN activations and/or visual observations as input. We then trained the model to solve a navigational task with ambiguities in visual observations. While agents with a limited view of the environment showed poor performance, agents relying on pRNN activations successfully learned the task, although slower than agents with a full view of the environment. When representations from the pRNN were combined with visual input, the agent's performance was improved to the same level as with a fully observable environment. These results show that representations provided by the pRNN convey more information than just the visual inputs. We also introduced an addition to the learning algorithm that utilizes the structure of pRNN's representational manifold - the internal reward. This reward is positive when the pRNN activity gets closer to the memorized representation of the goal location and negative otherwise. With internal rewards, agents achieved learning speeds faster than those with full observability of the environment. Together, our results indicate that hippocampal cognitive maps provide informative representations of navigational tasks' features and a valuable metric to act as a learning signal in such tasks.

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Late-Breaking Poster

LBP034: I.10. Human Learning and Cognition

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Program #/Poster #: LBP034.01/LBP118

Topic: I.10. Human Learning and Cognition

Support: NIH Grant R01 MH126971

Title: Behavioral signatures of rotational transfer learning in a spatial predictive inference task

Authors: *H. FAN[1], M. R. NASSAR[2];
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Abstract: Humans can transfer relational knowledge from past experiences (e.g., milk and eggs are often adjacent in grocery stores) to guide behavior in novel contexts (e.g., navigating a new store). Theoretical accounts suggest that such generalization is supported by a cognitive map, which might be transformed (rotated or stretched) to best match the current situation. However, this idea has not been thoroughly tested behaviorally, nor is it clear whether people are capable of such transformation in complex environments where the number of cognitive anchors (ie. items at the grocery store) exceeds working memory capacity and there exist multiple cognitive maps to choose from. Here, we examine behavioral signatures of rotational transfer using a spatial predictive inference task. In the task, participants predicted the locations of colored targets, with spatial layouts fixed within each latent state. A given latent state would persist for several presentations of each color before either being rotated or replaced with another one. Participants were informed that state transitions (i.e., changes in target-location associations) could occur, but not when or how the new layout related to the previous one. Study 1 (N=96) employed a between-subjects design to compare transfer learning when target rotations were spatially coordinated (N=57) as a coherent map vs. independently rotated for each color (N=39). Following unsignaled state transitions, prediction errors decreased rapidly and were significantly lower in the coordinated condition. Moreover, angular error distributions in the coordinated condition deviated from uniformity, while those in the independent condition did not, suggesting that participants leveraged preserved spatial relationships to transfer knowledge after coherent rotations. Study 2 (N=20) increased task complexity by using 8 (rather than 4) colored targets. Consistent with Study 1, error reduced rapidly after state transitions. Study 3 (N=41) tested whether participants could learn and rotate multiple spatial layouts. Each latent state was a rotated version of one of two prototype maps (each with four colored targets). Again, participants adapted quickly following state changes. Together, these findings suggest that humans can infer and apply structured spatial relationships—without explicit instruction—to support adaptive behavior in novel contexts. This transfer learning effect is robust and can be detected even in scenarios with the number of items exceeding memory capacity and multiple spatial maps. Future work will focus on developing cognitive models to uncover the mechanisms underlying rotational transfer learning.

Disclosures: H. Fan: None. **M.R. Nassar:** None.

Late-Breaking Poster

LBP034: I.10. Human Learning and Cognition

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Topic: I.10. Human Learning and Cognition

Support: This work was supported by the MnDRIVE Brain Conditions and the Minnesota Medical Discovery Team on Addictions initiatives.

Title: Grid-like Code of Cognitive-Control Space in the Human Hippocampal Complex and Its Modulation by Internal Capsule Stimulation

Authors: *J. KIM[1], A. S. WIDGE[2];
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Abstract: Grid-like code in the human entorhinal-hippocampal system supports navigation in physical and abstract spaces. Cognitive control likewise requires navigating a multidimensional "control space" defined by task features, yet it is unknown whether hippocampal-entorhinal grid-like codes represent this space, or whether neuromodulation can alter such codes.We analyzed intracranial EEG data from 18 epilepsy patients performing the Multi-Source Interference Task (MSIT). Trial states were embedded in a 2-D cognitive-control space with orthogonal axes for target position (left/middle/right) and target identity (digits 1-3). For electrodes in the hippocampal complex and frontal cortex (dlPFC, vlPFC, ACC, OFC), we computed theta-band power and tested hexadirectional (6-fold) modulation by movement direction through cognitive control space using standard grid-angle fitting and n-fold (4/5/6/7/8) symmetry tests. In a subset of six patients receiving internal capsule stimulation (ICS), we asked whether ICS acutely modulates grid strength; leads were subsequently classified as dorsal versus ventral capsule.Left hippocampal-complex (LHC) electrodes showed significant 6-fold modulation of theta power during cognitive control space navigation ($pFDR < 0.05$), whereas no grid-like modulation was detected in the right hippocampal complex or in dlPFC, vlPFC, ACC, or OFC (all $pFDR > 0.6$). Alternative symmetries (4/5/7/8-fold) were not significant in the LHC (all $pFDR > 0.1$). LHC grid strength correlated with better performance (faster mean RT; Spearman's rho = −0.55, $p = 0.02$), whereas average theta power did not ($p = 0.30$). In the ICS subset, stimulation increased LHC grid strength, most prominently with dorsal capsule contacts.These results show that human hippocampal theta exhibits a grid-like code for a task-defined cognitive control space, and that the magnitude of this code tracks control efficiency. Moreover, internal capsule stimulation can upregulate this representation, suggesting a mechanistic biomarker for neuromodulation targeting cognitive control. These findings link hippocampal-entorhinal cognitive maps to executive control and motivate closed-loop strategies that enhance grid-like coding when control demands are high.

Disclosures: J. Kim: None. **A.S. Widge:** None.

Late-Breaking Poster

LBP034: I.10. Human Learning and Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP034.03/Web Only

Topic: I.10. Human Learning and Cognition

Title: Sex-Specific Links Between Personality and Cognitive Profiles: A Data-Driven and Machine Learning Approach

Authors: *H. SHAHI[1,2], B. MOGHADAMPANAH[1,2], A. GHADERI[3,1];
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Abstract: Research on the relationship between intelligence and personality has largely treated fluid (Gf) and crystallized (Gc) intelligence as independent constructs, examining their correlations with the big five traits independently. However, there is limited understanding of whether individuals form joint Gf–Gc profiles, and how these profiles align with personality. To broaden this perspective, we investigated interactions between Gf, Gc and personality traits using machine learning (ML) approaches.Analyses were conducted on females (N = 87) and males (N = 155) aged 22–25 years using dataset from HCP. Spearman's rank correlation was used to examine associations between Gf, Gc, and the big five traits. Then, individuals were clustered based on two dimensions (normalized scores of Gf and Gc) using k-means. The number of clusters was optimized by the Calinski–Harabasz criterion. Following clustering, participants were grouped by sex, and permutation t-tests (corrected by FDR) compared personality traits among clusters. Predictive ML modeling was further conducted using support vector machine (SVM) models (six different kernels) with 5-fold cross-validation to assess whether personality traits could predict Gf and Gc scores. Results revealed sex-specific associations between intelligence and personality traits. In females, Gf positively correlated with extraversion (E), and Gc positively correlated with agreeableness (A) and openness to experience (O). In males, both Gf and Gc were negatively correlated with neuroticism (N), while Gc correlated positively with A and O. Cluster analysis identified four distinct Gf–Gc profiles (K = 4). Females showed no personality differences across clusters after FDR correction, but males differed significantly in A, O, and N. ML further demonstrated predictive links: O and E consistently predicted Gc for both female and male groups, while Gf was best predicted by E and Conscientiousness (C) in females, and by A and N in males. Overall, these findings highlight sex-specific relationships using multidimensional factor analyses, uncovering latent Gf–Gc subgroups, and demonstrating the predictive capacity of personality traits for Gf and Gc. This multidimensional approach underscores the value of clustering and machine learning in refining models of cognitive diversity.

Disclosures: H. Shahi: None. **B. Moghadampanah:** None. **A. Ghaderi:** None.

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Program #/Poster #: LBP034.04/Web Only

Topic: I.10. Human Learning and Cognition

Support: JSPS Grant KAKENHI_24K23818

Title: Decoded fMRI-neurofeedback of frontopolar activity rapidly facilitates prospective memory performance

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Abstract: Motivation/problem statement Prospective memory (PM) is a form of memory to perform future intentions and plays an essential role in daily life. While PM is often impaired by aging or brain injury, no effective training method has been established to date. Since PM is known to heavily rely on the frontopolar cortex (FP), we used real-time fMRI to examine whether brief neurofeedback (NF) training of FP activity can modulate behavioral PM performance in healthy adults. **Methods** Thirty right-handed participants volunteered for the study. They first performed a pre-training PM task in which they detected deviant visual targets while performing a background word classification task. Participants then underwent a functional localizer fMRI run while performing another PM task and received either a real or sham NF training (30 minutes) followed by a post-training assessment. During NF training, frontopolar cortex activity was measured and decoded by computing Pearson's correlation coefficients between real-time frontopolar activation and activation maps derived from the localizer run. The resulting correlation coefficients were visualized every 1 s as the diameter of a circle on the screen. Guided only by visual feedback, participants attempted to enlarge the circle without explicit instruction. Participants in the sham group received the same training with feedback stimuli irrelevant of actual FP activity. **Results** Behavioral effects of NF were examined by submitting reaction time (RT) data for the PM task to a two-way ANOVA with factors Intervention (pre vs. post) × Group (NF vs. sham). The main effect of Intervention was significant ($p < 0.001$), whereas that of Group was non-significant ($p = 0.67$). Critically, there was a significant Intervention× Group interaction ($p = 0.035$), indicating that the reduction of RT after training was greater for the NF group than for the sham group (135 ms vs. 76 ms). For the NF group, the magnitude of this behavioral improvement was correlated with behavioral performance during NF training ($r = -0.63$, $p = 0.012$). **Conclusion**
Our results demonstrate that brief fMRI- NF training of frontopolar activity can effectively enhance behavioral PM performance and serve as novel and individually-customized tool for neurocognitive rehabilitation.

Disclosures: S. Takeda: None. **K. Takano:** None. **K. Nakamura:** None.

Late-Breaking Poster

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Program #/Poster #: LBP034.05/Web Only

Topic: I.10. Human Learning and Cognition

Support: DARPA contract #HR001124C0497 as part of the Objective Prediction of Team Effectiveness via Models of Performance Outcomes (OP TEMPO) program

Title: Identifying Objective Markers of High Performing Teams Using Hyperscanning and Functional Connectivity Measures

Authors: *J. SUSSMAN-FORT[1], J. T. FOLSOM-KOVARIK[1], J. CRAIGHEAD[1], A. WOODS[1], D. WILSON[1], S. KLINE[1], T. HILSABECK[1], N. PETROFF[1], J. COHN[1], D. SCHMORROW[1], E. SALAS[2], L. BERGER[2], M. KHALID[2], R. LINHARDT[2], C. BERKA[3], E. THUNEN[3], S. DODEL[4];
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Abstract: Measuring and predicting operational readiness is paramount to establishing effective teams across the military. Despite there being a standard sequence of training, team level performance to determine readiness remains a challenge. The goal of this study is to identify objective biomarkers of high-performing teams. We present our initial results based on data collection from a five-member Marine Fire Support Team (FiST) engaged in a virtual simulation-based training environment. Our approach is based on operationalizing *Team Behavioral Competency Theory (TBCT)*, which maps behavioral windows to team level skills such as Leadership, Mutual Performance Monitoring, Back-up behavior, Team Orientation, and Adaptability. Within the FiST we measure standard electroencephalography (EEG) along with high-resolution tripolar concentric ring (tEEG). Characterization of these signals is accomplished using functional connectivity metrics to identify a set of features to populate the edges of a graphical causal model that predicts overall team performance. Marine instructors provide a ground truth subjective *mission rating score*. We test two hypotheses by comparing *main windows* of activity, *Mission Brief* (orienting team to the task) *and Attention to FiST* (call made by team prior to passing information), to a *pre-stimulus window* prior to mission start. Hypothesis 1 (H1) tests if a greater change in phase-locking value (PLV) across the team between *pre-stimulus* and *main* windows correlates with a higher mission rating score. Hypothesis 2 (H2) tests if a greater delta in spectral coherence (COH) connections across the team between pre-stimulus and *main* windows correlates with a higher mission rating score. Changes in functional connectivity metrics across the team between *pre-stimulus* and *main windows* correlate with a higher mission rating score (n=8, four total FiSTs, two simulation runs/team). For H1, the change in PLV across the team between *pre-stimulus* and *main* windows correlates with a higher mission rating, score, in the delta frequency band for EEG ($r = 0.70$, $p = 0.08$). For H2, the change in the number of significant COH connections across the team between

the pre-stimulus and the *Attention FiST* window correlates with a higher mission rating score in the delta frequency band for EEG ($r = 0.50$, $p = 0.25$), tEEG ($r = 0.45$, $p = 0.31$). Our results suggest that changes in functional connectivity metrics across the team during key behavioral windows are features of team synchrony that can drive a causal model for predicting team performance. By grounding our approach in TBCT this sets the stage for practical scalability and generalizability across other DoD teams and settings.

Disclosures: J. Sussman-Fort: None. **J.T. Folsom-Kovarik:** None. **J. Craighead:** None. **A. Woods:** None. **D. Wilson:** None. **S. Kline:** None. **T. Hilsabeck:** None. **N. Petroff:** None. **J. Cohn:** None. **D. Schmorrow:** None. **E. Salas:** None. **L. Berger:** None. **M. Khalid:** None. **R. Linhardt:** None. **C. Berka:** None. **E. Thunen:** None. **S. Dodel:** None.

Late-Breaking Poster

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Topic: I.10. Human Learning and Cognition

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National Research Foundation of Korea RS-2023-00266120

Title: Aberrant cerebellar interactions in the cortico-thalamo-cerebellar triple network model across high risk states for psychosis and first-episode psychosis

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Abstract: In recent years, the cerebellum has been highlighted as a key contributor to neural network dysfunction in psychosis. Cerebellar alterations in psychopathology have been observed alongside established disruptions in thalamic and cortical regions. In addition, these alterations may converge within the framework of the triple network model, which posits that dysregulation among the salience (SAL), default mode, and executive control intrinsic functional networks underlies psychopathology. Despite these patterns in the literature, cerebellar interactions across these networks remain understudied, particularly across stages of psychosis vulnerability, including those at clinical high risk for psychosis (CHR), those with a genetic predisposition, and the patients with first-episode psychosis (FEP). Therefore, we analyzed resting-state functional MRI data from four groups: 37 FEP, 63 CHR, 41 unaffected relatives (URs) of patients with schizophrenia, and 100 healthy controls (HCs). Functional connectivity (FC) was assessed between cerebellar and cortical networks as well as cerebellar and thalamic networks. Within the FEP group, we further explored correlations between FC patterns and error processing performance of the Spatial Working Memory Task. Relative to HCs, FEP participants exhibited increased connectivity between the cerebellum and cortical networks, along with decreased

cerebellar-thalamic connectivity. CHR individuals displayed more localized, yet abnormal, connectivity patterns across the same regions. In contrast, URs did not differ significantly from HCs. The reduced cerebellar-thalamic SAL connectivity in FEP was associated with higher error rates during performance tasks. Our results point to a trajectory of network disruption that progresses from regionally specific abnormalities to large-scale cortico-thalamo-cerebellar dysconnectivity across psychosis stages. The link between connectivity and error processing underscores the integrative role of cerebellum in predictive coding and salience attribution, which is the processes central to the underlying psychotic symptoms. By embedding cerebellar dynamics within the triple network framework, present study expands existing models of psychosis and offers insight into foundational network-level disturbances.

Disclosures: M. Ha: None. **E. Choe:** None. **M. Kim:** None.

Late-Breaking Poster

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Program #/Poster #: LBP034.07/LBP121

Topic: I.10. Human Learning and Cognition

Support: NSF CAREER Award BCS1943767

Title: Selective activation of orthogonal neural subspaces supports attentional modulation of learning in multidimensional environments

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Abstract: Real-world decisions involve choice options with many features, though only a subset of features—or their conjunctions—predict reward, making efficient value learning challenging. Humans tackle this by allocating attention to learning the values of informative stimulus dimensions and generalizing these values across similar options, a process captured by reinforcement learning models with separate ad-hoc value-learning and attentional-selection components. Yet it remains unclear how biologically plausible neural network models with mixed selectivity could implement such interactions between learning and attention. To address this, we trained multi-area excitatory-inhibitory recurrent neural networks to perform a multi-dimensional probabilistic reward learning task. Critically, the networks receive input about stimulus options in a dedicated input area, which is transformed to a decision in the output area using recurrent connections with plastic synapses undergoing reward-dependent Hebbian learning. After training on diverse reward schedules, we tested the networks on a task previously studied in humans where the reward probability of each option depended on a feature and the conjunction of two other features. The networks exhibited human-like attentional biases in credit assignment, where reward was primarily associated with both the informative feature and conjunction. To uncover the mechanisms underlying this behavioral bias, we aligned the

topographies across networks and discovered a shared latent circuit organization: distributed but orthogonal subspaces encoded information about features and their conjunctions. Within-area connectivity integrated input through recurrent excitation in these subspaces, while between-area connectivity relayed information through orthogonal communication subspaces. Reward-dependent plasticity modified these subspaces independently, allowing for the values associated with different dimensions to be encoded and recalled accurately. Critically, this circuit organization allows for selective activation of subspaces encoding the informative attributes, explaining the observed attentional biases in credit assignment. Overall, our results reveal novel circuit-level mechanisms supporting the interaction between selective attention and reward learning, offering testable predictions for future empirical research.

Disclosures: M.C. Wang: None. **A. Soltani:** None.

Late-Breaking Poster

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Title: A striosome-centered basal ganglia circuit model in which dopamine computes information gain, not reward prediction error

Authors: *D. BECK[1], A. FRIEDMAN[2];
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Abstract: Optimal decision-making and learning require dynamic, context-sensitive integration across the striosome-centered basal ganglia circuit. We show how cortex, striosomal spiny projection neurons (sSPNs), globus pallidus interna (GPi), lateral habenula (LHb), rostromedial tegmental nucleus (RMTg), dopaminergic neurons of the substantia nigra pars compacta (daSNC), and matrix SPNs (mSPNs) together form a multi-dimensional "decision-space." Cortical inputs are normalized via fast-spiking interneurons (FSIs) and projected into orthogonal "decision-dimensions" by striosomes; striosome outputs modulate parallel direct and indirect pathways to prioritize which dimensions constitute the decision-space; mSPNs then compute action and inaction values. The model captures cortex→SPN dimensionality reduction, decision-space formation, and temporal interactions. We validate predictions against the results of 20+ experimental studies and new data analysis showing that functional connectivity between sSPNs and mSPNs scales with the decision-space. The model forecasts individual differences in

disorder susceptibility, symptom comorbidity, and trial-to-trial circuit adaptation. Additionally, our model suggests that the dopamine in this circuit, released by daSNC back to the striatum, is not a scalar reward prediction error but is a signal measuring the information gained by policy updates. By combining information-theoretic surprise with reinforcement-learning principles, policy-information-gain naturally emerges from striosome→daSNC→matrix microcircuits. As we show by fitting to experimental data, it reproduces classical RPE signals in associative tasks while also accounting for dopamine's diverse roles in movement vigor, novelty responses, and decision speed across contexts. Policy-information-gain predicts how policy modulation drives learning, exploration, and motor control, offers a mechanistic basis for psychiatric comorbidities, and suggests that behaviorally inferred information-gain can proxy striosome and dopaminergic activity without invasive imaging. Together, our model delineates how the entire striosome-centered circuit constructs, navigates, and adapts high-dimensional decision and information spaces to enable flexible, context-specific behavior. Our work points to new experimental tests and AI algorithms inspired by basal ganglia policy control.

Disclosures: D. Beck: None. **A. Friedman:** None.

Late-Breaking Poster

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Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP034.09/LBP123

Topic: I.10. Human Learning and Cognition

Title: Pupillary fluctuations predict human neural replay events

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Abstract: Hippocampo-neocortical neural replay during wakeful rest supports rapid consolidation of complex motor skills in humans. These replay events are tightly linked to sharp wave ripples (SWR) in the hippocampus. Importantly, recent rodent studies have shown a strong correlation between SWR rates and changes in pupil diameter. This raises the hypothesis that pupil diameter could be a useful biomarker in the interaction of neural replay with motor learning and memory formation. In this study, we investigated the relationship between pupil diameter and neural replay in 24 human participants performing a procedural motor learning task in a magnetoencephalogram (MEG) environment. Participants repeatedly typed a keypress sequence (4 − 1 − 3 − 2 - 4: 1 = little finger, 2 = ring finger, 3 = middle finger, and 4 = index finger) separated by intervals of rest. We compared pupil diameter fluctuations during rest periods interspersed with practice with the timing of neural replay events characterized in MEG activity, testing the hypothesis that pupil diameter would be reduced at the time replay events occur. Next, we trained machine learning classifiers with statistical pupil diameter features to predict replay events. Across participants, pupil diameter was significantly smaller (1-tailed *t*-

test, $p < 0.05$) surrounding replay events than when no replay events were present. Pupil diameter features during replay and no-replay periods were accurately classified with 90.03% average classification accuracy (chance = 50%) across all subjects using a polynomial support vector machine classifier. These results demonstrate that pupil diameter may be a highly reliable indicator of the likelihood of the occurrence of replay events. Moreover, a subject-independent classifier (i.e., training a model with N-1 subjects' pupil diameter data and testing with a new subject's pupil diameter, repeated N times for each subject) achieved a 76.59% classification accuracy (F1=0.75, Sensitivity=0.71, Specificity=0.82, AUC=0.79), demonstrating that these pupil diameter patterns during replay events are consistent across individuals. These findings suggest that the neural states underlying the modulation of pupil diameter also influence wakeful neural replay in healthy humans. Furthermore, pupil diameter emerged as a robust, non-invasive behavioral marker for the emergence of neural replay events and their interaction with skill learning and memory formation.

Disclosures: D. Dash: None. **L.G. Cohen:** None. **E.R. Buch:** None.

Late-Breaking Poster

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Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP034.10/LBP124

Topic: I.10. Human Learning and Cognition

Title: Neural dynamics of flexible representation learning under uncertainty

Authors: *N. MENGHI[1], S. VIGANÒ[2], S. FUSI[3], C. F. DOELLER[4];
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Abstract: The start of the school day may be signaled by the ring of a bell, the same sound that later marks the end of classes. The sensory input is identical, yet the appropriate response depends entirely on context. Such flexibility in stimulus–response mapping is a hallmark of adaptive behavior. While the role of explicit context in guiding behavior is well established, less is known about how the brain represents and reinstates contextual and response information when context is hidden.
To address this, we designed a two-tasks associative learning paradigm with two contexts and four stimuli, and recorded EEG signal. Stimulus–response associations were context-dependent: two stimuli required the same response across contexts, while the other two required opposite responses.In the first task, participants viewed the context before the stimulus, allowing unambiguous mapping. In the second one, the stimulus appeared first, while for half of the stimuli they had to wait for the context to know the correct response, for the other half, participants had to withhold their response until the context was revealed.

Behaviorally, participants demonstrated clear learning curves in the first task. In both tasks, they responded more quickly and accurately to stimuli with context-invariant responses than to those requiring opposite responses.
Neurally, we used the EEG activity of the first task (acting as ground truth) to train a classifier to decode responses and contexts and test it on the second task. This revealed a robust response decoding for stimuli associated with the same response across contexts, suggesting that participants prepared responses even when context was unavailable but clearly predictable.
Analyses for the stimuli with context-dependent responses are currently ongoing, and they will test whether the brain 1) alternates possible representations until contextual information becomes available (neural flickering), or 2) maintain them in parallel, adapting the neural geometry of these representations to meet the higher demands of an unpredictable task.
Together, our findings will shed light on the neural dynamics of flexible learning and cognition in uncertain environments.

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Topic: I.10. Human Learning and Cognition

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JSPS KAKENHI 17H00891

Title: Persistent Hippocampal Representation and Neocortical Reorganization in Human Remote Memory

Authors: *K. NAKAHARA[1,2], R. WANG[3], M. TAKEDA[2], I. HASEGAWA[4], K. JIMURA[5]; [1]Kochi University of Technology, Kami, Kochi, Japan; [2]Research Center for Brain Communication, Kochi University of Technology, Kami, Japan; [3]Saga University, Saga, Japan; [4]Niigata Univ., Niigata, Japan; [5]Informatics, Gunma University, Maebashi, Japan

Abstract: The hippocampus (HPC) is critical for encoding declarative memories and orchestrating their gradual reorganization across the neocortex through systems consolidation. Standard consolidation theory (SCT) posits a temporary hippocampal role, after which memories are permanently stored in the neocortex. In contrast, multiple trace and trace transformation theories (MTT/TTT) argue for persistent hippocampal involvement. To adjudicate between these accounts, we developed a novel paradigm using Pokémon face-name associations, enabling precise control over memory age and stimulus familiarity. Thirty young adults with extensive childhood experience of the 2006 Pokémon games (remote memories) but little exposure to the 2019 version (recent memories) retrieved associations during fMRI scans. Memory representations were identified with cross-modal (face-name) multivariate pattern analysis

(MVPA), complemented by task-based connectivity (gPPI) and graph-theoretical hub analyses. Cross-modal MVPA revealed that recent memories were represented in the right posterior HPC, whereas remote memories engaged both right posterior and left anterior HPC. This dual localization suggests long-lasting hippocampal representational roles: the posterior HPC sustaining detailed traces and the anterior HPC supporting gist-based retrieval. Beyond the HPC, remote memories recruited a distributed network spanning frontal, parietal, and limbic cortices, while recent memories relied more on ventral visual and frontal regions. Critically, remote retrieval was associated with globally enhanced neocortical-limbic connectivity and the emergence of distributed hubs in the medial prefrontal cortex (mPFC) and bilateral inferior parietal lobule. In contrast, recent retrieval showed weaker, locally confined connectivity, with hubs restricted to the mPFC. These findings demonstrate that the HPC continues to represent remote memories even after more than a decade, while the broader memory network undergoes large-scale reorganization. We propose a two-phase consolidation model, where Phase 1 relies on perceptual reinstatement and mPFC schema integration during recent retrieval, and Phase 2 relies on semantic integration and distributed parietal hubs during remote retrieval. This framework reconciles SCT with MTT/TTT, showing how episodic memories are simultaneously preserved in hippocampal circuits and transformed within neocortical networks. Our results provide mechanistic insight into long-term memory consolidation and inform models of memory decline in aging and dementia.

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Late-Breaking Poster

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Title: Effects of visual consequent stimulus complexity on audiovisual associative learning in migraine

Authors: *N. HARCSA-PINTÉR[1], K. TÓT[1], A. PAPP[1], G. EÖRDEGH[2], A. CSÁTI[3], J. TAJTI[3], A. NAGY[1];
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Abstract: Acquired equivalence learning is based on linking distinct antecedent stimuli to common outcomes and involves the basal ganglia and hippocampus. Audiovisual associative learning benefits from multisensory integration, yet this mechanism may be impaired in migraine. Our recent study reported enhanced performance of migraine patients in such learning paradigm, where complex visual consequent stimuli were applied. The present work examined whether reduced complexity and semantic load of visual consequents affect audiovisual associative equivalence learning similarly in adults with migraine. Audiovisual learning was assessed in two tasks: the SoundFace test (applying complex cartoon-like faces as visual consequents) and the SoundPolygon test (featuring simple geometric figures). Both tests used the same set of four auditory antecedents. Participants progressed through three stages: acquisition (learning with feedback), retrieval (recalling the acquired associations), and generalization (transferring learned associations to novel pairings). Outcomes were evaluated by the number of acquisition trials needed, error rates across phases, and reaction times. Within-group differences in migraine patients (SoundFace vs SoundPolygon tests) were analyzed with Wilcoxon matched-pairs tests, while between-group effects (patient group vs matched healthy controls in the SoundPolygon test) were examined with the Mann-Whitney U test. Migraine patients, similarly to healthy controls, demonstrated significantly better performance in the SoundFace test, which applied more complex visual stimuli, compared to the SoundPolygon test, where reduced visual stimuli were used. Both groups required significantly fewer acquisition trials, made fewer errors during acquisition, retrieval, and generalization, and responded faster in every phase. However, in the SoundPolygon test, there were no significantly different performance between migraine patients and matched control participants. A comparable performance pattern across the two applied audiovisual tests was observed in both migraine patients and the healthy controls. Simplified visual consequents reduced performance in audiovisual learning and the connected memory processes. Furthermore, when reduced visual consequents were applied, there were no alteration in performance of migraine patients compared to that of the healthy controls in audiovisual learning. This suggests that reduced visual consequent stimuli could elicit weaker compensatory mechanisms compared to more complex and verbalizable visual stimuli in audiovisual associative learning.

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Topic: I.10. Human Learning and Cognition

Support: SZAOK-KKA-SZGYA Grant No. 2023/5S479
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151490/EXCELLENCE-24
TKP2021-EGA-28

Title: Preserved associative learning function in pediatric patients with obsessive-compulsive disorder cannot be attributed to cortical compensation

Authors: *K. TÓT[1], S. SINGH[1], N. HARCSA-PINTÉR[1], A. PAPP[1], G. EÖRDEGH[2], A. NAGY[1];
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Abstract: Several studies have addressed possible cognitive differences in children with obsessive-compulsive disorder (OCD). Pertich et al. (2020) reported no differences in cognitive performance during visually and audiovisually guided associative equivalence learning between children with OCD and healthy controls. This finding raises the question of whether cortical compensation or other mechanisms underlie the preserved performance. To address this, we investigated the EEG correlates of decision-making and reward-related processes in these two populations during associative equivalence learning. Seventeen pediatric OCD patients and matched healthy controls completed a visual and an audiovisual associative learning test while EEG was recorded with a BioSemi64 system. Data were preprocessed with notch (50/60 Hz) and 1-100 Hz band-pass filtering, average rereferencing, and ICA with ICLabel-assisted artifact rejection. Epoched data (−500 to + 500 ms around decision making) underwent multitaper power spectral density estimation in θ (4-7 Hz), α (8-12 Hz), β (13-30 Hz), and γ (31-80 Hz) bands, expressed in decibels relative to baseline. Group contrasts were assessed with cluster-based permutation testing (1000 iterations), in which patient and control labels were randomly shuffled to generate the null distribution. Observed statistics were compared across all EEG channels, frequency bands, task phases (acquisition, test), and pre- vs. post-press windows. Consistent with previous findings we found no differences in the psychophysical performances and the reaction times in both visual and audiovisual association learning between the OCD and the control groups. EEG analysis also revealed no significant differences across EEG channels, frequency bands, task phases, or time windows between the two groups. This suggests that cortical activity associated with decision execution and reward anticipation was similar between pediatric OCD patients and healthy controls. Our findings demonstrates no loss of function in sensory guided associative learning in pediatric OCD patients and no evidence of altered cortical activity. A possible explanation for this preserved function is that OCD primarily affects the ventral frontostriatal loop rather than the basal ganglia-connected dorsal one. However, we cannot exclude subcortical compensation mechanisms, which have to be addressed with furtherexperiments.

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Late-Breaking Poster

LBP034: I.10. Human Learning and Cognition

Location: SDCC Hall B

Time: Sunday, November 16, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP034.14/LBP128

Topic: I.10. Human Learning and Cognition

Title: Contribution of superficial layers of the primary motor cortex to rapid consolidation during early skill learning

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Abstract: Humans learn a motor skill better when they take short periodic breaks from practicing (spaced practice) compared to when they do not (mass practice). Consistently, it has been shown that early learning of a difficult skill develops predominantly over rest intervals (offline) interspersed with practice (offline). While the primary motor cortex (M1) and its broad connections are known to be pivotal to this phenomenon, it is still unclear how much of it is driven by inputs to M1 from cortical areas such as the premotor cortex and the SMA, or by outputs from M1 to the spinal cord, and how this varies during periods of rest and practice. Here we sought to address this gap in knowledge using vascular space occupancy functional MRI (VASO fMRI) to measure neural activations across cortical laminae in M1 - from superficial layers that receive cortical inputs to deep layers that send signals out to the spinal cord - as participants learned to tap a four-finger sequence (main task) repeatedly as fast as possible during twenty trials of alternating practice and rest periods. We also recorded VASO responses of the same participants during a separate run in which they tapped different four-finger sequences under the same schedule as the main task to serve as a control task (i.e., tapping button sequences without learning).
To examine the layer-specific contributions to learning over the course of the main task, we used a cross-validated ridge regression model to fit the speed gains of thirteen participants to cumulative average responses across cortical layers during online and offline periods, while controlling for the responses during the control task. Between subjects, the main task elicited behavioral gains of 0.31 ± 0.03 correct sequences/s, significantly higher than the control task that yielded 0.10 ± 0.04 sequences/s (Paired T-test, df=12, T=4.71, $P<0.001$). These behavioral gains inversely correlated with average activity in superficial layers that reflect cortico-cortical interactions targeting M1 but not with deeper layers that originate corticospinal output ($P<0.05$, FDR corrected). Thus, in spaced motor sequence learning, suppression of cortico-cortical inputs to M1 during rest intervals of early learning may contribute to rapid consolidation of skill.

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Program #/Poster #: LBP034.15/LBP129

Topic: I.10. Human Learning and Cognition

Support: National Science and Technology Innovation 2030 Major Project 2021ZD0204100

Title: Adaptive Coding of Sequence Structure in Human Prefrontal Neurons

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Abstract: Grouping sequential information (e.g., language and music) into hierarchical chunks is a key foundation of human cognitive flexibility. While previous studies have found neural dynamics supporting chunking at the local field potential level, its neural basis at the single-neuronal level remains unclear. By recording single-neuron activity in awake human patients, we identified prefrontal neurons selectively responding to sequence completion, chunk boundaries, and sub-chunk boundaries. Neural trajectory analyses revealed that distinct chunks were constrained to separate subspace planes, while sub-chunks occupied different vectors within these planes. Cross-task generalization further showed that, despite modality-specific cues (spatial, semantic, rhythmic), chunk-boundary responses were partially shared. These results provide the first single-neuron evidence in the human brain for hierarchical chunking, outlining an abstract and generalizable hierarchical information organization mechanism.

Disclosures: W. Fang: None. **X. Jiang:** None. **P. Gui:** None. **L. Wang:** None.

Late-Breaking Poster

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Program #/Poster #: LBP035.01/LBP130

Topic: I.11. Language

Support: The Leadership Alliance
Dana Next Gen
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Title: Sentence comprehension and neuromodulation: exploring tDCS effects across PPA subtypes

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Abstract: Primary Progressive Aphasia (PPA) is a neurodegenerative disorder characterized by progressive loss of language abilities. The non-fluent/agrammatic variant (naPPA) and logopenic variant (lvPPA) are associated with deficits in grammar and working memory, respectively. These overlapping features can complicate differential diagnosis, especially during sentence comprehension tasks that rely on both processes. Emerging evidence suggests that a form of noninvasive brain stimulation, called transcranial direct current stimulation (tDCS), can facilitate behaviorally-beneficial neuroplastic reorganization in individuals with PPA when applied to the frontal cortex. However, whether these improvements generalize across PPA subtypes, and in turn, patterns of neurodegeneration associated with different language-related cognitive processes remains to be established. Participants were individuals with a diagnosis of naPPA (n=19; 7 males, 12 females; mean age 69.7 years) and lvPPA (n=39; 23 males, 16 females; mean age 71.1 years) who enrolled in this double-blind, sham-controlled, within-subject crossover study. We administered the Linguistic Test for the Reception of Grammar (LTROG), which presents sentences of varying grammatical complexity (control, cleft, and center-embedded structures) in both written and oral modalities. Participants were required to select one of two images that corresponded to a given sentence. LTROG was assessed prior to receiving high-definition tDCS (HD-tDCS) to the left frontal cortex (baseline) and at 0, 6, and 12 weeks post-HD-tDCS. HD-tDCS was administered at 1.5 mA for 20 minutes across 10 semi-consecutive days paired with speech-language therapy. Repeated measures ANOVA revealed significant sentence type effects in both lvPPA ($p = 0.007$) and naPPA groups ($p < 0.001$) for written modality. For oral modality, lvPPA showed syntactic sensitivity ($p < 0.001$), while naPPA showed uniform performance ($p = 0.062$). Independent t-tests revealed significant differences between active and sham stimulation conditions at week 12 in lvPPA for written modality ($p = 0.030$), suggesting delayed stimulation benefits. These exploratory findings suggest syntactic complexity impacts PPA variants by modality, with lvPPA showing broader sensitivity. The delayed tDCS effects in lvPPA indicate potential therapeutic benefits of tDCS requiring larger-scale trials. Understanding these differential impacts can enhance diagnostic precision and inform targeted interventions.

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Late-Breaking Poster

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Program #/Poster #: LBP035.02/LBP131

Topic: I.11. Language

Support: NRF (No.RS-2024-00397674)

Title: Comparative EEG ERSP Analysis of Language Processing in Post-Stroke Aphasia and Healthy Controls

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Abstract: Stroke-induced aphasia patients who have lost language function in specific brain regions due to stroke, require targeted rehabilitation strategies. Functional magnetic resonance imaging (fMRI) has been widely utilized for this purpose, as it enables localization of language areas, taking into account the variability in lesion sites and severity across individuals. A previous study used fMRI to perform a language task on 170 healthy subjects and found that the brain was lateralized to the left hemisphere and localized to the left anterior quadrant. However, fMRI has limitations such as high cost, low accessibility, and the necessity for in-hospital use. As a complementary approach, electroencephalography (EEG), a non-invasive and increasingly utilized method, is being considered for language area targeting in aphasia rehabilitation. The goal is to develop personalized EEG-based rehabilitation strategies for aphasia patients referring to the results of healthy individuals and compensating for the limitations of fMRI-based targeting with a more accessible EEG-based approach.In the object naming task employed in our study, participants were first presented with a white fixation cross, followed by an image stimulus. Upon viewing the image, they were instructed to covertly generate a response. Subsequently, a yellow fixation cross appeared, during which participants were instructed to overtly verbalize the name they had previously retrieved. The inclusion of the yellow fixation phase served a critical purpose: it enabled the researchers to verify whether participants had indeed engaged in the cognitive process of lexical retrieval during the covert response phase, thereby ensuring task compliance and participation validity.In the control block, a resting state was incorporated between trials to allow for a washout period before the presentation of the next stimulus. In healthy controls, the active block elicited rapid left fronto-central beta ERS, subsequent centro-parietal alpha ERS/beta ERD, and later theta ERS. Aphasia patients showed attenuated or displaced beta ERS, prolonged posterior ERD, and compensatory right/midline theta ERS. Statistical analyses highlighted alpha-band differences in active blocks and frontal/central theta-alpha differences in control blocks.Pre-speech ERS/ERD dynamics differ markedly between groups, reflecting impaired left-hemisphere language-motor networks and compensatory right-

hemisphere engagement in aphasia. EEG-based time-frequency mapping thus offers translational value for developing individualized neurofeedback and neuromodulation strategies in language rehabilitation.

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Late-Breaking Poster

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Program #/Poster #: LBP035.03/LBP132

Topic: I.11. Language

Title: Closed-Loop Adaptive Striatal Stimulation for Language Learning Enhancement: Implications for Aphasia Treatment

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Abstract: Post-stroke aphasia disables over 2 million Americans and remains one of the costliest neurological sequelae. There are no approved pharmacologic or neuromodulatory treatments for restoring lost language capability. Converging evidence now implicates striato-cortical circuitry—specifically the caudate-anchored Caudate Language Network (CLN) and accumbens-anchored Nucleus Accumbens Salience Network (NASN)—as powerful but untapped drivers of associative learning that could be harnessed for language recovery. Prior work in rodents, non-human primates, and humans has demonstrated that brief 200 Hz stimulation of NASN during stimulus presentation, coupled with CLN stimulation immediately after correct responses, dramatically boosts learning rate. To test whether precisely-timed engagement of these striatal hubs can causally enhance language learning, and potentially functional recovery, we conducted a study in epilepsy patients undergoing seizure monitoring with depth electrodes implanted in or adjacent to the relevant structures. Subjects performed a foreign language learning task, associating Swahili words (novel to the subject) with corresponding images (up to 16 novel word-image pairs). Intracranial recordings from 4 subjects revealed robust theta-band (4-8Hz) modulation across distributed language networks during word learning, with frontal regions showing bilateral theta power increases time-locked to stimulus onset and temporal cortex exhibiting pronounced bilateral theta modulation consistent with ventral stream processing of novel word-meaning associations. Building on these network dynamics, we tested targeted striatal stimulation in two subjects where 50% of Swahili words received bilateral NAc and Cd stimulation at word presentation and after correct choices, respectively (200 Hz, 1 s, 2 mA charge-balanced pulses, 200 μsec/phase); unstimulated words served as controls. Combined NAc+Cd stimulation significantly enhanced learning rate, reducing median trials to criterion

from 19 to 7 trials (Wilcoxon rank-sum test; $P < 0.05$). Furthermore, the functional plateau for stimulated words was, on average, 44% higher for stimulated vs unstimulated words. These findings demonstrate that appropriately timed striatal stimulation significantly enhances language learning even in intact individuals, establishing the proof-of-concept that engaging striato-cortical circuits accelerates language acquisition and supports a network-targeted DBS intervention aimed at restoring language capability in stroke survivors—directly addressing a critical unmet need for mechanism-based aphasia therapies.

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Late-Breaking Poster

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Topic: I.11. Language

Support: Internal Research and Development funds, APL

Title: Strong decoding of spoken keywords from audio recordings of a dysarthric individual in a multimodal neural decoder

Authors: M. OGG[1], C. A. BISHOP[1], S. LUO[2], M. ANGRICK[3], I. WESTERN[1], M. WOLMETZ[1], F. TENORE[1], N. E. CRONE[4], ***M. S. FIFER**[5];
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Abstract: Amyotrophic lateral sclerosis (ALS) and other disorders impacting the strength and/or coordination of the articulators can make it difficult for affected individuals to produce intelligible speech. Technologies for decoding both the acoustic and neural signals generated during attempted speech are both progressing rapidly, driven by the use of artificial intelligence (AI) for modeling and decoding these signals. In this effort, we sought to evaluate the capability of state-of-the-art automatic speech recognition (ASR) models for decoding intended speech from dysarthric participants, either via acoustic information alone, using neural signals recorded from an electrocorticographic (ECoG) array or by combining these signals in a new, multimodal model. We leveraged several different embedding models to represent speech audio, including Hidden Unit Bidirectional Encoder Representations from Transformers (HuBERT), WavLM, and Bring Your Own Latent for Audio (BYOL-A). While these acoustic models struggled to provide separability in word representations across the multiple speakers present in the UASpeech dataset, they were sufficient to learn a keyword classifier with relatively limited training data when customized to a single participant, achieving near-ceiling performance with very limited training data on a 50-keyword classification task (i.e., 86% after 4 repetitions/word

in 1 session, peaking at 96% after 34 repetitions/word spanning 8 sessions) and was at-ceiling on a 6-keyword classification task after just one session of training data (99% after 40 repetitions/word). This acoustic model out-performed an ECoG-only time-delay neural network (TDNN) decoder. A fused neural and acoustic multimodal decoder was also explored wherein a simple fully connected layer was learned on a training set and evaluated on a test set. Unexpectedly, given the strong performance of the audio data decoding and the relatively lower signal-to-noise ratio in the neural data, the multimodal model did not contribute significantly to the decoding performance observed with the audio data alone. Additional investigation is needed to explore how complementary audio and neural embeddings are across a range of neural recording modalities (e.g., ECoG, microelectrode array, etc.) and speaker intelligibility (e.g., varying by disease progression, audio quality, etc.). Nevertheless, in this participant, these findings provide preliminary evidence that decoding of intended speech from audio signals may provide a strong basis for the use of assistive technologies, and should be considered when benchmarking and assessing speech brain-computer interfaces (BCIs).

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Late-Breaking Poster

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Program #/Poster #: LBP035.05/LBP134

Topic: I.11. Language

Title: Toward cognitive processing elucidation via transformers

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Abstract: The Transformer algorithm, basis of most Large Language Models (LLMs), has facilitated incredible levels of linguistic capability. Far beyond simple token prediction, Transformer-based LLMs demonstrate superior perplexity and, at times, even seem to converse intelligently. Some of the emergent properties arising from these LLMs present as human-like. In the relatively new field of LLM Psychometrics, human-based psychometric techniques are leveraged to qualify human-like linguistic traits emanating from LLMs. Trait examples include (but are not limited to) Openness, Conscientiousness, Extraversion, Agreeableness, and Neuroticism. Given the existence of comparatively performant Transformer implementations on virtual biological substrates (i.e. Artificial vs. Spiking Neural Networks), the implication is that we can utilize Transformer-based LLMs for human linguistic-process modeling. This is somewhat analogous to how we currently use experimental models to emulate conserved features. As such, we posit here that Transformers can legitimately be used for human linguistic modeling toward deepening our understanding of cognitive processing.

Disclosures: D.J. Hamilton: None.

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The Hock E. Tan and K. Lisa Yang Center for Autism Research
The Simons Center for the Social Brain at MIT

Title: Sensory sensitivity as a novel moderator of brain processing of prosodic cues in autism

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Abstract: Autism often involves differences in motor, sensory, and communication experiences. Compared to their nonautistic (NA) peers, some autistic (AUT) individuals display challenges with prosody perception: the ability to detect and interpret patterns of stress and intonation in speech.
While some prior work has noted altered AUT brain responses during prosody processing, research is limited, with little inquiry into predictors of activation in AUT adults. Focus has also centered on emotional rather than linguistic prosody (i.e. speakers' emotions vs. statement meaning). Moreover, despite both speech-motor and sensorimotor networks being implicated in NA prosody experiences, sensorimotor regions of interest (ROI) remain underexplored in AUT prosody research.
The present study addresses this gap by examining predictors of AUT and NA brain activation in speech-motor and sensorimotor regions during linguistic prosody perception. 43 adults (21 AUT, 22 NA, aged 18 - 43) completed a passive fMRI task involving listening to sentences with dynamic (DP) or flat (FP) prosodic contours. Assessments of nonverbal intelligence, reading fluency, self-report prosody experiences, and the Comprehensive Autistic Trait Inventory (CATI) were also administered.
fMRI contrast activation (DP - FP) was extracted from individually-localized and group-constrained speech-motor ROIs. Prior research with this task (O'Brien, et al., in prep) found lower contrast activation in the AUT vs NA group in right Prefrontal Cortex, right Planum Temporale, right Anterior Insula (rAI), and bilateral Supplementary Motor Area (SMA).
Present elastic net regression identified contrast activation predictors as AUT diagnosis, age, nonverbal intelligence and reading fluency, as well as the Cognitive Rigidity and Sensory Sensitivity (SS) subscales of the CATI. In a subsequent linear mixed effects model adjusted for

covariates, the interaction of AUT diagnosis and SS was the only predictor of contrast activation (EMM_{Δ} = .625, t(33) = 2.16, p = .038), with greater SS challenges linked to increased activation in AUT but lower activation in NA adults. Post-hoc analyses per ROI adjusted for multiple comparisons suggested trending AUT × SS interactions in the SMA (EMM_{Δ} = .817, t(34) = 2.39, p = .023, q = .068) and rAI (EMM_{Δ} = .701, t(35) = 2.21, p = .039, q = .068).
These results suggest that sensory sensitivity may moderate AUT brain processing of prosody, particularly in regions related to sensorimotor integration, planning, and control. This highlights sensory processing difficulties and sensorimotor regions as underexplored yet potentially significant areas within autistic speech perception.

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Topic: I.11. Language

Support: Kakenhi 24K03875

Title: EEG source connectivity reveals reward system involvement in pragmatic inference for indirect expressions

Authors: *S. TOKIMOTO[1], N. TOKIMOTO[2];
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Abstract: In everyday conversation, speakers often convey intentions implicitly by indirect expressions (e.g., an interrogative for a request: “Can you reach the salt?”). A central unresolved question is why such expressions—less efficient for information transfer—are preferred in human communication. One prominent hypothesis posits that indirect expressions confer greater utility to speakers than direct ones (Pinker & Lee, 2008, PNAS). To examine whether the use of indirect expressions is motivated by utility, we recorded EEG during the comprehension of indirect expressions to analyze the relationship between pragmatic inference and the reward system. Experimental dialogues in Japanese were constructed with 3 speakers: the 1st introduced a topic, the 2nd asked a question, and the 3rd replied indirectly. Two factors were manipulated: (1) the degree of implicitness (less vs. more implicit) and (2) the temporal reference of the reply’s implicit meaning (past experience vs. present intention for future acts). We predicted that indirect expressions conveying present intentions would yield greater interlocutor utility—and thus stronger engagement of the reward system—than those referring to past experiences. EEG was recorded from 24 right-handed native Japanese speakers (10 males; age 18-28) using 64 scalp electrodes. Thirty-two regions of interest (ROIs) were defined, informed by prior fMRI studies on indirect expression processing (25 ROIs) and the social reward system (7 ROIs).

Following EEG source localization, effective connectivity among ROIs was estimated using partial directed coherence (PDC) across theta, alpha, beta, and gamma bands in 200-ms windows following the onset of a critical word signaling implicit meaning (Yes/No). Connectivity differences between more vs. less implicit conditions were calculated separately for past-experience and present-intention dialogues. Results revealed that in the 100-300 ms latency window for present-intention dialogues, there was a significant increase in information flow toward the right ventral striatum (VS) (25 ROI pairs across all four frequency bands) and the right anterior insula (3 ROI pairs in alpha, beta, and gamma bands). In contrast, for past-experience dialogues, increases were limited to the left ventral tegmental area (4 ROI pairs in beta and gamma) and the right VS (1 ROI pair in gamma). These findings suggest that, at an early stage of discourse comprehension, the reward system is preferentially engaged in interpreting indirect expressions that convey intentions for future behaviors. This supports the hypothesis that the use of indirect expressions is motivated by interlocutor utility.

Disclosures: S. Tokimoto: None. **N. Tokimoto:** None.

Late-Breaking Poster

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Title: Left-hemispheric push-pull interactions assemble sentences from letters via sublexical and lexical combinatorial processing

Authors: *I. HASEGAWA[1], R. KASEDO[1,2,3], K. NAKAHARA[4], F. HOMAE[5], R.-I. HASHIMOTO[5], Y. ADACHI[6,7], M. FUKUDA[8], H. SHIROZU[9], K. JIMURA[10], A. IIJIMA[11,2]; [1]Niigata Univ School of Medicine, Niigata, Japan; [2]Niigata University Graduate School of Science and Technology, Niigata, Japan; [3]Tokyo Women's Medical University, Tokyo, Japan; [4]Kochi University of Technology, Kami, Japan; [5]Tokyo Metropolitan University, Tokyo, Japan; [6]Niigata Univ. Sch. of Med., Niigata, Japan; [7]Juntendo Univ, Tokyo, Japan; [8]Nishiniigata Chuo Hospital, Niigata, Japan; [9]Fukuoka Sanno Hospital, Fukuoka, Japan; [10]Gunma University, Maebashi, Japan; [11]Niigata University School of Medicine, Niigata, Japan

Abstract: Human language shows dual combinatorial structure (Martinet, 1960), in which morphemes or words—the building blocks of a sentence—are themselves composed of meaningless elements: phonemes in speech and graphemes in text. Psycholinguists have posited that “grapheme parsing” proceeds serially one letter at a time (e.g., Joubert & Lecours, 2000), yet the neural mechanisms linking this sublexical operation to lexical-level phrase structure building

remain poorly understood, partly due to the temporal limitations of standard neuroimaging procedures. We addressed this issue by introducing a self-paced Japanese kana grapheme reading paradigm, which slowed down grapheme-by-grapheme parsing processes sufficiently to be detected by functional magnetic resonance imaging (fMRI) while preserving the participants' spontaneous reading rhythm (Kasedo et al., 2024). To capture the neural dynamics during letter-wise grapheme parsing, we adopted a bottom-up left-to-right parser model, consistent with the "Now-or-Never bottleneck" hypothesis that linguistic input must be immediately chunked to avoid loss (Christiansen & Chater, 2016). By conducting parametric fMRI analyses dissociating buffering and integration loads, we revealed rapid push-pull interactions among the left-hemispheric language-related areas. Activity in the anterior superior temporal sulcus (STS) encoded hierarchy-invariant buffer loads across sublexical and lexical levels, whereas the posterior STS displayed both transient activity encoding the number of graphemes combined and sustained activity reflecting lexical buffer load, suggesting a relay function between levels. Notably, Broca's subregions exhibited level-specific deactivations: Brodmann area 44 (BA44) at sublexical closures and BA45 at lexical closures. Psychophysiological interaction analyses indicated that these deactivations were negatively coupled with activity in the bilateral supramarginal/angular gyri and precuneus, as well as the left middle frontal gyrus, while positively correlated with STS hubs. These findings reveal dynamic interactions between the frontal-temporal perisylvian core language network and its surrounding margins. Our findings indicate that sentence-level structure emerges from letter-wise operations through state-dependent inhibitory-excitatory coordination across the core and marginal language networks. This framework refines dual-route neurocognitive models (Coltheart et al., 2001) by emphasizing state-dependent coupling, providing a circuit-level account of serial length effects and their disruption in reading disorders.

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Topic: I.11. Language

Support: TKP2021-EGA-28, KKP133871/KKP20 and 151490/EXCELLENCE_24 grants of the National Research, Development and Innovation Office, Hungary

Title: The temporal dynamics of visual letter recognition and its invariances

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Abstract: Letters with clear visual differences can convey the same abstract meaning (e.g., a = *a* = A), suggesting that letter recognition is invariant to certain features. This process is typically linked to the ventral visual pathway, particularly the visual word form area, yet its precise time course is largely unknown. We attempted to uncover the timeline of invariant letter recognition, using Representational Similarity Analysis (RSA) on 64-channel EEG data. Twenty-six healthy participants were presented with single letter stimuli (a, e, f, g), each shown in ten different forms (5 fonts in two cases), for a total of 1600 times (40 per stimulus). Stimulus dissimilarity matrices were calculated from the epoched EEG data at every timepoint with each matrix entry derived from the cross-validation accuracy of an SVM classifier algorithm trained on data from a pair of stimuli. Patterns in the neurally derived matrices were evaluated by Spearman correlation with binary predictor matrices. Significant time periods were identified by two-tailed TFCE with 10000 iterations. To control for visual similarity among the stimuli, partial correlations with a Wasserstein distance matrix were also calculated. To examine the cortical distribution of the neural patterns, the RSA pipeline was run on all 64 electrodes, and on 6 different scalp regions separately. The "letter identity" predictor was significant from 100 ms and lasted throughout the stimulus presentation (500 ms); this effect was primarily localized to posterior scalp regions, with additional clusters in the central and anterior regions. The "across-case letter identity" predictor's correlation was significant almost exclusively in the left posterior region, whereas the "within-case" predictor showed a more symmetrical pattern; both time periods closely matched that of the overall "letter identity" predictor. Partial correlations of the identity predictors with the Wasserstein-distance matrix also showed a leftward tendency, supporting the unilaterality of invariant letter detectors. Predictors of visual features were informative mostly in the posterior regions, although in much shorter time windows. The "case" predictor's effect started at 90 ms, peaked around 150 ms and phased out quickly. The "font" predictor started later and peaked at 190 ms. Our results show that abstract letter information could emerge as early as 100 ms in the left posterior cortical regions, substantially earlier than the often-cited N170 ERP component. The separate peaks of "case" and "font" predictors further suggest distinct stages of task-irrelevant visual processing.

Disclosures: A. Benyhe: None. **S. Sáringer:** None. **A. Berenyi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); owner of Amplipex Kft., Szeged, Hungary a manufacturer of signal-multiplexed neuronal amplifiers, CEO of Neunos ZRt, Szeged, Hungary, a company developing neurostimulator devices, has equity in Blackrock Neurotech, listed as an inventor on patents and patent applications related to ISP stimulation and various aspects of closed-loop neurostimulation. **P. Kaposvári:** None.

Late-Breaking Poster

LBP036: F.01. Eye Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP036.01/Web Only

Topic: F.01. Eye Movements

Support: JSPS KAKENHI Grant 23K24749

Title: Differences in cortical activity to smooth pursuit eye movements in response to first-order and second-order visual stimuli

Authors: *S. ONO[1], Y. YOSHIMURA[1], K. MIURA[2], S. GLASAUER[3];
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Abstract: Smooth pursuit eye movements are driven by the visual motion of the attended target on the retina, and especially, pursuit initiation is closely related to retinal slip motion. Retinal slip motion signals are transformed into pursuit commands, and thereby smooth pursuit is initiated. Several studies have revealed that smooth pursuit is generated by visual motion-related signals from cortical areas, including the middle temporal (MT) and medial superior temporal (MST) areas. In fact, it has been demonstrated that the variability of pursuit initiation is mostly due to retinal slip in estimating target motion. The purpose of this study is to demonstrate whether cortical control of smooth pursuit differs between first-order and second-order visual stimuli. Smooth pursuit is known to be induced by visual stimuli even without primary luminance cues. First-order motion is defined by low-level visual motion, such as luminance, whereas second-order motion (theta motion) is defined by the higher-level visual motion, such as contrast and flicker of motion. A difference in visual motion stimuli affects the behavioral properties of eye movements, such as pursuit latency, initial eye acceleration, and steady-state velocity. Furthermore, neurons in areas MT and MST that code for the direction of target motion have been shown to have weaker responses when the visual motion stimulus is formed by theta motion compared to first-order motion. Our results showed significantly higher pursuit gain and velocity in response to the first-order than theta motion stimuli. This could be due to the fact that retinal slip in the ongoing direction is significantly reduced in the theta motion compared to first-order motion. Notably, theta motion maintains about half of the gain even though there is no retinal slip input in the ongoing direction of target motion. Furthermore, we attempted to determine the effect of EEG-based frequency analysis on the pursuit gain. The results showed that at the parietal electrodes (Cz), the lower frequency, delta waves, increased during the first-order motion, while the higher frequency, gamma waves, increased during the theta motion. As the EEG electrodes at Cz are known to be located close to the intra-parietal sulcus (IPS) in humans, these results suggest that different brain activity is associated with the two conditions.

Disclosures: S. Ono: None. **Y. Yoshimura:** None. **K. Miura:** None. **S. Glasauer:** None.

Late-Breaking Poster

LBP036: F.01. Eye Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP036.02/LBP001

Topic: F.01. Eye Movements

Support: McGovern Institute for Brain Research
Howard Hughes Medical Institute
The Simons Foundation

Title: Perturbing the brain to investigate the neural mechanisms of internal error detection

Authors: *Y. FENG[1], H. SUNG[2,1], M. JAZAYERI[2,1,3];
[1]McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA; [2]Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA; [3]Howard Hughes Medical Institute, Chevy Chase, MD

Abstract: Most of the time, our experience feels seamless—yet remarkably, we notice instantly when things go awry: when vision blurs, when the heart races without cause, when a familiar name slips from memory. Such phenomena suggest that the brain harbors dedicated neural modes—"error subspaces"—that are selectively engaged when internal discrepancies arise. To test this hypothesis, we trained monkeys on a memory-saccade task. On randomly chosen trials, right before saccade initiation, we delivered brief (200 ms, ~50-80 μA, biphasic) electrical microstimulation in the Frontal Eye Field (FEF), inducing involuntary saccades. This perturbation created a misalignment between intended and executed saccades, allowing us to probe whether FEF activity signals such conflicts through a dedicated error subspace. Using Neuropixels recordings, we identified a low-dimensional subspace specifically recruited when the stimulation-evoked and memory-guided saccades diverged. This subspace (1) was nearly orthogonal to baseline or general microstimulation-related activity (cosine similarity < 0.1), (2) predicted the occurrence of erroneous saccades on a trial-by-trial basis, and (3) emerged within milliseconds of stimulation onset, preceding any visual feedback. Consistent with this rapid neural signature, animals produced corrective saccades within 100 ms of error onset. These results provide direct evidence for an intrinsic error subspace within a local cortical circuit. We propose that such local error detection constitutes a canonical cortical computation, supporting flexible error correction and the brain's robust capacity for self-organization. We discuss this finding and its implications in the context of existing theories, including predictive processing and Bayesian models, and argue for an alternative, which we term the "Disagreement Theory."

Disclosures: Y. Feng: None. **H. Sung:** None. **M. Jazayeri:** None.

Late-Breaking Poster

LBP036: F.01. Eye Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP036.03/LBP002

Topic: F.01. Eye Movements

Support: NS120562

Title: Functional organization for pursuit eye movements in marmoset frontal cortex

Authors: *J. J. PATTADKAL, B. ZEMELMAN, N. J. PRIEBE;
The University of Texas at Austin, Austin, TX

Abstract: Smooth pursuit eye movements are voluntary tracking eye movements in animals to help stabilize the image of selected objects on the retina. The pursuit system in primates provides a fitting setup to investigate the neural processes spanning the arc of sensation to action. Motion information from motion-sensitive visual areas such as area MT provides a sensory signal that is then converted into a motor eye-movement signal in the frontal pursuit area (FPA) of the frontal cortex, among other areas. Critically, this simple behavior shows rich adaptive dynamics, changing with learning and dependent on internal and external context. Easy access to underlying circuitry in marmosets using optical, electrophysiological and genetic tools allows us to study the mechanistic basis of such flexible sensori-motor computations in primates. We have previously demonstrated pursuit behavior in marmosets (Mitchell et al., 2015, Pattadkal et al., 2024a) and reported cell-resolved population motion representation in marmoset area MT using calcium imaging (Pattadkal et al., 2024b). We now take advantage of the smooth marmoset cortex to report for the first time an organization for pursuit responses in the FPA using calcium imaging with GCaMP. We identified multiple regions of frontal cortex that responded to eye movements, but the region we specify as the FPA displayed increased activity throughout the duration of pursuit eye movements and those responses are higher in magnitude and sustained for pursuit relative to the responses to saccades. Furthermore, FPA neurons exhibit selectivity for the direction of pursuit. Nearby neurons shared their preference for smooth pursuit direction and preference for pursuit direction is organized as a single pinwheel. Additionally, tuning width also shows an organization with neurons at the center of the pinwheel showing weaker direction selectivity. Sensitivity for speed of target motion is expressed in the response amplitude of neurons, as opposed to different neurons being selective for different speeds as in area MT. This cellular resolution map of pursuit direction suggests that functional organization in the primate neocortex is not merely a feature of sensory areas but instead a common motif across cortical areas. Combining such imaging studies with other tools and behavioral paradigms will allow us to study the mechanistic basis of adaptive sensori-motor primate behavior.

Disclosures: J.J. Pattadkal: None. **B. Zemelman:** None. **N.J. Priebe:** None.

Late-Breaking Poster

LBP036: F.01. Eye Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP036.04/LBP003

Topic: F.01. Eye Movements

Support: NIH Grant EY032066
NIH Grant P30 EY003039

Title: Express disjunctive saccades elicited during gap paradigm in monkeys

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Abstract: Under natural circumstances, orienting our gaze in a three-dimensional world to targets that lie at both different distances and eccentricities involves the combination of vergence eye movements and disjunctive saccades, also called saccade-vergence eye movements. These eye movements cause both a change in the vergence angle between the eyes and in the conjugate gaze angle. It has been shown that the latency of conjugate saccades directed toward targets located in the same plane is affected by the timing between the extinction of the fixation target and the appearance of the peripheral target. When there is a gap period between both targets, in some proportion, the initiation of conjugate saccades is faster, and these saccades are called "express saccades". Here, we investigate saccade-vergence eye movements during a gap paradigm to determine whether express disjunctive saccades and express vergence eye movements would be elicited. In two male nemestrina monkeys, we recorded binocular eye movements using the scleral eye coil technique. During each experiment, saccades, either alone or combined with a vergence eye movement, were generated randomly. The monkeys' task was to orient their gaze towards targets in the three-dimensional space. Targets termed FAR were projected onto a tangent screen, while targets termed NEAR were generated by an LED on a rod which could be programmatically moved both in depth and eccentricity from the animal. Conjugate saccades and combined eye movements were tested with or without a gap interval. During the No-Gap trials, the peripheral target appeared while the fixation target turned off, whereas it appeared after a delay of 200 ms during the Gap trials. Both Gap and No-Gap trials were intermixed randomly. Targets were located on the horizontal meridian at different eccentricities to the left or to the right and different distances (near or far position relative to the animal). Convergent saccade-vergence movements were tested during the experiment. We also investigated the evolution of the proportion of express eye movements elicited during this task over ten consecutive days. Our results show that in both animals, during Gap trials the latency of conjugate saccades was shorter than during No-Gap trials, as reported before. When convergent saccade-vergence movements were tested, we observed that during Gap trials, disjunctive saccades have a shorter latency than during No-Gap trials. The same result was also observed for the vergence component of the saccade-vergence movements. The results indicate that express convergent disjunctive saccades and express vergence eye movements can be elicited in monkeys.

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Late-Breaking Poster

LBP036: F.01. Eye Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP036.05/LBP004

Topic: F.01. Eye Movements

Title: Gaze intersection point-locking and fixation-locking support P300 detection in virtual reality under free head and eye movement

Authors: ***N. GREEN**[1], E. CARRILLOSULUB[2], C. STEVENSON[2], C.-Y. CHANG[2], S. M. THURMAN[3], R. COHEN HOFFING[3], Y. WU[2];
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Abstract: Understanding how gaze and head movements interact with event-related potentials (ERPs) is critical for advancing brain-computer interfaces and neuroscience paradigms. We analyzed event-locking strategies for isolating P300 responses during a 3D visual oddball task in virtual reality (VR). Eighteen healthy adults (EEG: 64-channel BioSemi) viewed standard (80%) and deviant (20%) targets presented at either 5° (eye-shifting) or 30° (head-turning) eccentricities and responded via trigger pull. EEG was recorded concurrently with eye- and head-tracking using the HTC Vive Pro Eye system. Three event-locking strategies were compared: stimulus-locking, aligned to stimulus onset; fixation-locking, aligned to the onset of fixations detected by a Tobii I-VT velocity threshold; and gaze intersection point (GIP)-locking, aligned to the 3D point where the gaze vector intersected the target. Data were preprocessed by removing artifactual channels and epoched, followed by plotting event onset distributions, computing ERPs, and applying false discovery rate (FDR)-corrected t-tests. Central channels Cz, Pz, and Oz were analyzed. Stimulus-locked ERPs primarily reflected motor/response-related activity. Both fixation- and GIP-locking produced robust P300 effects: 200-400 ms at Pz during eye-shifting and 200-600 ms in head-turning, with deviants eliciting more positive potentials than standards. Notably, fixation-locking yielded an earlier P300 than GIP-locking. This phenomenon is likely due to fixation onset marking the earliest stabilization of gaze during visual processing, while GIP-locking depends on geometric gaze-target intersection, which may precede the stabilization of gaze. These findings demonstrate that GIP-locking can be advantageous for capturing cognitive processing during saccadic eye shifts, while fixation-locking may be preferable during head-turning movements. Choosing event-locking strategies appropriately is essential for reliable P300 measurements in immersive VR, informing the design of future real-world BCI applications.

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Late-Breaking Poster

LBP037: F.02. Cerebellum

Location: SDCC Hall B

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

Program #/Poster #: LBP037.01/LBP005

Topic: F.02. Cerebellum

Support: R35 NS116854

Title: Spatiotemporal patterns of spiking by cerebellar Golgi cell populations recorded with voltage imaging during sensory-evoked whisking in awake mice.

Authors: *S. T. BROWN, I. M. RAMAN;
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Abstract: The granule cell layer of the cerebellar cortex participates in pattern separation. Within this input layer, inhibitory Golgi cells receive excitatory input from mossy and parallel fibers and send feedback and feedforward inhibition to granule cell dendrites. *In vitro*, Golgi cells can set the threshold/gain of granule cell firing, suitable for aiding in expansion and sparse coding. Assessing Golgi cell function *in vivo* has been complicated by challenges in identifying them electrophysiologically and by their physical dispersion. Here, to record the activity of populations of Golgi cells with high spatial and temporal resolution *in vivo*, we expressed the voltage indicator pAce in Golgi cells located in crus I and performed 3 kHz voltage imaging of their action potentials in awake mice during air puff stimulation of the whisker pad and the consequent reflexive whisker protraction. A total of 521 Golgi cells were imaged across 6 fields of view, with up to 153 Golgi cells imaged at once, during ~100 trials of single air puffs. In the pre-stimulus period, Golgi cells fired spontaneously at 14 spikes/sec. Upon stimulation, the majority of Golgi cells showed two cycles of increased firing probability, an early, rapidly rising (<4 ms) increase that peaked 8 ms post-puff, and a later, slowly rising (tens of ms) increase that peaked at 50 ms post-puff, during the whisk. The latency and relative temporal precision of the two phases resembled those previously associated with the sensory puff and motor whisk in molecular layer interneurons (MLIs) and Purkinje cells. The early Golgi cell response outlasted that of MLIs, however, consistent with feedforward inhibition onto granule cells suited to constrain sensory-evoked spiking of MLIs to a few ms. During the early response, 20-100% of Golgi cells fired within a 4-ms window on each trial, with a mean of 70%, indicative of a high degree of sensory-evoked synchrony. Trial-by-trial synchrony varied directly with whisk amplitude, indicating a relation between the degree of Golgi-mediated inhibition and movement magnitude. Golgi cell spiking also synchronized intermittently in the absence of puffs, though to a lesser degree. During periods of submaximal synchrony, a spatial organization of coactivity was evident. This synchrony was greater during whisking than rest, suggestive of subnetworks of Golgi cells driven by shared mossy or parallel fiber input. Together, the data offer the first view of widespread, well-timed sensory-evoked Golgi cell activity correlated with whisking, and provide insight into how the spatially patterned, synchronous activity of these cells may shape signals passing through the cerebellar input layer.

Disclosures: S.T. Brown: None. **I.M. Raman:** None.

Late-Breaking Poster

LBP037: F.02. Cerebellum

Location: SDCC Hall B

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

Program #/Poster #: LBP037.02/LBP006

Topic: F.02. Cerebellum

Title: Climbing fiber-driven changes in Purkinje cell activity after vestibulo-ocular reflex adaptation

Authors: *A. BLACK[1], K. SHEPHERD[1], T. CHRISTENSEN[1], T. STAY[2];
[1]Neurosci., [2]Psychology; Neurosci., Brigham Young Univ., Provo, UT

Abstract: The cerebellum plays an important role in fine-tuning motor output in the vestibulo-ocular reflex through error correction learning mechanisms. Climbing fibers (CF) convey these error signals to the Purkinje cells (PC) of the cerebellum. While CF activity is known to encode motor errors during behavioral adaptation, it remains unclear whether post-training CF activity contributes to consolidation of motor memory. Here, we investigated sustained changes in CF signaling following short-term VOR adaptation and identified the clear CF-driven complex spiking (CS) signature of Purkinje cells in a subset of neurons. We used these CS's to identify prolonged changes from baseline in the consolidation period. We recorded *in vivo* floccular activity in awake mice both before and after gain-up VOR training and analyzed the firing statistics to identify PCs. Preliminary analysis of three PCs revealed a decrease in CS firing rate after training, with the average firing rate decreasing from 0.755 Hz (before training) to 0.647 Hz (after training) yielding a 14.2% decrease. Additionally, 20 cerebellar neurons, including putative Purkinje cells, molecular layer interneurons, Golgi cells, and other cerebellar neurons were recorded to obtain baseline firing rates. Across the population, these rates averaged 42.1 Hz (SD = 34.1 Hz). To account for skewed firing distributions, these rates were transformed with a log(1+x) transformation, yielding an average of 3.47 (SD = 0.8). Cluster analysis revealed clear groups consistent with reported differences in cell-type firing properties. We are applying published classification algorithms to further delineate the cell types in our recordings. Sustained CS activity after training termination would support a model where post-training cerebellar dynamics contribute to long-term modifications in sensorimotor circuits. We are currently comparing the changes in complex spiking that occur over adaptation in a larger neural sample. Establishing the baseline activity of our population provides a critical reference point for interpreting post-training changes in PC and CF activity. Ultimately, our results will help clarify the neural mechanisms that contribute to motor skill memory consolidation.

Disclosures: A. Black: None. **K. Shepherd:** None. **T. Christensen:** None. **T. Stay:** None.

Late-Breaking Poster

LBP037: F.02. Cerebellum

Location: SDCC Hall B

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

Program #/Poster #: LBP037.03/LBP007

Topic: F.02. Cerebellum

Title: Optogenetic testing of Purkinje cell sufficiency parameters in vestibulo-ocular reflex adaptation

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Abstract: Vestibulo-ocular reflex (VOR) adaptation has been linked to changes in neural firing of cerebellar Purkinje cells (Lisberger and Pavelko, 1988). However, the specific changes in neural firing required for long-term adaptation are not fully understood, as previous studies have used limited stimulation protocols (Voges et al., 2017). One study, using 250-ms optogenetic stimulation of Purkinje cells, demonstrated that pairing stimulation with ipsiversive or contraversive head movements was sufficient to drive VOR adaptation (Bonnan et al., 2021). Yet, results differed significantly based on the intensity of the light stimulation, such that timing relative to a specific phase of head movement was entangled with calcium influx. We sought to determine whether stimulation across a broader range of phases relative to head movement could clarify the time window for VOR adaptation plasticity. Conditional genetic cross mice expressing channelrhodopsin (ChR2) specifically in Purkinje cells were tested through a battery of optogenetic stimulation assays. We compared the effect of continuous optogenetic stimulation of the flocculus to stimulation of crus I, normalizing responses to eye movements during head rotation without stimulation. Utilizing eye-tracking technology, we found that the degree of eye rotation during continuous stimulation of the flocculus was 3.74 times higher than the eye movements in the condition without stimulation. The control stimulation of crus I had normalized eye responses of 0.94 relative to the eye responses in head rotation alone, confirming that stimulation of crus I had no significant effect on eye movement. We suggest that the large changes in eye response upon stimulation of the flocculus could be due to high synchrony and disinhibition across the population of Purkinje cells, similar to the high light-intensity conditions in Bonnan et al., 2021. We are conducting ongoing experiments to determine whether lower intensities and discrete stimulation epochs are sufficient to drive similar increases in VOR gain.

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Late-Breaking Poster

LBP037: F.02. Cerebellum

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Program #/Poster #: LBP037.04/LBP008

Topic: F.02. Cerebellum

Support: NIH Grant NS128416
NIH Grant EB028156

Title: Decoding Sensorimotor Information in the Mossy Fiber Inputs to the Cerebellum

Authors: *M. HEYDARI[1], M. FAKHARIAN[1], A. SHOUP[1], A. VASSERMAN[1], N. MOHAMMADREZAEI[2], R. SHADMEHR[1];

[1]Biomedical Engineering, Johns Hopkins University, Baltimore, MD; [2]Biomedical Engineering, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract: Numerous regions in the cerebral cortex, brainstem, and the spinal cord send inputs to the cerebellum through mossy fibers, which in turn allows the cerebellum to make predictions and guide behavior. Recording from these axons during tasks is possible, but determining the type of information they encode is challenging, especially when many cerebellum-related processes occur simultaneously. How can each unit be categorized when behavioral variables covary?

Here we present a general framework to map the spiking activity of each neuron to behavioral data at each time point, without aligning to specific behavioral events. Inspired by GLM fitting, where binary spiking is the output of a linear system with behavioral inputs, we add a nonlinear spatial mapping before temporal convolution. Nonlinear spatial maps are included because neurons in many brain regions have spatial fields that encode, for example, directions or amplitudes of movements. In our approach, each group of behavioral data, like eye position or tongue velocity, is treated as a channel. This channel passes through a learnable nonlinear spatial function to model variability in direction. The outputs are then convolved with temporal kernels to capture variability in time and any possible delays. The framework is trained via gradient descent.

We applied this model to 1128 mossy fibers recorded across 50 sessions in two marmosets as they moved their eyes to earn rewards, and then moved their tongue to harvest that reward. We found that some mossy fibers encoded eye velocity in a specific direction, resembling a copy of the motor commands to the extraocular muscles. The presence of a visual target affected some units' responses to eye velocity without any changes in direction, amplitude, and vigor. These groups were generally copies of premotor neurons in the brainstem. Another group encoded eye position on the screen, resembling output of neural integrators, also in the brainstem. We found some units that encoded the disparity between the left and right eye. Other units responded only to the presence of a visual object at a specific location. These units presented the goal of the movement to the cerebellum.

Surprisingly, mossy fibers that encoded eye movements were near the mossy fibers that encoded tongue movements. Indeed, some units eye and tongue movements simultaneously.

Overall, our method maps behavioral variables to neurons without aligning to events, modeling spatial nonlinearities and temporal delays. Applied to mossy fiber, it categorizes them according to information sources from regions projecting to the cerebellum.

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Late-Breaking Poster

LBP037: F.02. Cerebellum

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NIH 2T32GM136577-06

Title: The presence of hazards biases cerebellar implicit adaptation

Authors: *N. AL-FAWAKHIRI[1], J. L. LEE[2], S. D. MCDOUGLE[3], V. S. CHIB[2];
[1]Johns Hopkins Medicine, Baltimore, MD; [2]Biomedical Engineering, Johns Hopkins University, Baltimore, MD; [3]Psychology, Yale University, New Haven, CT

Abstract: Motor skills are calibrated and maintained by an implicit process of adaptation that updates our internal models after an unexpected error. However, a conflict may arise when the update to the internal model leads to the generation of actions that bring us closer to a known hazard (e.g., a hot stove). Previous work has shown that we can adapt our motor programmes to optimally avoid penalized regions while seeking rewards in a reaching task. However, these studies often do not preclude the use of explicit aiming strategies during action selection. Here, we isolate implicit adaptation using a "clamp" paradigm. Participants first made reaches to one of two displayed targets on the screen. Next, participants underwent "mini-blocks" of adaptation, where the cursor, which previously represented their hand position, followed a fixed ("clamped") trajectory off-center from the target. This introduced a salient error signal which drove implicit adaptation to counter the error. Importantly, the direction of the error alternated between blocks; thus, the adaptive corrections could force participants to make reaches closer to the non-goal target or force them away from the non-goal target. Participants next learned to associate rewards and punishments with each of the targets, with one target becoming the beneficial target and the other hazardous. After learning this association, participants again underwent alternating "mini-blocks" of adaptation at the beneficial target which could either bring their hand toward or away from the hazardous target. Before learning the reward association, no significant bias was observed in the degree of adaptation toward or away from the non-goal target. However, after participants learned the association, adaptation toward the hazardous target was significantly suppressed, revealing a bias away from the hazardous target and suppressing updates to the internal model which were toward the hazard. This bias was independent of movement direction and was instead tied to the location of the hazardous target, even when its position changed. These results demonstrate significant interactions between reward learning and implicit motor adaptation. This behavioral bias may offer insights into the role of functional connections between the basal ganglia (integral to reward learning) and the cerebellum (integral to implicit adaptation).

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Late-Breaking Poster

LBP037: F.02. Cerebellum

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Program #/Poster #: LBP037.06/LBP010

Topic: F.02. Cerebellum

Support: Chan Zuckerberg Initiative
Whitehall Foundation
Research Corporation for Science Advancement

Title: Cerebellar representations of a perceptual timing behavior in mice

Authors: M. CHEN[1], A. SHAMSNIA[1], T. STAMM[1], Y. HUANG[2], Z. SALAMTABRIZI[1], *F. NAJAFI[1];
[1]Georgia Institute of Technology, Atlanta, GA; [2]Wallace H. Coulter Department of Biomedical Engineering, Georgia Institute of Technology / Emory University, Atlanta, GA

Abstract: Predictive processing theory posits that the brain maintains internal models that generate predictions about sensory inputs. Discrepancies between predicted and actual inputs produce prediction errors, which update the model and drive adaptive behavior. A fundamental dimension of prediction is about the timing of future events, yet the neural mechanisms that generate and update temporal predictions remain unclear.
The cerebellum is well established in motor timing, but its contribution to temporal processing in perceptual domains is poorly understood, particularly at a mechanistic level.
Here, we investigated how the cerebellum supports the generation and updating of temporal predictions during a perceptual timing task. We developed a novel behavioral paradigm in mice, involving interval disrimination, with distinct blocks of trials imposing different timing demands. We combined the behavior with two-photon calcium imaging and optogenetics. Our findings reveal cerebellar encoding of perceptual timing parameters. Furthermore, we identify a causal role for cortical interneurons in ensuring accurate behavioral performance.
Future work will determine how cerebellar-cortical interactions implement temporal prediction, providing mechanistic insight into perceptual timing behavior.

Disclosures: M. Chen: None. **A. Shamsnia:** None. **T. Stamm:** None. **Y. Huang:** None. **Z. Salamtabrizi:** None. **F. Najafi:** None.

Late-Breaking Poster

LBP037: F.02. Cerebellum

Location: SDCC Hall B

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

Program #/Poster #: LBP037.07/LBP011

Topic: F.02. Cerebellum

Support: AMED under Grant Number JP25wm0625418h0001

Title: Examination of the relationship between morphological variations in Purkinje cell main dendrites and pattern recognition ability

Authors: *T. KOBAYASHI;
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Abstract: Purkinje cells are capable of discriminating input sequence patterns. This discriminative ability is thought to emerge from membrane potential dynamics and intracellular Ca^{2+} signaling along with the dendritic morphology. However, the relationship between morphological features and discriminative ability are largely unknown. Nedelescu et al. (2017) reported that the number of proximal dendrites with large diameters (main dendrites) in mouse Purkinje cells varies across cerebellar regions: Purkinje cells in the vermal anterior lobule V typically exhibit a single main dendrite, whereas those in posterior lobule IX often possess two bifurcating main dendrites. This raises the question of how such morphological features influence the pattern recognition ability of Purkinje cells.
To address this, I conducted pattern recognition simulations using biophysical models that incorporated realistic dendritic morphology. The models were reconstructed from morphological data provided by Nedelescu et al. (2017) and received excitatory synaptic inputs from parallel fibers (PFs) applied to distal dendrites. For both bifurcating and non-bifurcating main dendrite models, I gave 30 randomly generated time-series synaptic inputs along with target firing patterns and subsequently evaluated the number of patterns that could be reliably discriminated. The results of ten pattern recognition task simulations demonstrated that models with bifurcating main dendrites exhibited, on average, a higher number of discriminable patterns in response to PF synaptic inputs. In contrast, non-bifurcating models showed lower average discrimination performance, but achieved high discrimination scores in a few test cases, resulting in a larger standard deviation. Comparable results were obtained even when inhibitory inputs from molecular layer interneurons were applied concurrently with PF synaptic inputs. These findings suggest that bifurcating models possess generally higher, or more versatile, discriminative capacity, whereas non-bifurcating models may exhibit specialized discrimination abilities, akin to a system finely tuned to specific stimulus patterns. Taken together, these simulation results indicate that differences in main dendrite morphology reflect distinct inference-like properties of Purkinje cells. In other words, the region-dependent presence of Purkinje cells with bifurcating versus non-bifurcating main dendrites implies that individual cerebellar lobules, despite sharing a similar microcircuit architecture, may nevertheless exhibit distinct computational or inferential capacities.

Disclosures: T. Kobayashi: None.

Late-Breaking Poster

LBP037: F.02. Cerebellum

Location: SDCC Hall B

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

Program #/Poster #: LBP037.08/LBP012

Topic: F.02. Cerebellum

Support: NIH Grant NS132926

Title: Does the cerebellum contribute to unsupervised learning?

Authors: Y. OU, J. E. TRACH, ***S. D. MCDOUGLE**;
Yale University, New Haven, CT

Abstract: Recent work in animal models has revealed that the cerebellum contributes to nonmotor forms of learning, in addition to its well-known role in supervised motor learning. One hypothesis is that the cerebellum might perform domain general prediction error computations that can be used for learning outside the motor domain (Sokolov et al., 2017). In line with this idea, prior research in animal models (Wagner et al., 2017) has provided initial evidence of cerebellar involvement in prediction-error based reward learning (reinforcement learning; RL). Recent research in our lab revealed that nonmotor regions in the human lateral cerebellum (Crus I & II) encode reward prediction errors during RL (Trach et al., 2025). In the present study, we further tested the hypothesis that the cerebellum might be involved in domain-general error processing during learning by investigating its role in another cognitive form of learning: unsupervised (i.e., statistical) learning (SL). We report two experiments, one using fMRI in healthy subjects, and another comparing SL behavior in individuals with cerebellar degeneration versus controls. In our fMRI study, Human participants (N = 20) performed a visual SL task where they viewed sequences of novel fractal stimuli. We manipulated the transitional probability between fractals such that certain transitions had a higher probability (0.75) than others (0.25). This allowed us to measure prediction error (surprise) signals across the brain. At the whole brain level, we found evidence of sensory prediction errors during statistical learning in the hippocampus, which showed increased activity during the less likely stimulus transitions. The strength of these hippocampal error signals was more robust during the second half of trials compared to the early stage of the task, a classic signature of SL. Critically, we did not find any reliable SL signals in the cerebellum even at relaxed significance thresholds. In our second experiment, individuals with cerebellar degeneration (N = 11) and controls performed a similar SL task. Both groups showed equally strong SL behavior in the task, further suggesting that the cerebellum does not contribute to SL. Together, these results impose limitations on the domain general prediction error hypothesis of cerebellar cognition.

Disclosures: Y. Ou: None. **J.E. Trach:** None. **S.D. McDougle:** None.

Late-Breaking Poster

LBP037: F.02. Cerebellum

Location: SDCC Hall B

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

Program #/Poster #: LBP037.09/LBP013

Topic: F.02. Cerebellum

Support: NIH Grant 1 UH3 NS128297

Title: Cerebellar deep brain stimulation in dystonic cerebral palsy

Authors: *A. STEINA[1], S. RIEMER[1], L. BOLO DAVE[1], K. FRANJIEH[1], B. SCHULTZ[1], S. S. WANG[1], C. R. OEHRN[2], P. A. STARR[1], M. SAN LUCIANO PALENZUELA[1];
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Abstract: Cerebral palsy is the leading cause of acquired dystonia in childhood. Deep brain stimulation (DBS) of the basal ganglia or thalamus has shown limited efficacy in dystonic cerebral palsy (DCP), likely due to structural damage in these regions. The cerebellum, typically spared from such damage, may serve as an alternate stimulation target. In this clinical trial (NCT06122675), we aim to evaluate the therapeutic efficacy of cerebellar DBS and to identify electrophysiological and kinematic markers reflecting disease severity and response to neuromodulation in DCP.

Three pediatric and young adult patients with DCP underwent bilateral DBS implantation targeting the dorsal motor region of the dentate nucleus. Local field potentials (LFP) were recorded one day postoperatively from the implanted device, with stimulation turned off, during rest and arm movements. Starting one month after surgery, stimulation was activated, and LFPs were recorded monthly during rest and various motor tasks. Movement kinematics were captured using a video-based markerless motion tracking system.

Recordings one day after surgery revealed prominent alpha (8-12 Hz) and beta (13-30 Hz) activity at rest, which decreased during voluntary movement. Similarly, movement-related reduction in alpha/beta activity was observed during follow-up visits during active stimulation. Additionally, we observed stimulation-related suppression of alpha activity, although the relation of this reduction to movement and symptom modification remains to be established at this early stage of the trial. Both patients who received stimulation reported subjective improvements in dystonic movements. Objective kinematic assessments are ongoing.

Our findings suggest that cerebellar oscillatory activity exhibits movement-related dynamics similar to those seen in other motor regions of the human brain, such as the motor cortex and basal ganglia. Moreover, cerebellar alpha activity may serve as a physiomarker for dystonia in cerebral palsy, analogous to low-frequency (4 - 12 Hz) activity in the basal ganglia reflecting symptom severity in isolated dystonia. Overall, the initial results support the potential of cerebellar DBS as an effective therapeutic approach for DCP.

Disclosures: A. Steina: None. **S. Riemer:** None. **L. Bolo Dave:** None. **K. Franjieh:** None. **B. Schultz:** None. **S.S. Wang:** None. **C.R. Oehrn:** None. **P.A. Starr:** None. **M. San Luciano Palenzuela:** None.

Late-Breaking Poster

LBP038: F.03. Basal Ganglia

Location: SDCC Hall B

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

Program #/Poster #: LBP038.01/LBP014

Topic: F.03. Basal Ganglia

Support: F99/K00
F31

Title: Impaired Synaptic Inhibition via KCC2 Downregulation Contributes to Aberrant SNr Activity in Parkinson's Disease Models

Authors: *J. WOO[1], A. UPRETY[2], A. OSTROUMOV[3];
[1]Georgetown University, 20007, DC; [2]Georgetown University, Washington, DC; [3]Pharmacology and Physiology, Georgetown University, Washington, DC

Abstract: Parkinson's disease (PD) is characterized by motor, cognitive, and reward-related deficits, which are partly driven by aberrant activity in the basal ganglia output structures, particularly the substantia nigra pars reticulata (SNr). While both firing rate abnormalities and network-level dysregulation in the SNr have been linked to PD symptoms, the underlying cellular mechanisms remain poorly understood. Our preliminary data in 6-hydroxydopamine (6-OHDA) lesion rat model of PD, indicate a downregulation of the chloride-extruding transporter KCC2 in SNr GABAergic neurons. This impairment shifts GABAA receptor signaling from inhibitory to excitatory, altering synaptic integration of inhibitory input onto SNr neurons. We hypothesize that KCC2 dysfunction contributes to both motor and non-motor symptoms of PD through altered synaptic inhibition and network synchrony in the SNr. Using optogenetics, in vivo electrophysiology, and behavioral assays, we (1) determine the impact of impaired KCC2 on basal ganglia circuit function, (2) assess its role in synchronized and oscillatory SNr firing patterns, and (3) evaluate its contribution to motor and reward-related deficits. In summary, our results define a novel, non-canonical mechanism of GABAergic dysfunction in PD and explore KCC2 as a potential therapeutic target for restoring basal ganglia output and alleviating diverse symptoms of the disease.

Disclosures: J. Woo: None. **A. Uprety:** None. **A. Ostroumov:** None.

Late-Breaking Poster

LBP038: F.03. Basal Ganglia

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Topic: F.03. Basal Ganglia

Support: NIH R01NS113746
NSF GRFP

Title: Comparative analysis of cortical innervation across functional regions of the subthalamic nucleus in healthy and parkinsonian monkeys

Authors: *V. BARRAGAN[1], S. WAGH[2], A. GALVAN[2], Y. SMITH[2];
[1]Emory National Primate Research Center, Emory University, Decatur, GA; [2]Emory University, Atlanta, GA

Abstract: Parkinson's disease (PD) is characterized by motor deficits but also involves non-motor problems, including cognitive and motivation impairments, which are not fully explained by current models of basal ganglia dysfunction. The subthalamic nucleus (STN) may be implicated in these functions because this structure receives inputs from associative and limbic cortical regions, and it is involved in networks mediating cognition and reward. Although previous studies have reported decreased cortical innervation in the sensorimotor region of the STN in rodent and primate models of PD, it remains unclear whether similar changes occur in the associative and limbic territories. We examined cortical vGluT1-positive terminals in all functional regions of the STN of control and MPTP-treated parkinsonian rhesus monkeys (3 monkeys per group) using confocal and transmission electron microscopy (EM). Confocal analyses revealed a reduction in the total volume of vGluT1-positive terminals in the sensorimotor and associative regions of parkinsonian animals, whereas terminal density was not significantly altered in any region. EM analyses revealed no differences in terminal surface area or density between groups, but area distributions showed an increased proportion of larger terminals in all functional regions with only the associative region reaching significance. Notably, we identified frequent axo-axonic contacts formed by vGluT1 terminals, a synaptic arrangement not previously reported in the rodent STN but occasionally seen in cat. Of the 1,032 post-synaptic elements analyzed, 45.4% formed axo-spinous synapses, 47.0% formed axo-dendritic synapses, and 7.6% formed axo-axonic synapses. These findings provide evidence that cortico-subthalamic terminals undergo region-specific structural remodeling in PD, with sensorimotor and associative territories most affected and the limbic territory relatively spared. The high frequency of axo-axonic vGluT1 synapses in the primate STN compared to rodents suggest species differences in cortico-subthalamic connectivity between rodents and primates. Together, these results broaden our understanding of cortical inputs remodeling in the STN and emphasize the need for future high-resolution 3D-EM and functional studies to further clarify the impact of these structural changes and the role of axo-axonic synapses on basal ganglia circuitry and potential implications for STN deep brain stimulation.

Disclosures: V. Barragan: None. **S. Wagh:** None. **A. Galvan:** None. **Y. Smith:** None.

Late-Breaking Poster

LBP038: F.03. Basal Ganglia

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Topic: F.03. Basal Ganglia

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U19-NS104649
FCT PD/BD/105950/2014
Simons 717104

Title: Specific ensembles of striatal neurons control granular forelimb actions

Authors: *I. RODRIGUES-VAZ[1,2,3,4], V. R. ATHALYE[5,1], D. S. PETERKA[6], R. M. COSTA[7,4];
[1]Allen Institute, Seattle, WA; [2]Columbia University, New York, NY; [3]Champalimaud Foundation, Lisbon, Portugal; [4]Aligning Sci. Across Parkinson's (ASAP) Collaborative Res. Network, Chevy Chase, MD; [5]Zuckerman Institute, Columbia University, New York City, NY; [6]Zuckerman Institute, Columbia University, New York, NY; [7]Zuckerman Mind Brain Behavior Institute, The Allen Institute, Seattle, WA

Abstract: Animals must execute appropriate actions for survival. The striatum is a critical center for movement and learning in the brain that is afflicted in movement disorders. Yet, the role of striatum in controlling ongoing actions is not understood. A classical view has been that the striatum controls when and how vigorously to move through opponent pathways. Two populations of spiny projection neurons (D1-SPNs heading the striato-nigral circuit and D2-SPNs heading the striato-pallidal circuit) are thought to having opposing effects on movement. Alternatively, D1- and D2-SPNs may control specific actions in concert. We performed 2-photon imaging and stimulation in the dorsolateral striatum as mice performed two forelimb actions in a self-paced manner, consisting of a push or pull isometric force on an immobile joystick. D1- and D2-SPNs equally predicted the preparation and execution of specific actions, irrespective of what action was reinforced. We developed a closed-loop system to model and manipulate action-specific dimensions of population activity using holographic optogenetics through a GRIN lens. Stimulation of action-specific ensembles of both D1- and D2-SPNs increased the force of only the congruent action. These results show that D1- and D2-SPNs control specific ongoing actions concurrently, with specific ensembles controlling actions as granular as forces of the same body part. These results have implications for Huntington's Disease and dystonia which afflict striatum and impair execution of specific movements.

Disclosures: I. Rodrigues-Vaz: None. **V.R. Athalye:** None. **D.S. Peterka:** None. **R.M. Costa:** None.

Late-Breaking Poster

LBP038: F.03. Basal Ganglia

Location: SDCC Hall B

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

Program #/Poster #: LBP038.04/LBP017

Topic: F.03. Basal Ganglia

Title: Output connectivity parcellates cortico-basal ganglia circuits

Authors: *M. BUI;
Neurobiology, University of Southern California, Los Angeles, CA

Abstract: The motor system is hierarchically organized: higher-order circuits plan, sequence, and adjust actions, while lower-level circuits execute movement. As part of this hierarchy, the basal ganglia select and modulate actions, yet how this network connects to divergent downstream targets to mediate specific behavioral functions remains poorly understood. We previously demonstrated that the substantia nigra pars reticulata (SNr), the largest basal ganglia output nucleus in mice, contains specialized classes of output neurons that form distinct connections to lower behavioral controllers in the brainstem. Here, we extend this work to parcellate the internal organization of the basal ganglia based on their indirect projections to lower motor systems. Using multisynaptic viral tracing and high-throughput neuroanatomical analyses, we identify anatomically distinct subdivisions of the striatum and globus pallidus that transsynaptically connect to distinct portions of the brainstem motor and modulatory systems. These output-defined territories assemble into separate, parallel basal ganglia subnetworks that target distinct regions of the lower motor system. Ongoing work relates these subnetworks to their cortical inputs and evaluates their contributions to behavioral impairment in a Parkinson's disease model. Together, these findings reveal anatomically distinct, parallel basal ganglia subnetworks that extend closed-loop models by identifying open routes to brainstem behavioral controllers. This newly defined topography enables more precise investigations of basal ganglia circuit function and downstream effects.

Disclosures: M. Bui: None.

Late-Breaking Poster

LBP039: F.04. Voluntary Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP039.01/LBP018

Topic: F.04. Voluntary Movements

Title: Effects of Vibrotactile Stochastic Resonance Stimulation on Upper-Limb Function in Stroke Survivors

Authors: *G. CORNIANI[1], I. TOYE[2], K. PIELA[3], Q. WANG[4], S. MICERA[2], P. BONATO[4]; [1]Harvard Medical School, Somerville, MA; [2]Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland; [3]Spaulding Rehabilitation Hospital, Charlestown, MA; [4]Harvard Medical School, Boston, MA

Abstract: Stroke is a leading cause of long-term disability, with survivors often experiencing persistent motor and sensory impairments that limit independence and recovery. Interventions that enhance sensorimotor integration may provide novel rehabilitation strategies. This study examined the acute effects of non-invasive vibrotactile stochastic resonance (SR) stimulation on upper-limb performance in chronic stroke survivors.Six participants with unilateral stroke (mean age: 60.2 ± 4.2 years) completed sensory and motor assessments under stimulation and no-stimulation conditions using a wrist-worn vibrotactile device. Sensory testing included the Semmes-Weinstein monofilament; motor testing comprised Wolf Motor Function Test (WMFT) subtests, maximal grip and pinch force, and gross movement assessment. Surface EMG from 12 upper-limb muscles per arm and accelerometry were used to quantify muscle recruitment and movement smoothness.Sensory outcomes were variable; SR stimulation improved tactile detection thresholds in 3 of 6 participants. The variability in response may reflect the cognitive demands and task difficulty for this population. Across WMFT subtests, stimulation was generally associated with reduced completion times in 4 out of 6 participants. Notably, one subject was unable to perform the lift paper clip and stack checkers tasks without stimulation, but successfully completed them under stimulation. Improvements were most evident when the task posed a significant challenge to the affected arm, suggesting stimulation may be particularly beneficial in demanding fine manipulation control. Force tests showed modest increases in grip and pinch strength in 5 of 6 participants, accompanied by higher EMG amplitudes in agonist muscles, suggesting more efficient recruitment. Gross movement assessments revealed heterogeneous changes in performance, with EMG and kinematic analyses highlighting improved movement quality in some participants, with smoother trajectories and reduced co-contraction of antagonistic muscles.These preliminary findings suggest that vibrotactile SR stimulation can facilitate motor performance in stroke survivors, particularly in dexterity-based tasks that rely on sensory feedback. However, the heterogeneous responses observed underscore the need for larger-scale studies to capture variability in stroke presentation and recovery profiles. Future work should aim to identify clinical or neurophysiological phenotypes of responders, enabling more targeted application of SR stimulation as a personalized rehabilitation tool.

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Late-Breaking Poster

LBP039: F.04. Voluntary Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP039.02/LBP019

Topic: F.04. Voluntary Movements

Title: Force Target Matching Accuracy and Variability in Children With Developmental Coordination Disorder

Authors: *J. SHAHID[1], V. W. CHU[2];
[1]Rehabilitation and Movement Sciences, Virginia Commonwealth University, Richmond, VA;
[2]Occupational Therapy, Virginia Commonwealth University, Richmond, VA

Abstract: Background: Children with developmental coordination disorder (DCD) often struggle with force regulation. This study examines the accuracy and variability of target force matching at submaximal levels sensitively compared to typically developing children (TDC).Objective: To characterize age-related trends and DCD-TDC differences in force target matching accuracy and variability.Methods: The study included 48 children, with 24 diagnosed with DCD (15 males, 9 females) and 24 TDC (16 males, 8 females). Participants were distributed across four age groups (4 - 6, 7- 9, 10-12, 13 and above years old) with 10-14 children per group, allowing for analysis of both age-related trends and group differences. Maximum voluntary contraction (MVC) was measured with an electronic grip dynamometer connected to a computer, then children matched 5%, 10%, 15%, 20%, and 25% of the MVC target with each hand. Outcomes were normalized target error (accuracy) and within trial variability. Between-subjects, two way ANOVA tested age groups and group (DCD vs TDC) differences. Statistical significance was prespecified as $\alpha=0.05$. Results: For age groups, significant differences were observed for target matching (Right: $p=.007$; Left: $p=.003$) and variability (Right: $p=.002$; Left: $p<.001$), indicating improved accuracy and stability with age. Younger children (4-6 yo) showed the largest target errors and highest variability, with DCD children showing higher errors and variability. As age increased, both groups demonstrated progressive reductions in target error and variability, with the most stable and accurate performance observed in the oldest age group (13 yo and above). These findings indicate that force regulation and consistency improve with development, although children with DCD continue to lag behind their typically developing peers. Group differences were significant for target matching error (Right: $p=0.04$; Left: $p=0.03$), and for variability (Right: $p=0.016$; Left: $p=0.07$). Conclusion: Target matching performance improves with age, yet younger children with DCD (4-6 years) exhibit persistently greater errors and variability than TDC. Findings support the need for interventions that emphasize force precision and stability in DCD.

Disclosures: J. Shahid: None. **V.W. Chu:** None.

Late-Breaking Poster

LBP039: F.04. Voluntary Movements

Location: SDCC Hall B

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Topic: F.04. Voluntary Movements

Support: NIH Grant R21HD111748
University of Minnesota Rehabilitation Science New Student Award

Title: Can augmented visual or auditory feedback enhance motor performance without increasing cognitive load?

Authors: J. CHENG, P. THAPA, *S. A. JAYASINGHE;
Univ. of Minnesota, Minneapolis, MN

Abstract: Movement requires coordination between cognitive, sensory, and motor execution processes. Previous studies using dual-task paradigms have shown that augmented sensory feedback can improve motor performance, but it is not clear whether these improvements were due to the nature of augmented feedback, changes in muscle coordination patterns, or reductions in cognitive load. We designed a challenging reaching task (6 blocks, 15 trials each) on the Kinereach system that requires the participant to store and then recall a sequence of shapes from memory. In Blocks 3 and 5, we introduced augmented sensory feedback of hand position error in the form of either visual feedback (the cursor turns from red to green as it moves closer to the target) or auditory feedback (a beeping sound that gets faster as the cursor moves closer to the target). Our central hypothesis was that augmented feedback of hand position error improves movement performance while also increasing the perceived cognitive load. We also explored whether the type of augmented feedback (visual vs. auditory) had a differential effect on these outcomes. Cognitive load was assessed using the Paas' mental effort rating scale after each block. We recruited 10 neurotypical adults (age: 28 +/- 1.48 years; 6 females, 4 males). The order in which the augmented feedback was provided was randomized across participants. Preliminary results suggest that with augmented feedback, movement performance (i.e., initial direction error, distance error at the end of the trial) improves significantly ($p < 0.05$) compared to the condition without augmented feedback. Our second prediction was not supported because the Paas' score was not significantly different with augmented compared to no augmented feedback conditions. We used paired t tests to examine performance differences with auditory vs. visual augmented feedback. We found that although auditory feedback tends to result in higher Paas' scores than visual feedback, this is not statistically significant ($p = 0.08$). No motor performance measures were significant except movement planning error, which was higher with visual compared to auditory feedback ($p < 0.05$). These results suggest that it may be possible to augment sensory feedback during a challenging movement without necessarily increasing the cognitive load on an individual. However, the type of augmented feedback (i.e., visual or auditory, in this case) may moderate any such performance improvements. We expect that

ongoing analysis of this dataset, which includes eye-tracking and EMG data will provide further insights into motor coordination and physiological cognitive load changes.

Disclosures: J. Cheng: None. **P. Thapa:** None. **S.A. Jayasinghe:** None.

Late-Breaking Poster

LBP039: F.04. Voluntary Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP039.04/LBP021

Topic: F.04. Voluntary Movements

Title: Error predictability shifts sensory prediction toward the error: An additional mechanism to reduce sensory prediction error

Authors: *W.-P. WU[1], T. HAYASHI[2], D. NOZAKI[1];
[1]Graduate School of Education, The University of Tokyo, Tokyo, Japan; [2]University of Tokyo, Tokyo, Japan

Abstract: As demonstrated by previous studies showing that contextual cues do not contribute to adaptation to opposing perturbations (e.g., Nozaki et al., Nat Neurosci, 2006), predictability of upcoming error directions provides only limited benefits for implicit motor learning. Nevertheless, the contribution of error predictability in motor control and learning remains insufficiently explored. In this study, we investigated whether such predictability could enhance the feedback response (FBR) or the learning response (LR). Nineteen participants performed 20-cm forward reaching movements. In perturbation trials, visual feedback was provided by a fully clamped cursor that was either rotated by ±15° or remained unperturbed (0°). Before each movement, a geometric cue was presented: a triangle indicated the direction of the upcoming perturbation (predictable condition), whereas a circle conveyed no directional information (unpredictable condition). The FBR was quantified as the directional movement correction that was made during the movement. In the subsequent trial, where the cursor was invisible, the LR was quantified based on the movement direction. Throughout the experiment, participants were instructed to reach directly toward the target without using any explicit strategy. Unexpectedly, the FBR was significantly smaller in the predictable condition than in the unpredictable condition [$F(2, 36)=8.22$, $p = 0.002$]. The LR also tended to be smaller in the predictable condition, although this effect did not reach statistical significance [$F(2, 36) = 2.89$, $p = 0.068$]. Given that the FBR and LR are driven by the sensory prediction error (SPE) - the discrepancy between actual and predicted sensory information, their reduction under the predictable condition suggests that the predictability of the upcoming error shifts sensory prediction toward the direction of error. Conventionally, motor adaptation is understood as a process in which hand movements shift opposite to the error in order to reduce SPE. The present results, however, indicate that this is not the only mechanism; rather, they highlight the possibility of reducing the sensory prediction error by shifting sensory prediction toward the error, thereby providing new insight into the interaction between cognition and motor learning.

Disclosures: W. Wu: None. **T. Hayashi:** None. **D. Nozaki:** None.

Late-Breaking Poster

LBP039: F.04. Voluntary Movements

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Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS117749

Title: The role of the lateral reticular nucleus in forelimb motor control, learning and rehabilitation

Authors: *J. D. ROSS[1], G. M. SMITH[2];
[1]Center for Neural Development and Repair, Lewis Katz School of Medicine, Philadelphia, PA;
[2]Dept of Neuroscience, Temple University, Philadelphia, PA

Abstract: Motor rehabilitation relies on our ability to adapt motor control circuits. While the cortico-pontine-cerebellar pathway is understood to originate motor plans, its inefficiency due to sensory delays necessitates quicker adaptation. Evolutionary pressures led to a system capable of real-time motor correction, using a forward model in which an efferent copy of motor commands is converted into sensory predictions for comparison with feedback. This efferent copy is relayed to the cerebellum via the LRN, allowing for faster motor adaptation. The lateral reticular nucleus (LRN), located in the medulla, is suggested to coordinate complex forelimb movements, but its specific function is not fully understood. Our research indicates that the LRN integrates and relays motor information to maintain forelimb precision and that the spinal-LRN-cerebellar pathway is essential for refining skilled motor patterns and rehabilitation.
To investigate the LRN's role, we developed a vGlut1-Cre Long Evans rat model to specifically target vGlut1 neurons in the LRN using the Cre-lox system. We created AAV viruses, including AAV8-mCherry-flex-dtA, which kills LRN neurons upon injection, leaving other tissue unharmed. Three groups were tested: one untrained before surgery, one pre-trained, and one pre-trained before a cervical spinal cord injury (SCI). Within each group, half received the ablating virus, and half received a control virus.
For the untrained group (n=10), LRN ablation hampered learning the skilled reaching task, with success rates declining significantly. Pre-trained rats (n=12) showed a partial recovery of skills after surgery, indicating the LRN is also important for maintaining skilled tasks. Ablated rats in this group plateaued at 60% success, while controls returned to 80%. For the SCI group (n=16), ablated rats failed to recover function after injury, unlike controls, highlighting the LRN's role in rehabilitation. All ablated rats exhibited kinematic deficits like overreaching. We conclude that the LRN is required for the recovery of forelimb function after SCI and maintenance of skilled forelimb motor ability.
Future studies using DREADDs will explore the LRN’s short- and long-term function by transiently silencing it, as well as its role in adapting to live perturbations during motor tasks.

Disclosures: J.D. Ross: None. **G.M. Smith:** None.

Late-Breaking Poster

LBP039: F.04. Voluntary Movements

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NIH Science Education Partnership Award 1R25GM132959-05

Title: High-throughput quantification of alcohol- and ghrelin-induced alterations in decision-making and motor behavior

Authors: *A. GIRI[1], A. FRIEDMAN[2];
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Abstract: We applied a high-throughput decision-making framework, REward-COst in Rodent Decision-making (RECORD) combined with DeepLabCut-based trajectory tracking and custom feature extraction (approach rate, psychometric function inflection point, fraction of sigmoidal fits, time in reward zones, distance traveled, trajectory curvature, and head-body angle) to examine how alcohol and ghrelin modulate choice and movement in rats.In the alcohol condition, sucrose concentrations (9%, 5%, 2%, 0.5%) were paired inversely with alcohol concentrations (1%, 4%, 10%, 20%) across the four quadrants of the RECORD arena, requiring rats to balance preference for sweetness against increasing alcohol content. Male rats shifted their preference toward alcohol-containing offers, abandoning prior high-sucrose options, and showed reduced time in reward zones, increased center occupancy, and more non-sigmoidal psychometric profiles. In contrast, females maintained stable choice patterns and resilient psychometric fits. We next examined the role of ghrelin receptor signaling using systemic administration of the ghrelin mimetic ibutamoren (IBU). Rats performed non-conflict tasks, in which a single rewarding or aversive stimulus was offered, and conflict tasks, in which reward pursuit required enduring an aversive light stimulus. At low-dose of IBU (2x, 2 mg/kg) rats showed reduced trajectory curvature ($p = 0.0005$), decreased velocity ($p = 0.005$), and increased head-body angle ($p = 0.049$). At high-dose IBU (10x, 10 mg/kg), curvature remained reduced ($p = 0.015$) while velocity and angle were unchanged. Reanalysis of an earlier RECORD dataset under 2x IBU confirmed this pattern, revealing reduced velocity and curvature together with greater time spent inside the nest ($p < 0.0001$). Thus, ghrelin receptor stimulation shapes movement in a concentration-dependent manner, with low-dose IBU consistently producing strong shifts in locomotor dynamics that are blunted at higher doses. Importantly, these changes emerged even in the absence of altered approach-avoid choice rates, indicating that gut hormones

can modulate motor features independently of overt decision outcomes. Together, these experiments demonstrate that alcohol and ghrelin exert distinct, sex- and dose-dependent effects on both decision-making and motor features. High-throughput quantification of trajectories reveals how internal and external modulators reshape choice strategies relevant to drug abuse.

Disclosures: A. Giri: None. **A. Friedman:** None.

Late-Breaking Poster

LBP039: F.04. Voluntary Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP039.07/LBP024

Topic: F.04. Voluntary Movements

Support: Yamaha Motor Foundation for Sports 2024
JSPS KAKENHI Grant Number 25K24332

Title: Coordinated control of the upper and lower limbs in a hand-foot reaching task

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Abstract: Although previous research in motor control has primarily focused on goal-directed upper-limb movements, humans often perform whole-body actions that require the coordination of both the upper and lower limbs, such as drumming and sport climbing. However, the mechanisms underlying such coordinated goal-directed actions remain poorly understood. Because the upper and lower limbs differ in their moments of inertia and conduction distances from the motor cortex to the muscles, simultaneous motor commands to the limbs lead to temporal lags in movement initiation (Swinnen et al., 1995). Therefore, the motor system must account for these limb-specific properties to achieve precise goal-directed actions. While studies on arm reaching have shown that motor planning reflects an internal representation of the arm's biomechanical properties (e.g., Cos et al., 2011), it is unclear how the motor system coordinates multiple limb movements with distinct properties. In this study, we aimed to clarify the mechanisms of goal-directed movements with both the upper and lower limbs from a temporal perspective. Twelve healthy adults, including 5 females, were recruited for this study. We developed a novel hand-foot reaching task, in which participants performed elbow and knee extensions in the dominant limb while seated. A monitor placed in front of the participants showed a target and a cursor. The cursor's horizontal position was mapped to the mediolateral position of the hand, and its vertical position was mapped to the anteroposterior position of the foot. Four potential targets with different movement distances were defined, and on each trial, one target was randomly presented as the target. Participants performed 40 trials at each target, resulting in a total of 160 trials. Analysis of movement onset timing showed that the temporal difference present in single-limb movements was maintained when the limbs were used simultaneously, reflecting the differences in limb properties. The movement onset timings of the

upper and lower limbs were positively correlated across trials, indicating the coordinated control of movement initiations of the limbs. In cases where the required movement distances of the limbs to the target differed, movement initiation of the limb with the shorter distance was delayed, indicating a temporal modulation for precise hand-foot reaching movement. Hand velocity was lower during hand-foot movements than during hand-only movements, suggesting a compensation strategy for interlimb temporal differences. Taken together, these findings highlight the strategies for goal-directed whole-body actions with flexible modulation of motor parameters.

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Late-Breaking Poster

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Program #/Poster #: LBP039.08/LBP025

Topic: F.04. Voluntary Movements

Support: NASA 80NSSC20K1499

Title: Coordination dynamics in alter gravity: A parabolic flight investigation

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Abstract: Objective & Rationale: Gravity is a fundamental external constraint on motor control, yet most spaceflight research contrasts only 0g vs 1g and focuses on unimanual actions. Guided by the Haken-Kelso-Bunz (HKB) framework, we asked whether graded reductions in gravity reorganize the stability of bimanual coordination, particularly for less-stable patterns (90°), with operational relevance for astronaut task performance. **Methods**: Twelve healthy, right-handed adults (6 M; mean age = 40.2 y) with prior altered-gravity experience performed three bimanual force-coordination tasks (0°, 90°, 180°) during parabolic flight (0g, 0.25g, 0.50g, 0.75g) and post-flight 1g baselines. Participants generated isometric forces with each limb against instrumented trays; forces were sampled at 200 Hz. From the force time series we computed unimanual timing/force metrics (inter-peak interval [IPI], SD-IPI, mean/peak force, SD of force, coefficient of variation) and bimanual accuracy/stability indices (absolute error [AE], variability of error [VE], proportion of time within ±30° of the target, constant error [CE]). Linear mixed-effects models (random intercepts per participant) tested effects of Gravity, Task, and Limb. This study is exploratory, with a priori expectations from HKB but without preregistration. **Results**: Coordination followed HKB predictions, 0° was most stable, 90° least stable, 180° intermediate. Microgravity (0g) disproportionately impaired the less-stable modes, AE increased and time-on-target decreased (particularly at 90°), timing variability (SD-IPI) and

force variability (SD force; CV) increased, CE showed larger directional drift from target phase. Mean force was reduced at 0g, and interlimb asymmetries emerged (greater right-limb force; greater left-limb variability). Partial-g levels mitigated, but did not eliminate these decrements, suggesting a dose-response across the gravity continuum. **Conclusions**: Findings support gravity as a stabilizing external constraint that deepens attractor basins for unstable bimanual patterns, improving timing and force regulation. Removing gravity shallows these basins, exposing inherent biases toward more stable states.

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Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP039.09/LBP026

Topic: F.04. Voluntary Movements

Support: KAKENHI-PROJECT-24KJ0982

Title: Muscle-dependent effects of intracortical inhibitory and facilitatory circuits on corticospinal excitability in the human primary motor cortex: Paired-pulse transcranial magnetic stimulation study

Authors: *K. ISHIKAWA, N. KANEKO, K. NAKAZAWA;
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Abstract: Intracortical inhibitory and facilitatory circuits in the primary motor cortex (M1) are crucial for flexible motor control. Paired-pulse transcranial magnetic stimulation (ppTMS) is used to assess specific intracortical circuits by measuring short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), short-interval intracortical facilitation (SICF), and long-interval intracortical inhibition (LICI). Muscles support motor functions ranging from fine movements to gross movements, and their roles differ depending on the muscle. Therefore, the influence of intracortical circuits in M1 on the corticospinal tract may vary depending on muscle characteristics. This study examined whether the modulation of motor-evoked potentials (MEPs) by ppTMS depends on muscle. Twenty-six subjects were recruited. Electromyography was recorded from ten muscles, including the intrinsic muscles of the hand and foot, as well as the extensor and flexor muscles of the forearm, upper arm, thigh, and lower leg. For SICI and ICF, a subthreshold conditioning stimulus (CS) was delivered before a suprathreshold test stimulus (TS) at 2 and 10 millisecond intervals. For SICF, the CS followed the TS at 3 ms interval. For LICI, two TS were delivered 100 ms apart. For all protocols, the TS was set at 120% of the resting motor threshold. The hotspot was optimized for each muscle. MEPs were normalized to those elicited by a single TS. Linear mixed-effects models were run for each ppTMS protocol. Muscles were categorized by limb (upper or lower), segment (distal or proximal), and function (extensor, flexor, or intrinsic) as fixed effects, with random intercepts for muscle and subject. Model-based

estimated marginal means were compared. The results showed significant main effects of limb, segment, and function for SICI and LICI; significant main effects of segment and function for SICF; and significant main effects of limb and function for ICF. Proximal muscles showed greater MEP suppression than distal muscles in SICI, whereas distal muscles showed greater MEP suppression than proximal muscles in LICI. Flexors showed stronger MEP facilitation than extensor in SICF, while extensors showed stronger MEP facilitation than flexor in ICF. Our findings suggest circuit selectivity, indicating that inhibitory and facilitatory effects depend on muscle. Efficient motor control may be achieved by modulating muscle-specific corticospinal excitability through distinct intracortical circuits according to the functional demands of each muscle. Such muscle-dependent modulation may provide perspective for future studies about motor impairment and recovery.

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Late-Breaking Poster

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Topic: F.04. Voluntary Movements

Support: Connected Minds Program
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Title: Prefrontal and Parietal Local Field Potentials Employ Different Visuospatial Codes for Reach: A Complex-Valued Network Classification Approach

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Abstract: Understanding how cortical oscillations coordinate spatial memory and motor planning presents a fundamental challenge in systems neuroscience. We tested if phase-amplitude dynamics in cortical local field potentials (LFPs) encode distributed vs. regionally specific signals for spatial memory and planning under varying visuospatial conditions. To do this, we developed a deep Complex-Valued Neural Network (CVNN) model (Benevenuto & Piazza, 1992; Georgiou & Koutsougeras, 1992) to decode landmark-dependent spatial states from local field potentials (LFPs) recorded from the posterior ventrolateral prefrontal cortex (pVLPFC, 128 channels) and intraparietal sulcus (IPS, 32 channels) in a female rhesus monkey

performing three memory-guided reaching tasks: in which visual landmarks either remained stable, shifted 8° in one of eight directions, or were absent (Lin et al. SFN, 2025; Sheldrick et al. SFN 2025). Preprocessed LFPs were transformed into complex-valued time series via Hilbert transform to retain phase and amplitude information (Freeman, 2007). We then trained CVNN models to classify between the three landmark conditions based on either IPS or pVLPFC data. Both versions achieved >90% training accuracy. However, validation performance revealed inter-regional specialization. The IPS model achieved 50% overall accuracy (significantly above 33% chance), excelling at No-Landmark trials (82% accuracy) compared to Stable-Landmark (46%) and Shifted-Landmark trials (20%). The pVLPFC model achieved 51% overall accuracy and performed best on Shifted-Landmark trials (65% accuracy) compared to Stable-Landmark (51%) and No-Landmark trials (36%). Temporal importance analysis showed IPS activation during motor execution (~1500ms post-target) with optimal No-Landmark performance, while pVLPFC exhibited two peaks for Shifted trials (~200ms and ~1300ms post-target) aligning with early processing and post-shift response. Hand-onset alignment confirmed these patterns: IPS had pre-movement peaks (~600ms and ~200ms before onset) across conditions, whereas pVLPFC showed sustained pre-movement activity with condition-specific timing. These preliminary results suggest that IPS specializes in maintaining spatial representations for reach plans in egocentric coordinates, whereas pVLPFC shows enhanced encoding in the presence of visual landmarks, especially in the dynamic landmark-shift conditions, indicating complementary computational roles in maintaining and updating spatial representations for reach.

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Late-Breaking Poster

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Topic: F.04. Voluntary Movements

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Title: Distinct contribution to grasp encoding in macaque parietal and premotor areas

Authors: F. ALUISI[1], M. DE VITIS[1], M. FILIPPINI[1,2], *M. GAMBERINI[1], F. E. VACCARI[1], S. DIOMEDI[3], P. FATTORI[1,2];
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Abstract: Neuronal populations in parietal and frontal cortices orchestrate visuomotor transformations crucial for successful reaching movements (De Vitis et al., 2025). Within this fronto-parietal network, two key nodes are the dorsal premotor area (F2) and the medial posterior parietal area (V6A), which are strongly and reciprocally connected (Gamberini et al., 2021). Importantly, these regions are not limited to encoding reaching but are also engaged in grasping behavior (Fattori et al., 2010, 2012; Raos et al., 2004). While both areas have been individually implicated in prehension, a direct comparison of their respective contributions to grasp encoding is still missing. To fill this gap, we trained two Macaca fascicularis to perform a delayed reach-to-grasp task in darkness. Objects were always presented at the same spatial location but varied in shape, each designed to evoke a different type of grip: whole-hand prehension, hook grip, finger prehension, primitive precision grip, advanced precision grip. In each trial, the object was briefly illuminated, and after a delay the animal executed the corresponding grasp. We compared neuronal responses in V6A with new data recorded from F2 by computing the mean firing rates in two temporal epochs (FREE, the baseline activity; R-to-G, the movement-related activity) and applying a two-way ANOVA (factor 1: grip type, 5 levels; factor 2: epochs, 2 levels). Our results show that 47% of V6A neurons were significantly modulated by both factors, whereas a lower proportion, 29%, was found in F2. Interestingly grip selectivity, quantified with a Preference Index (PI), reached comparable values in both areas (F2: 0.36±0.13, n=39; V6A: 0.39±0.17, n=111). The discrimination between the best and worst grips was robust in both regions (F2: 52.5±15.1%; V6A: 56.7±18.3%), while best vs. second-best grip differences were modest (F2: 17.5±11.6%; V6A: 20.6±17.9%). Notably, while V6A neurons could span the full range of grip selectivity, F2 activity profiles remained more overlapped, never reaching complete separation across grip types. At population level, the two areas also diverged in their temporal dynamics: F2 activity increased and peaked earlier, well before movement onset. In contrast, V6A responses peaked later, around movement onset. These findings highlight a division of labor within the fronto-parietal grasping network, with V6A providing a sharper representation of grip type and F2 contributing to the early temporal structuring of grasp-related commands.

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Late-Breaking Poster

LBP039: F.04. Voluntary Movements

Location: SDCC Hall B

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

Program #/Poster #: LBP039.12/LBP028

Topic: F.04. Voluntary Movements

Support: Raynor Cerebellum Project
T32HD040127

Title: High-resolution, non-invasive transcranial functional ultrasound imaging combined with targeted neuromodulation in awake, behaving animals

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Abstract: Traditional neuroimaging techniques lack the spatial and temporal resolution needed to capture detailed, distributed brain activity, especially in awake animals. 4D functional ultrasound imaging (fUSI) provides non-invasive, transcranial, high-resolution access to whole-brain dynamics, with intravenous microbubbles enhancing signal sensitivity. Transcranial focused ultrasound (tFUS) enables non-invasive, reversible modulation of targeted neural circuits. Here, fUSI and tFUS were combined into a single registered apparatus, allowing simultaneous high-resolution imaging and targeted neuromodulation of motor circuits in awake, behaving animals. This platform offers a powerful tool for mapping the functional organization of the primary motor cortex (M1) and its interconnected cortical and subcortical networks, providing insight into how these circuits coordinate fine motor behavior. fUSI was used to measure whole-brain, task-evoked changes in cerebral blood volume (CBV) as an indirect marker of neuronal activity in awake, head-fixed mice. Food-restricted mice were trained to reach for and eat food pellets using their right paw, while motor behavior was recorded with two high-speed cameras. Neuronal activity was assessed in six mice across four 6-minute reaching scans and compared to 90-second resting-state scans when no task was performed. During task performance, tFUS was applied to M1 (1 s on, 4 s off, 6 min total; 50% duty cycle) to assess effects on motor behavior. CBV and paw kinematics were analyzed to evaluate tFUS modulation. Intravenous microbubbles were injected via the tail vein to enhance transcranial fUSI signals. fUSI provided high spatial (200 μm) and temporal (20 ms) resolution, enabling precise mapping of neural activity with controlled targeting for both imaging and neuromodulation. During reach behavior, CBV changes were observed across cortical and subcortical regions, with activation peaking bilaterally in M1 approximately one second post-reach. tFUS targeting M1 increased CBV variability at peak activation and during the return to baseline. Neuromodulation also reduced reach velocity by 10-31% and altered reach profiles. These findings demonstrate that fUSI combined with tFUS is a powerful approach to map and manipulate whole-brain activity during skilled motor behavior in mice. Reduced movement velocities and increased CBV variability during neuromodulation suggest tFUS disrupts motor circuitry. Integrating high-resolution CBV imaging with paw-tracking allows precise identification of affected networks and mechanisms, creating potential for a non-invasive, closed-loop system to study motor circuits.

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Late-Breaking Poster

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Topic: F.04. Voluntary Movements

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Title: High-frequency transcranial random noise stimulation enhances motor training and neural adaptation for virtual prosthesis control

Authors: E. FENOGLIO[1], V. ZANELLI[2], V. RISPOLI[3], F. CONTÒ[4], C. CASADIO[2], D. ENRICO[5], F. RICCI[6], G. ELLENA[7], A. CASILE[8], S. LI GIOI[9], R. BILLARDELLO[10], F. CORDELLA[9], L. ZOLLO[9], F. LUI[11], F. BENUZZI[12], L. BATTELLI[13], *M. SEMPRINI[5];
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Abstract: Controlling upper limb prostheses with multiple degrees of freedom (DoFs) demands significant cognitive effort, limiting intuitive use and contributing to high abandonment rates. Although motor cortices of amputated subjects remain capable of controlling movements, prosthetic does not restore the sense of agency. Increasing cortical excitability in the motor cortex may enhance sensory-motor encoding, strengthen agency, and reduce abandonment. We hypothesized that high-frequency transcranial random noise stimulation (hf-tRNS), could enhance neuroplasticity and improve virtual prosthesis training. Twelve healthy participants (6 ACTIVE, 6 SHAM) underwent a 20-minute, 3-day EMG-based training to control a 4-DoF virtual prosthesis with their non-dominant hand. Pre/post training assessments included behavioral embodiment questionnaires, motor-evoked potentials (MEPs), resting motor threshold (%RMT), and resting-state EEG (rsEEG). Due to variability in MEPs morphology when recording from larger proximal muscles, the onset-to-peak (OTP) amplitude was extracted. EEG signals were source-localized to 21 cortical regions of interest (ROIs) using eLORETA and grouped into 6 canonical networks. Functional connectivity was then estimated across delta to gamma bands. Connectivity metrics quantified intra- and inter-network coupling. We tested the normality of the data (Kolmogorov-Smirnov), followed by a within-factor analysis: TIME (PRE vs POST) and GROUP (SHAM vs ACTIVE) using an rm-ANOVA with false discovery rate correction (Benjamini-Hochberg). No significant differences emerged in the embodiment questionnaire. In the ACTIVE group, normalized %RMT significantly decreased post-intervention in the trained muscles (first dorsal interosseus: $p<0.02$; extensor carpi radialis: $p<0.05$). Across all recorded muscles except the biceps (flexor carpi radialis, extensor carpi radialis and first dorsal interosseus), MEPs showed a main effect of GROUP, with the ACTIVE group exhibiting higher OTP amplitudes compared to the SHAM group (all $p<0.01$). There was

also a trend for GROUP × TIME interaction (post-ACTIVE > post-SHAM, p = 0.08). rsEEG showed trends toward differences between groups and within the ACTIVE group in somato-motor and language networks across theta and gamma bands, but these did not survive correction. Although the sample size is small so far, the preliminary results of this ongoing study suggest that hf-tRNS may modulate cortical excitability and network-level dynamics during prosthetic training, and that this multimodal approach may identify neurophysiological markers of prosthetic embodiment.

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Late-Breaking Poster

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National Institute of Neurological Disorders and Stroke (R01NS091236 and R21NS133913_
National Institute of Child Health and Human Development (P50HD103573 and T32HD040127)

Title: Using fMRI to Investigate Whole-Brain Networks During the Performance of a Skilled Motor Task

Authors: *C. FREEMAN[1], S. SONG[2], A. W. HANTMAN[3], Y.-Y. I. SHIH[4], S. ALBERT[1]; [1]Neuroscience, UNC Chapel Hill, Chapel Hill, NC; [2]University of North Carolina, Chapel Hill, NC; [3]Cell Biology and Physiology, Neuroscience Center, UNC-CH, RCP, Chapel Hill, NC; [4]University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract: The planning and execution of motor sequences rely not just on one brain area but on a distributed motor circuit. This brain-wide network includes both cortical and subcortical regions such as the thalamus, basal ganglia, and the primary motor cortex (M1). Traditionally, attempting to understand activity within the motor network entails in-vivo electrophysiological recordings, which capture continuous activity from a subpopulation of neurons within a given functional region. However, this approach neglects the highly distributed nature of this network, rendering the whole-network picture largely incomplete. Another approach is to acquire whole-brain images using functional magnetic resonance imaging (fMRI); however, traditional imaging sequences are highly sensitive to movement artifact, making it impossible to image complex,

ethologically relevant movement sequences. Here, we balanced these concerns in inventing a novel fMRI imaging sequence which is both acoustically silent and robust to movement artifact. Using this sequence, we were able to acquire thousands of whole-brain images in each of 15 behaving VGAT-ChR2-EYFP mice during the performance of a reach-to-grasp task. With these images in hand, we were then able to appreciate unique network signatures associated with variations in behavior and task performance. Activity across the trial sequence was separated by reach number, by success, and by amount of prior training across several functional regions within the motor network, and trajectories as well as amplitudes were compared to understand the relative importance of each region to that behavior. As a result we found both that activity across the motor network scales with the number of reach attempts performed and that subcortical regions demonstrate differences in activity on successful trials whereas cortical regions do not demonstrate this trend. Plots within functional regions were paired with high resolution whole-brain images to understand widespread interactions throughout the trial. These analyses demonstrate the validity of our fMRI method in eliminating movement artifact as well as the stress inherent to the fMRI environment, and they shed light on the network dynamics which both contribute to and result from skilled motor control.

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Topic: F.04. Voluntary Movements

Support: ERC Grant 885192

Title: Central amygdala Isl1 neurons encode physical properties of food and control bite force

Authors: *W. DING, R. KLEIN;
Max Planck Institute for Biological Intelligence, Martinsried, Germany

Abstract: The precise control of bite force is vital for safe and effective breakdown of food inside the mouth. Apart from the orofacial sensorimotor cortex and the premotor circuits in pons and medulla, the roles of other brain areas in bite force control remain poorly understood. The central amygdala (CeA) was previously implicated in prey hunting and biting, but the neural activities of the responsible CeA neurons remained elusive. Here, we identify a subpopulation of CeA GABAergic projection neurons marked by the transcription factor *Isl1* (CeA^{Isl1} neurons) that plays a crucial role in modulating biting behavior in mice. Using in vivo calcium imaging, we show that CeA^{Isl1} neurons are robustly activated at the onset of biting across materials of varying physical properties, with distinct neuronal ensembles selectively encoding responses to the physical rather than palatable properties of the object. Notably, CeA^{Isl1} neuronal activity

scales positively with the hardness of the object, suggesting a role in bite force modulation. Optogenetic activation of CeA^{Isl1} neurons enhances biting behavior toward edible and non-edible objects, induces fictive feeding in the absence of physical targets and exerts a reinforcing effect on behavior. Conversely, photoinhibition of CeA^{Isl1} neurons disrupts efficient biting of hard food (uncooked noodles), but not soft food. Anatomical tracing and functional manipulations reveal that CeA^{Isl1} neurons project to the parvocellular reticular nucleus (PCRt), a brainstem region previously implicated in oromotor control, and this projection is sufficient for the execution of effective biting. These findings uncover a previously unrecognized sensorimotor function of a central amygdala neuron population in calibrating bite force and precision, linking motivational states to skilled oromotor output.

Disclosures: W. Ding: None. **R. Klein:** None.

Late-Breaking Poster

LBP040: F.05. Brain-Machine Interface

Location: SDCC Hall B

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

Program #/Poster #: LBP040.01/LBP032

Topic: F.05. Brain-Machine Interface

Support: JST PRESTO Grant Number JPMJPR23I1
Moonshot R&D Grant Number JPMJMS2012

Title: Closed-loop neurofeedback training combined with kinesthetic motor imagery exercise enhances task-related beta activity in motor cortex: a double-bilnd randomized sham-controlled trial

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Abstract: Neurofeedback training (NFT) combined with kinesthetic motor imagery exercise enables individuals to voluntarily modulate neural activity through real-time feedback. This process facilitates plastic changes in targeted brain regions and can improve motor performance. However, it remains unclear whether these effects reflect genuine neural learning or non-specific placebo effects, making it difficult to establish that NFT truly induces plastic changes in targeted neural circuits. To address this issue, we conducted a single-day, double-blind randomized sham-controlled trial. 52 right-handed healthy adults (46 males and 6 females) were randomly allocated to either an experimental group (n = 26) or a placebo group (n = 26). Both groups performed kinesthetic motor imagery of right index finger movement while observing visual feedback of hand images. The experimental group received real-time feedback of event-related desynchronization (ERD) magnitude of motor cortical beta oscillation from the contralateral sensorimotor cortex, whereas the placebo group received yoked-sham feedback based on ERD

magnitude calculated from previously recorded data of another participant. Electroencephalogram (EEG) and transcranial magnetic stimulation (TMS) were used to assess motor cortical excitability before and after NFT. EEG analysis focused on beta-band ERD during motor imagery, while TMS analysis quantified resting-state cortical excitability through motor evoked potentials in the right first dorsal interosseous muscle.EEG analysis using a two-way repeated-measures ANOVA revealed significant interaction between group and time ($F(1,45) = 4.41$, $p = 0.042$). Post-hoc t-test showed a significant increase in ERD magnitude of the targeted motor cortical beta activity enhanced after veritable NFT($t(24) = 3.23$, $p = 0.014$, $d = 0.91$), whereas no such change was observed in placebo group. TMS analysis, in contrast, demonstrated a significant main effect of time ($F(2.54,116.86) = 3.22$, $p = 0.03$). Post-hoc t-test indicated a significant enhancement in resting-state corticospinal excitability in both groups ($t(47) = 2.90$, $p = 0.026$, $d = 0.15$), regardless of feedback types. Notably, the magnitude of this increase did not differ between groups. This dissociation implies that NFT selectively modulates the neural circuits engaged by the task (i.e. those recruited during kinesthetic motor imagery) rather than inducing global synaptic changes detectable at rest.

Disclosures: T. Fujimaki: None. **S. Iwama:** None. **M. Takemi:** 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..

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP040.02/LBP033

Topic: F.05. Brain-Machine Interface

Title: Chronic preclinical evaluation of in vivo reliability of a novel high density intracortical brain-computer interface

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Abstract: Brain-computer interfaces (BCIs) have the potential to provide life-changing restoration of function to people with disabilities. Early demonstrations in pilot clinical trials have enabled speech, typing, handwriting, cursor control, and digital device control. The highest performing of these systems used intracortical electrode arrays implanted in motor areas; however, these research devices were not optimized for clinical deployment and lost signal fidelity after a few years. We designed, built, and tested a novel intracortical microelectrode platform demonstrating multi-year in vivo stability to serve as a platform for next-generation BCI therapies. Here, we present the results of 2 in vivo electrophysiology studies in ovine

auditory cortex that evaluate the potential of this system for clinical adoption.
The first study reports three years of longitudinal testing of the novel intracortical microelectrode array. The second study is a prospective evaluation of the functionality and reliability of the BCI system, incorporating an updated microelectrode array designed for early feasibility studies in human clinical trials. To assess the stability of clinically relevant neural features required for high-performance intracortical BCI applications, we tracked longitudinal neural signal metrics including spike signal-to-noise ratio (SNR) and firing rates, and quantified information throughput by decoding acoustic tone frequencies.
In the first study, 2 sheep were implanted in auditory cortex with a high-density intracortical microelectrode array with similar electrode count and density to the final finished device. Over 3 years, we have observed no electrode array migration, the animals are healthy, the recorded neural signals remain stable (with spiking SNR > 4), and up to 19 tone frequencies continue to be reliably decoded (63% ± 1.2% and 78% ± 1.9% accuracy; chance 5.3%). In the second study, 6 sheep were implanted with the fully implantable system for more than 10 months (ongoing). Spiking SNR ranged from 4.6 ± 0.02 to 5.2 ± 0.03, and accuracy of decoding among 7 tones ranged from 73% ± 1.4% to 92% ± 1.5% (chance 14%). Spatial maps of the neural features from tone modulation were stable, further supporting implant stability. Across the 6 animals, an average of >90% of channels sustained stable functionality throughout implantation for >10 months.
Together, these preclinical in vivo results support long-lasting reliability of neural feature recording using this device, showing promise for long-term robustness of BCI applications in future clinical trials.

Disclosures: **M. Trumpis:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **S.M. Perkins:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **B. Jarosiewicz:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc., Neuralink, Corp., Neuropace, Inc. **A. Patel:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **M.E. Reitman:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **A. Weiss:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **B. Kerr:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **A. Tadic:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **D. Yan:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **D. Savacool:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership

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Late-Breaking Poster

LBP040: F.05. Brain-Machine Interface

Location: SDCC Hall B

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

Program #/Poster #: LBP040.03/LBP034

Topic: F.05. Brain-Machine Interface

Title: Information transfer rate exceeds 200 bits/second in a high-density intracortical brain-computer interface

Authors: *S. M. PERKINS, M. TRUMPIS, M. E. REITMAN, B. JAROSIEWICZ, A. PATEL, A. WEISS, K. NISHIMURA, M. R. ANGLE, S. QIAO, V. GILJA;
Paradromics, Inc., Austin, TX

Abstract: Brain-computer interfaces (BCIs) extract information about brain state to drive actions. The information transfer rate (ITR), measured in bits per second (BPS), captures both the speed and accuracy of this extraction. Although some BCI applications are low bandwidth (e.g., mouse point-and-click), many involve complex behaviors that are varied and temporally complex, like speech synthesis, making a high ITR a prerequisite for strong performance. We designed a benchmarking paradigm to evaluate the ITR of BCI systems and applied it to a novel, fully implanted BCI system. The system uses a high-density intracortical microelectrode array, with wireless power and fast data transmission (~1 ms device delay). The paradigm sends information into the brain by playing tone sequences to sheep implanted with the BCI system, then decodes those sequences from neural activity in the auditory cortex. This treats the brain and BCI as a noisy communication channel where ITR is computed from the mutual information between the acoustic inputs and the decoded outputs. ITR can be limited by (1) task complexity, (2) neural responsiveness, (3) recording hardware, and (4) downstream signal processing and decoding. As our intent was to benchmark the BCI system (3 and 4), we made design choices to

maximize (1) and (2) so that measured ITRs would better reflect the BCI system's limitations. We generated an information-rich input by playing rapid sequences of pure tones (100 tones/second, 14 unique frequencies). The tone pacing and frequencies were optimized based on neural selectivity, theoretical channel capacity, and empirical ITR experimentation. We trained a neural network to classify tone frequency from sequences of binned neural features (spike counts and spike-band power) and applied it to held-out data. Across two sheep, the highest offline ITR achieved to date, ~9 months post-implantation, was 212 BPS, with a 5 ms bin size. ITR was dependent on the data aggregation window (bin size x sequence length), but remained high for small windows (e.g., >100 BPS for a 5 ms window) . This suggests that fine-timescale neural dynamics convey information in this task, and that the BCI system was able to capture them. The achieved ITR (212 BPS) exceeds estimated ITRs needed for language encoding (~40 BPS) and speech sound encoding (e.g., FocalCodec: ~160 BPS). The achieved ITR is not an upper bound for the system, nor does this benchmark guarantee the rate will translate to other applications. However, it demonstrates that the BCI system is capable of decoding information from neural activity with exceptional speed and accuracy, supporting the potential for translation to highly advanced BCI applications.

Disclosures: S.M. Perkins: A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **M. Trumpis:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **M.E. Reitman:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **B. Jarosiewicz:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc., Neuralink, Corp., NeuroPace, Inc. **A. Patel:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **A. Weiss:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **K. Nishimura:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **M.R. Angle:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **S. Qiao:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc. **V. Gilja:** A. Employment/Salary (full or part-time); Paradromics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Paradromics, Inc., Neuralink, Corp..

Late-Breaking Poster

LBP040: F.05. Brain-Machine Interface

Location: SDCC Hall B

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

Program #/Poster #: LBP040.04/LBP035

Topic: F.05. Brain-Machine Interface

Support: Progetto BioInterNect (PR23-PAS-P2)

Title: Swine pudendal nerve intraneural stimulation enables selective neuromodulation of urethral and anal external sphincters

Authors: *F. CASTELLANI[1,2], A. GIANNOTTI[2], N. CEYLAN[3], C. DI FRANCO[3], K. GABISONIA[2], S. MUSCO[4], G. DEL POPOLO[4], A. BRIGANTI[3], V. MIRAGLIOTTA[3], S. MICERA[5,2];
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Abstract: Lower urinary tract dysfunctions, leading to incontinence or urinary retention, profoundly impair quality of life. Current neuromodulation therapies, such as sacral or posterior tibial nerve stimulation, typically rely on lead or needle electrodes that lack selectivity, i.e. the capability to precisely stimulate portions of the nerve, often causing off-target effects and limiting efficacy.
To address this limitation, we investigated Transverse Intrafascicular Multichannel Electrode (TIME) in the pudendal nerve of the swine, a relevant model for urinary tract neuromodulation studies (Giannotti et al., 2024). The pudendal nerve is a promising alternative to common stimulation sites as it carries afferent signals of bladder filling and efferent commands to the external urethral and anal sphincters, enabling direct modulation of continence and micturition reflex (Ouyang et al., 2022).
In this study, two male farm pigs (Sus Scrofa Domesticus, 35-40 kg, 3-4 months old) underwent transgluteal exposure of the pudendal nerve, followed by implantation of a 16-channel TIME. During the first experiment, the electrode was implanted proximally, about 2 cm before trunk consolidation, whereas in the second it was placed more distally, 1 cm beyond the convergence of sacral contributions. Biphasic, cathodic-first pulses (200 μs width, 10-600 μA, 3 Hz) were delivered, while electromyographic activity from the external urethral sphincter (EUS) and external anal sphincter (EAS) was recorded using needle electrodes. Normalized recruitment curves were derived for each muscle, and selectivity was quantified as their maximum difference, yielding values constrained between -1 and +1 to indicate greater recruitment of the EAS or EUS, respectively.
Proximal stimulation selectively recruited the EAS, with all 16 active sites yielding selectivity values between -0.28 and -0.68. In contrast, during distal stimulation only 9 sites were selective for the EAS (-0.11 to -0.87) and the rest for the EUS (+0.54 to +0.57).

These findings suggest the presence of a functional fascicular gradient along the pudendal nerve that can be leveraged to selectively modulate key effectors of urinary and fecal continence, highlighting the need for further anatomical and functional studies. Our results provide a foundation for refined neuroprosthetic strategies targeting lower urinary tract control via the pudendal nerve. Importantly, the high translational potential of these outcomes underscores their relevance for clinical applications in patients with neurogenic bladder or spinal cord injury.

Disclosures: F. Castellani: None. **A. Giannotti:** None. **N. Ceylan:** None. **C. Di Franco:** None. **K. Gabisonia:** None. **S. Musco:** None. **G. Del Popolo:** None. **A. Briganti:** None. **V. Miragliotta:** None. **S. Micera:** None.

Late-Breaking Poster

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Topic: F.05. Brain-Machine Interface

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project MNESYS (PE0000006) – A Multiscale integrated approach to the study of the nervous system in health and disease (DN. 1553 11.10.2022)
PRIN2022–2022BK2NPS

Title: Multi-horizon neural decoding enables delay-free, biologically plausible kinematic forecasts for brain-computer interfaces

Authors: *R. BONINI[1], M. FILIPPINI[1,2], M. DE VITIS[1], F. E. VACCARI[1], P. FATTORI[1,2]; [1]Biomedical and Neuromotor Sciences, University of Bologna, Bologna, Italy; [2]Alma Mater Research Institute for Human-Centered Artificial Intelligence, University of Bologna, Bologna, Italy

Abstract: Artificial Neural Network-based neural decoders often produce noisy trajectories or use non-causal filtering that introduces latency. Here, we introduce HorizonDilateANN (HDANN), a compact causal neural decoder trained with the sequence-aware DILATE loss to generate smooth, biologically plausible forecasts in brain-computer interfaces (BCIs). HDANN maps summed spikes over a causal window to future velocity sequences (horizons); in buffer mode horizons are fused by Horizon-Averaging (HA), i.e., the output is the mean of overlapping past predictions that target the present time step. Alternatively, one can select a single horizon element per step, introducing a positive neural-kinematics delay. In **Study 1**, we used the NeuroBench suite (https://arxiv.org/abs/2304.04640), which provides six multi-unit activity recordings (4 ms time bins) from two nonhuman primates performing continuous 2D reaching movements on a monitor: Indy (96 channels, primary motor cortex array) and Loco (192 channels, primary motor and somatosensory arrays). Subject-specific Bayesian optimization accounted for implant differences. Compared to the NeuroBench ANN2D baseline,

HDANN+HA reduced or matched dense-layer parameter counts (− 21.09% for Indy, + 2.06% for Loco) and multiply-accumulate operations (− 20.18% for Indy, − 1.75% for Loco) while improving mean test R^2 to **0.600** (**+ 4.14%**). In **Study 2**, to assess generalization in a naturalistic scenario, we recorded from the dorsal premotor area F2 of a *macaca fascicularis* performing a delayed reaching task to 9 targets (three depths × three directions) in 3D space. Wrist kinematics were reconstructed with a markerless motion capture system (DeepLabCut). On trial-based single-unit data (10 ms bins), HDANN achieved **R^2=0.867 ± 0.008** (recording A: 70 units, 180 trials) and **R^2=0.755 ± 0.021** (recording B: 45 units, 117 trials) under five-fold target-stratified cross-validation. Analyses of full horizons and single-horizon elements show HDANN generates plausible trajectories surpassing classical instantaneous neural-kinematics mappings. In Study 1, frequency- and time-domain analyses of absolute error (averaged across Vx and Vy) using five metrics—spectral centroid, entropy, slope, RMS acceleration, and total variation—showed HDANN+HA predictions were significantly closer to ground truth than ANN2D (paired Wilcoxon signed-rank test with Benjamini-Hochberg correction; **N=6**; FDR-adjusted **q=0.031** per metric; large effect sizes, **|d|=2.44 - 8.80**). These findings support HDANN as a compact method for smooth, biologically plausible real-time neural decoding, eliminating the need for post-hoc filtering.

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Late-Breaking Poster

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Program #/Poster #: LBP040.06/LBP037

Topic: F.05. Brain-Machine Interface

Support: NIH Grant UH3NS120191
NIH Grant R90DA060340

Title: Comparing machine learning models to assess channel count effects on motor decoding in an endovascular BCI

Authors: *M. TODESCO[1], A. K. FELDMAN[2], L. PAROLA[3], K. KACKER[4], N. CHETTY[3], D. J. WEBER[5];
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Abstract: Brain-computer interfaces (BCIs) enable people with paralysis to interact with their surroundings using only their brain. Endovascular BCI is a minimally invasive approach to BCI

that does not require craniotomy, and placement of stent electrode arrays in the superior sagittal sinus enables bilateral recording of neural activity from the primary motor cortex. It is essential to to understand the optimal machine learning approach for decoding motor intent using this endovascular approach. Previous work explored linear decoding strategies (Kacker et al, 2025); in this analysis, we compare the classification accuracy of nonlinear shallow learning models such as support vector machine (SVM), k-nearest neighbors (k-NN), and random forest (RF), and a deep learning approach using a convolutional neural network (CNN). Additionally, we aim to identify the point at which adding more electrodes no longer yields significant performance gains for classifying motor intent.Here, we present data from one participant from an early feasibility clinical trial in the United States (ClinicalTrials.gov, NCT05035823). The participant was prompted to attempt movement of either their left ankle, right ankle, or both ankles. Classifier models were trained to categorize the neural activity as belonging to one of the three movement classes or rest. To train the shallow learning models, we calculated features by bandpass filtering the signal to extract neural activity in the high- (70-200 Hz) and low-gamma (30-70 Hz) range, then computed the mean amplitude of the signal in 500-ms windows. To train the CNN, entire segments of high- and low-gamma data were used as inputs without windowing or feature extraction. All models were trained on 80% of the data, then tested on the remaining 20% of the data. The accuracy of each model was compared across all combinations of channels from 1-13 channels.We determined that the k-NN and RF models achieved high accuracy at all channel combinations, outperforming both the polynomial SVM and CNN models, and that the k-NN classification accuracy did not improve with the inclusion of additional channels beyond 6 electrodes. Future work might involve determining which machine learning models can achieve high-accuracy classification with input from fewer electrodes.

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Late-Breaking Poster

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Location: SDCC Hall B

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Topic: F.05. Brain-Machine Interface

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Searle Scholars
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ALS Pilot Clinical Trial Award (AL220043) from the Office of the Assistant Secretary of Defense for Health Affairs, CDMRP

Title: Restoring conversational communication in pontine stroke-induced dysarthria using an intracortical brain-computer interface

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Abstract: Restoring communication for people with dysarthria secondary to pontine stroke remains a critical challenge. Intracortical brain-computer interfaces (iBCIs) have demonstrated great potential for speech restoration in people with amyotrophic lateral sclerosis (ALS), with word error rates (WERs) between 1-24% with a 125,000-word vocabulary. In stroke, electrocorticography (ECoG) based BCIs have hinted at similar possibilities, but with higher WERs (~25% on a 1,024-word vocabulary). Whether the potential performance of iBCIs extends to people with pontine stroke-induced dysarthria remains unclear. We placed four 64-channel microelectrode arrays in the precentral gyrus of BrainGate2 clinical trial participant T16 (ClinicalTrials.gov: NCT00912041), a 54-year-old woman with dysarthria secondary to a pontine stroke. One array targeted ventral Brodmann's area 6v, associated with orofacial motor control. We recorded neural activity as T16 mimed (mouthed without vocalization) sentences from a large vocabulary, and trained a neural network decoder to predict phoneme probabilities in 80-ms timesteps from electrode spiking rates and spike-band power. A 125,000-word, 5-gram language model (LM) converted these probabilities into word sequence hypotheses, which were rescored with a large language model (OPT-6.7b) to select the final transcript. Using this architecture, we achieved a median phoneme error rate (PER) of 21.4% (before LM assistance) and a median WER of 21.5% at 29.6 words per minute across 26 sessions spanning 179 days. On the 1,024-word vocabulary previously used in ECoG studies, our approach achieves 7.3% median WER. We found that despite day-to-day recording instabilities, decoding accuracies have remained stable after more than a year of implantation, an important demonstration of the longevity of speech-related iBCIs. Furthermore, we compensated for instabilities by beginning each research session by fine-tuning the decoder with ~50 sentences, which rapidly restored high-performance decoding in the new session. Finally, we established that this framework can generalize beyond cue repetition, enabling T16 to communicate, via miming, in a question-and-answer setting with a WER of 36.2%. These results demonstrate that spiking activity from a single array can decode text more accurately than ECoG in pontine stroke and is comparable to early speech iBCIs in ALS. Further, recent ALS iBCIs have achieved ~1% WER with 4 times more electrodes in the speech motor cortex; together with prior evidence of an inverse PER-electrode relationship, this indicates that increased intracortical coverage could further lower WER in pontine stroke.

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diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. **L.R. Hochberg:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Ability Neuro, Neuralink, Neurobionics, Paradromics, Precision Neuro, Synchron, Reach Neuro, Blackrock Neurotech. F. Consulting Fees (e.g., advisory boards); Speak Your Mind Foundation – Non-compensated member of the Board of Directors. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Stanford, patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Sonera. **D. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); patent applications related to speech BCI owned by the Regents of the University of California. F. Consulting Fees (e.g., advisory boards); Paradromics Inc.. **N. Au Yong:** None. **C. Pandarinath:** A. Employment/Salary (full or part-time); Meta Reality Labs.

Late-Breaking Poster

LBP040: F.05. Brain-Machine Interface

Location: SDCC Hall B

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

Program #/Poster #: LBP040.08/LBP039

Topic: F.05. Brain-Machine Interface

Support: R01NS121079 (National Institute of Neurological Disorders and Stroke, NIH)

Title: Stabilizing iBCI Decoders Using Pseudo-Trials Extracted from Unstructured Behavior

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Abstract: Intracortical brain-computer interfaces (iBCIs) translate neural activity into control signals for external devices. Long-term use is limited by neural signal instability, which degrades performance and necessitates frequent recalibration. Stabilization methods that align activity to a stable neural manifold can automate this, but usually rely on structured, trial-based tasks. Here we test whether unstructured BCI use can provide sufficient data for decoder stabilization and how performance compares to standard approaches.
Data were collected from three participants (P2, P3, P4) with intracortical BCIs in motor cortex as part of an ongoing clinical trial (NCT01894802). Sessions comprised pre-session observation calibration, closed-loop calibration, structured cursor task, unstructured BCI use, and post-session observation. During observation calibration participants imagined following along with a computer cursor and a BCI decoder was trained on these data. Unstructured use included digital painting and playing video games. “Pseudo-trials” (fixed-length segments of unstructured cursor activity) were extracted to sample movement directions. Factor analysis defined each day’s neural manifold, which we aligned to a multi-day reference (18-57 structured sessions) via

Generalized Procrustes Analysis (GPA). Fixed decoding weights mapped activity to kinematics. The same procedure was applied to pre-session observation data. Decoder performance was evaluated offline for four decoders: two stabilized (structured vs. unstructured) and two unstabilized (same-day vs. multi-day).
We analyzed unstructured sessions from P2 (n=9), P3 (n=5), and P4 (n=3). Pseudo-trial counts (240 ± 89) exceeded structured calibration (40 trials). A one-way ANOVA showed a main effect of decoder type on angular error ($F(3,6)=59.85$, $p=.0001$). Structured (30.6 ± 7.5°), same-day (31.2 ± 7.6°), and unstructured stabilization (58.5 ± 2.7°) performed better than the multi-day decoder (88.7 ± 4.3°). Post hoc tests confirmed unstructured stabilization differed from the multi-day decoder ($p=0.02$) but not from structured-task ($p=.21$) or same-day observation ($p=.25$). The multi-day decoder also differed from structured-task stabilization ($p=0.03$). No other comparisons were significant (all $p \geq 0.05$). These results show unstructured stabilization matches standard approaches while outperforming the unstable multi-day decoder, highlighting online BCI use as a path to real-time, at-home stabilization.

Disclosures: J. Steele: None. **J.L. Collinger:** None. **W. Hockeimer:** None. **B. Dekleva:** None.

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Topic: F.05. Brain-Machine Interface

Support: NIMH Grant R01MH121350
IBACS (Institute for the Brain and Cognitive Sciences)

Title: Decoding lever pressing behavior from multi-area local field potentials across drug, sex, and task conditions

Authors: *A. MANKILI[1], A. ECEVITOGLU[2], G. EDELSTEIN[3], R. A. ROTOLO[4], J. J. CHROBAK[5], J. D. SALAMONE[6], I. H. STEVENSON[7];
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Abstract: A major question in systems neuroscience is how oscillatory activity in multiple brain regions is coordinated during operant behavior and how neural activity changes under different task conditions. In this study, we use a decoding approach to predict lever pressing behavior in rats from local field potentials (LFP) recorded bilaterally in the hippocampus, nucleus accumbens, and prefrontal cortex. We extract LFP features for band power and peak frequency and predict behavior across all animals and conditions with a Poisson Generalized Linear Mixed

Effects Model (GLME). We use data from both male and female rats performing either fixed-ratio 40 (FR40) or progressive (PROG) operant lever-pressing tasks, under vehicle (VEH) or tetrabenazine (TBZ), a VMAT-2 inhibitor that depletes dopamine and induces depressive-like motivational dysfunction. Using stepwise regression and across-animal cross-validation, we find that we can accurately predict lever pressing from multi-region LFP on a timescale of seconds with >40% variance explained, and these results are robust across drug, sex, and task conditions. We then consider whether LFP features can be used to decode an abstract task representation: the number of presses until the next reinforcer. Here we find LFP features can also predict this representation above chance level, but that the task representation decoding relies on different LFP features for prediction than those for lever pressing. Altogether, these results suggest that there are robust distributed patterns of LFP that predict immediate lever-pressing behavior under multiple drug, task, and sex conditions and that there may be similar patterns for more abstract task features.

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Late-Breaking Poster

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Program #/Poster #: LBP040.10/LBP041

Topic: F.05. Brain-Machine Interface

Support: Bavarian Hightech Agenda

Title: Preventing Abandonment and Unwanted Explantation in Clinical Neurotechnology: A Policy and Legal Framework

Authors: *M. IENCA;
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Abstract: Unwanted explantation—the removal of implanted medical technologies against patients' wishes and in the absence of medical necessity—has become a pressing issue across psychiatry and neurology. Devices such as deep brain stimulation (DBS) systems, cortical stimulators, and psychiatric brain-computer interfaces (BCIs) can provide sustained therapeutic benefits for disorders ranging from major depression and obsessive-compulsive disorder to Parkinson's disease, epilepsy, and dystonia. Yet their continued efficacy depends on uninterrupted technical maintenance, institutional support, and financial coverage. When these supports collapse (for instance through trial termination, withdrawal of reimbursement, or company bankruptcy) patients may face the forced removal of devices they perceive as essential to their well-being and identity. Existing legal frameworks, grounded in contract law, frequently privilege institutional and commercial interests over patient needs, thereby permitting explantation even when patients explicitly request device retention. The stakes are especially

high in psychiatry, where implants may stabilize emotion regulation, executive function, or agency, but equally consequential in neurology, where they preserve motor control, prevent seizures, or sustain communicative capacity. Removal can therefore precipitate severe therapeutic regression, psychological distress, loss of independence, and disruption of personal identity. Examining emblematic cases of abandonment-related explantation across psychiatric and neurological contexts, this article reveals how regulatory systems remain ill-equipped to safeguard patient autonomy, continuity of care, and protection from harm. To address these deficiencies, we propose a ten-point policy and legal framework designed to ensure long-term patient protection. Central measures include: recognizing device continuity as essential medical care; requiring continuity plans as a condition of regulatory approval; establishing insurance schemes and contingency funds to cover maintenance when sponsors withdraw; enforcing interoperability standards to facilitate transfer of care; and advancing neurorights to enshrine protections against technological disenfranchisement. Collectively, these measures reposition implanted neurotechnologies not as disposable experimental goods but as durable components of therapeutic identity, reframing unwanted explantation as a preventable form of harm that demands proactive legal, institutional, and ethical safeguards.

Disclosures: M. Ienca: A. Employment/Salary (full or part-time); Technical University of Munich.

Late-Breaking Poster

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Topic: F.05. Brain-Machine Interface

Support: Michael J Fox Foundation MJFF-010435
NIH R01NS130183
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Tianqiao and Chrissy Chen Institute

Title: Classification of at-home movement states using cortical-pallidal neural activity in Parkinson's disease

Authors: *R. RAMESH[1], H. FEKRI AZGOMI[2], K. H. LOUIE[2], J. BALAKID[2], J. MARKS[2], D. D. WANG[2];
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Abstract: While conventional deep brain stimulation (DBS) effectively treats appendicular symptoms of Parkinson’s disease (PD) such as tremor, it inadequately addresses gait impairments due to its continuous, activity-agnostic parameters. Adaptive DBS (aDBS), which modulates stimulation based on real-time neural states, shows promise but lacks reliable neural

biomarkers capable of classifying specific movement states in naturalistic settings. This project leverages chronic at-home cortical-pallidal recordings in PD patients to classify key locomotor states: walking vs non-walking and turning vs straight walking. Local field potentials from the globus pallidus (GP) and electrocorticography from the premotor (PM) and primary motor (M1) cortices were recorded from four PD patients (2M/2F, age 62-68) with unilateral (n=2) or bilateral (n=2) bidirectional neurostimulators (Summit RC+S, Medtronic Inc). Wearable ankle sensors (Rover, Sensoplex Inc) tracked at-home movement. Spectral analysis was performed on 10-second walking/non-walking epochs and 1-second turning/straight walking epochs. Logistic regression and linear discriminant analysis (LDA) models classified movement states using power within canonical and custom frequency bands of variable widths (1-50Hz). Random forest feature selection identified walking/non-walking biomarkers compatible with Summit RC+S on-device classification; decoding performance was assessed with *in silico* simulations. Across over 80 hours of data, M1 alpha (8-13Hz) and beta (13-30Hz) power decreased during walking versus rest in all hemispheres ($p<0.001$). M1 and PM theta (4-8Hz), alpha, and beta power decreased during turning versus straight walking in all but one hemisphere ($p<0.01$). Pallidal features were most important for walking/non-walking classification, while cortical features predominated for turning/straight walking. Walking/non-walking LDA classifiers achieved strong performance (AUC:0.77-0.96; $p<0.001$), with simulations of closed-loop on-board classification demonstrating above-chance decoding (AUC:0.63-0.85; $p<0.001$).These results support the hypothesis that cortical-basal ganglia oscillations are modulated by movement state and establish a pipeline for identifying personalized movement biomarkers from long-term naturalistic neural-kinematic recordings. These neural signatures will enable adaptive DBS algorithms to automatically switch to gait-optimized stimulation parameters during specific movement states, better addressing both appendicular and gait-related PD symptoms.

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Late-Breaking Poster

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

Program #/Poster #: LBP040.12/LBP043

Topic: F.05. Brain-Machine Interface

Title: Leveraging neural dynamics to reduce noise in neural recordings for brain-computer interfaces

Authors: *C. CIUCCI[1,2], M. PIZZINGA[3], S. MICERA[4,2,3], E. RUSSO[5];
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Abstract: A challenge in developing brain-computer interfaces is the presence of noise in neural recordings. Noise may arise from hardware limitations or from fluctuations in the subject's internal state, both of which occur independently of the intended motor command. This raises a key question: can we improve the quality of noisy neural signals by exploiting their underlying temporal dynamics? To address this issue, we developed a stabilization framework that integrates nonlinear dynamical models of neural activity with the recorded signal. Specifically, we trained a latent nonlinear recurrent neural network to reconstruct and generate the observed neural signals. To estimate the neural state of a subject at a target time point, the model was initialized with recordings from past time steps and iterated forward along the dynamical map, yielding multiple predictions of the same state. Since experimental recordings are affected by temporally varying noise, combining these estimates yielded a more accurate reconstruction of the underlying neural state. We implemented two strategies to combine model-based predictions with observations. In the *linear stabilization* approach, the recorded signal is linearly combined with model predictions from multiple past time points. In the *uncertainty-weighted* stabilization approach, a variational autoencoder framework estimates both the latent state and its covariance at each time step, where the covariance reflects the reliability of the observation relative to the learned neural manifold. Model predictions are then integrated using inverse covariance weighting, such that more reliable estimates contribute more strongly to the stabilized signal.We validated both methods on simulated data and benchmarked them against autoregressive (AR) models. Results show that both stabilization strategies markedly reduce noise, improving the prediction of the underlying state of the system. Preliminary analyses further suggest that the linear approach performs best under stationary noise conditions, while the uncertainty-weighted strategy is more effective when noise levels fluctuate, significantly outperforming both the linear stabilization and AR models. By explicitly leveraging latent neural dynamics, our framework provides a principled and scalable solution for stabilizing noisy neural recordings, with the potential to enhance the precision and reliability of BCI control in real-world applications.

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Late-Breaking Poster

LBP040: F.05. Brain-Machine Interface

Location: SDCC Hall B

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

Program #/Poster #: LBP040.13/LBP044

Topic: F.05. Brain-Machine Interface

Title: Federated learning for privacy-preserving SSVEP-Based biometric authentication in BCIs

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Abstract: Brain-computer interfaces require secure authentication that protects user privacy while maintaining high accuracy. Steady-state visual evoked potentials (SSVEPs) offer unique

biometric signatures, but centralized neural data collection raises privacy concerns. We developed a federated learning framework for SSVEP authentication that preserves privacy through distributed training. Twenty-four participants (YSU-CS dataset) viewed 8 flickering stimuli (8-15 Hz) across 4 sessions. EEG was recorded from 8 occipital-parietal channels at 5,000 Hz, downsampled to 250 Hz, finally a bandpass (7-70 Hz) and notch (50 Hz) filtering was applied for preprocessing. We implemented federated EEGNet with a novel three-tier RETAIN-ALIGNADAPT strategy: foundational temporal convolution layers RETAIN participant-specific neural signatures by remaining frozen without global aggregation, intermediate spatial filtering layers ALIGN through complete parameter replacement from the global model to capture universal SSVEP response patterns, and classification layers ADAPT via weighted fusion combining local personalized features with global discriminative knowledge. The protocol used 25 global rounds with 5 local epochs per round, batch size 32, learning rate 0.001, and Adam optimizer. Validation included traditional splits, progressive leave-one-blockout (LOBO) with 3-12 blocks, sliding window LOBO, and leave-three-session-out testing. Traditional split achieved 100% accuracy. Progressive LOBO showed 99.72±0.39% (3 blocks), improving to 99.93±0.23% (12 blocks) with perfect success across 75 folds. Sliding window maintained 99.93±0.23% mean accuracy with 7/12 windows at 100%. Cross-session generalization achieved 99.93±0.04%, with Session-1 training yielding perfect authentication on later sessions. The hybrid synchronization enables collaborative learning while maintaining individual neural signatures for biometric identification. Consistent performance across 135+ folds demonstrates SSVEP features as robust biometric identifiers for privacy-critical BCI applications without centralized data collection.

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Topic: F.05. Brain-Machine Interface

Support: NSF EFRI 2223822

Title: Compositional Decoding of Neural Activity Enhances Generalization in BCIs

Authors: *S. NARASIMHA, J. HUANG, R. SRISTI, V. GILJA, G. MISHNE;
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Abstract: Most brain-computer interface (BCI) systems are trained in controlled settings on a small set of constrained, repetitive and well-characterized instructed behaviors. While effective in such settings, these systems often fail to generalize to real-world settings, where behavior is variable, context-sensitive, and structurally complex. Yet, behavior can be decomposed into reusable, overlapping motifs, for example, sequential combinations of phonemes form words and in handwriting, strokes form characters. We hypothesize that compositionality can enable neural

decoders to be more sample-efficient in capturing variability, particularly when generalizing to novel combinations of familiar motifs. Motivated by recent Brain-to-Text BCI via attempted speech or handwriting, we design a compositional neural decoder for BCI.
Despite explicit behavior not being observed in human BCI studies, we find that neural activity for different instructed behaviors carries a clear signature of motif compositionality; distinct temporal segments across different behavior classes reuse similar neural patterns. Leveraging this compositional structure, we propose a temporal model that jointly predicts both the compositional motifs (strokes/phonemes) and the behavior class (characters/words) from neural activity. The model is trained with a multi-objective loss, comprising a motif prediction branch, and a behavior prediction branch that integrates motif outputs. This hierarchical supervision guides the decoder to leverage the compositional structure while maintaining behavior prediction performance. We evaluate the models on intracortical recordings from human participants performing attempted handwriting of single letters or attempted speech of words (Willett 2021, 2023).
We benchmark against a capacity-matched baseline trained solely for behavior classification. On a 50-50 train-test split, the performances are comparable, although the compositional models exhibit a trade-off between the representations for motif and behavioral class prediction. To assess generalization, we conduct a two-shot learning experiment in which for one of the behavioral classes only two trials are included in training (i.e. all other trials for that class are held out), while maintaining the 50-50 split for the remaining classes. In this setting, the compositional model consistently outperforms the baseline on the held-out class. These results demonstrate that motif-level decoding enhances performance on infrequent behaviors and compositionality improves generalization to novel settings.

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Late-Breaking Poster

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Carnegie Mellon University's Center for Machine Learning and Health Fellowship (YD)
National Institutes of Health grant T32EB029365 (MK; PI: BH)

Title: Training effects on real-time robotic finger control using an electroencephalography-based brain-computer interface in naïve stroke survivors

Authors: *Y. DING[1], M. KARRENBACH[2], B. HE[1];
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Abstract: Restoring hand function is a priority for people with motor impairment. Noninvasive brain-computer interfaces (BCIs) offer an accessible solution to augment function by translating neural intent into robotic assistance [1]. EEG-based, precise, naturalistic control of individual robotic fingers was recently introduced and demonstrated in BCI responders [2]. Yet noninvasive finger-level control has not been shown in BCI-naïve populations. In addition, whether stroke-affected individuals can achieve reliable, individual-finger control using motor imagery (MI) remains unknown.

Nine stroke-affected participants without previous BCI experience completed two limb-level MI training sessions (n = 9), followed by two offline finger-MI sessions without feedback (n = 8) and five online sessions with real-time robotic feedback (n = 5). Online sessions included binary (thumb vs. pinky) and ternary (thumb, index, vs. pinky) classification of imagined finger movements. Participants controlled the robotic hand with their stroke-affected hand when applicable, or with their dominant hand if no limb was affected.

After five online sessions and model fine-tuning, mean real-time decoding accuracies were 76.50% for two-finger MI and 55.16% for three-finger MI. Accuracy improved significantly across sessions (two-class: $F = 8.13$, $p < 1e\text{-}4$; three-class: $F = 3.42$, $p = 0.01$), whereas model fine-tuning did not significantly enhance online finger performance (two-class: $F = 0.56$, $p = 0.45$; three-class: $F = 1.03$, $p = 0.31$). Performance was comparable between dominant vs non-dominant hand use and affected vs unaffected hand use. Limb-level and finger-level MI performance were positively correlated (Pearson $r = 0.65$). Contralesional event-related desynchronization was observed in the affected-hand group.

These results demonstrate the feasibility of achieving finger-level BCI robotic control with a noninvasive system in BCI-naïve, stroke-affected individuals after a small number of training sessions. The ability to control with the non-dominant or stroke-affected hand, together with robust session-wise gains, supports the translational potential of finger-level BCIs for robotic assistance in post-stroke rehabilitation.

References:

[1] Edelman, B. J., Zhang, S., Schalk, G., Brunner, P., Müller-Putz, G., Guan, C., & He, B. (2024). Non-invasive brain-computer interfaces: state of the art and trends. *IEEE reviews in biomedical engineering*.

[2] Ding, Y., Udompanyawit, C., Zhang, Y., & He, B. (2025). EEG-based brain-computer interface enables real-time robotic hand control at individual finger level. *Nature Communications*, *16*(1), 1-20.

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Late-Breaking Poster

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Topic: F.05. Brain-Machine Interface

Support: NYSDOH SCIRB C37718GG
Feinstein Institutes for Medical Research, Northwell Health

Title: Towards restoring function in complete tetraplegia via iBCI-mediated spinal cord and neuromuscular stimulation

Authors: *I. A. ROSENTHAL[1], A. JANGAM[1], Z. ELIAS[1], E. IBROCI[1], C. MAFFEI[1], S. CHANDRASEKARAN[1], D. GRIFFIN[2], S. BICKEL[1], N. BEN-SHALOM[3], A. B. STEIN[5], A. D. MEHTA[4], C. BOUTON[1];
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Abstract: Transcutaneous spinal cord stimulation (tSCS) has the potential to improve motor and sensory function in individuals with spinal cord injury (SCI). However, improvements are often limited, particularly in complete injuries. The effectiveness of tSCS may potentially improve if stimulation is delivered within a closed-loop intracortical brain-computer interface (iBCI) system, which allows the user to learn to produce stronger, more specific motor commands by receiving feedback on their neural activity during motor actions. In a first-in-human study, a participant with tetraplegia (C4/C5 SCI) recovered bilateral biceps strength from tSCS delivered while performing an elbow flexion/extension task over 39 weeks. The gains in bicep strength were significant but did not reach pre-injury levels, and the participant did not regain triceps strength. Following this, tSCS was paired with an iBCI in a 17-week intervention. The iBCI used a LSTM regressor based on neural data from M1 and S1 microelectrode arrays (Blackrock Neurotech) to decode the magnitude and direction of elbow flexion/extension. The participant performed elbow extension and flexions in pairs, alternating between performing the cued action while viewing the regressor output and performing it while tSCS (250-300mA peak) was delivered to dorsal roots associated with biceps contraction (C5-C6) or triceps contraction (C6-C7). Although microelectrode arrays were implanted in cortical hand areas, the LSTM regressors consistently decoded elbow flexion/extension with an average correlation coefficient of 0.55 (std: 0.14). Neural activity was tuned to both the direction of the movement and the magnitude of the intended force. Relative to the baseline prior to iBCI-mediated tSCS, the participant exhibited a 20-30% increase in biceps strength bilaterally. However, there continued to be no significant changes in triceps strength on either side. Following this result, delivering iBCI-mediated neuromuscular stimulation simultaneously with iBCI-mediated tSCS is now being investigated as a mechanism to recover triceps strength. This work represents an important

proof-of-concept for advanced, combined iBCI-neurostimulation approaches to restore function in challenging, complete spinal cord injuries.

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Late-Breaking Poster

LBP040: F.05. Brain-Machine Interface

Location: SDCC Hall B

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

Program #/Poster #: LBP040.17/LBP048

Topic: F.05. Brain-Machine Interface

Support: NYSDOH SCIRB C37718GG
Feinstein Institutes for Medical Research

Title: Double Neural Bypass: Restoring cortically mediated upper-limb movement and sensation in complete tetraplegia

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Abstract: Spinal cord injury (SCI) is a leading cause of tetraplegia and regaining upper limb movement is consistently ranked as the highest priority. We demonstrated that an intracortical brain-computer interface (iBCI) linked to real-time muscle stimulation can restore hand function in complete tetraplegia. But, BCI-mediated sensorimotor restoration if often acute with persistent recovery remaining elusive. For this unmet need of persistent restoration of upper limb function

in individuals with complete SCI, we developed a 'double neural bypass' (DNB) approach - a hybrid system that can provide assistive and therapeutic benefits. It integrates a bidirectional iBCI to record and stimulate sensorimotor cortex, a stable neural decoder to infer user intentions, deep reinforcement learning (RL) for precision movements, and targeted transcutaneous spinal cord stimulation (tSCS) for promoting persistent recovery. In our first-in-human DNB clinical trial, we enrolled a participant with complete C4 sensory/C5 motor tetraplegia. Activity-based training with tSCS alone resulted in persistent increase in upper-limb strength by up to 89%. However, no significant increase in hand muscle strength, or tactile sensation in the distal arm was observed. To facilitate grasping and lifting of objects, we developed a 3D-printed low-profile active orthosis (AO) with an artificial tendon system. An LSTM decoder inferred grasping intention from neural activity while a deep RL agent modulated the AO grasp aperture based on real-time tactile force feedback. Using the BCI-AO system enabled the participant to grasp and lift hollow eggshells demonstrating real-time force control (87% success with RL, and 27% success without RL). Building on the motor gains obtained from tSCS therapy alone, the cortically mediated AO enabled the participant to successfully perform activities of daily living, such as drinking from a cup and self-feeding. Also, we hypothesized that pairing naturalistic S1 spatial activation with peripheral stimuli could promote short and/or long-term plasticity, potentially leading to persistent recovery of sensation. We delivered S1 stimulation with the same spatial pattern as the activity observed during imagined or physical touch - 'cortical mirroring' (CM). We observed that tactile accuracy and sensitivity on the right wrist significantly improved during the tSCS+CM intervention period. Thus, we show that combining a bidirectional iBCI with brain and spinal neuromodulatory approaches can enable functional and precision grasping tasks, while potentially unlocking persistent recovery of motor and sensory functions in the upper limb.

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Topic: F.05. Brain-Machine Interface

Support: NYSDOH SCIRB C37718GG
Feinstein Institutes for Medical Research

Title: Interhuman brain-body interfacing enables shared and cooperative sensorimotor function

Authors: *E. IBROCI[1], S. CHANDRASEKARAN[1], A. JANGAM[2], Z. ELIAS[1], D. FRIED[1], A. MILLER[2], D. GRIFFIN[3], S. BICKEL[1], N. BEN-SHALOM[4], A. B. STEIN[5], A. D. MEHTA[6], C. BOUTON[2];
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Abstract: Implanted brain-computer interfaces (BCIs) and brain-body interfaces (BBIs) have shown promise for restoring function after spinal cord injury (SCI), with research traditionally focused on the individual user and their rehabilitative goals. Here we demonstrate the feasibility of a cooperative 'human avatar' paradigm involving two individuals with tetraplegia, with one of them using an implanted BCI system to enhance functional recovery and foster mutual support. In this study, participant P1 (complete C5 SCI) used his BCI to wirelessly modulate targeted transcutaneous spinal cord stimulation (tSCS) and neuromuscular electrical stimulation (NMES) while the non-implanted participant P2 (incomplete C5 SCI) performed a motor task. The stimulation was delivered as P2 performed grasping, lifting, and pouring motions with a bottle. During this cooperative task, based on P2's verbal cues ("open", "close", "rest"), P1 used motor imagery that was decoded by an LSTM decoder in real-time to activate pre-defined NMES and tSCS stimulation patterns. Participants were seated face-to-face, allowing P1 to see P2's hand and performance across three 3-minute blocks. The goal of this paradigm was to collectively achieve functional goals while promoting plasticity and rehabilitation, and also potentially improving psychosocial well-being. BCI-mediated tSCS+NMES assisted pouring trails had a 63% success rate compared to 22% without assistance, in 8 sessions. Moreover, refining the communication strategies between the participants had a considerable effect, with the success rate in the assisted trials improving from 45% in the first five sessions to 94% in three subsequent sessions. These results highlight the importance of effective communication strategies for successful collaborative BCI control. Post-session qualitative feedback indicated positive experiences for both participants, suggesting that there is a psychometric impact of cooperative rehabilitation utilizing BCI and BBI technology. P1 reported a positive affective response from helping P2 perform the task, while P2 expressed increased motivation and enjoyment when working cooperatively. This novel paradigm investigated the feasibility of interhuman cortically mediated rehabilitation between individuals with SCI, exploring the potential for enhanced rehabilitation outcomes through cooperative engagement.

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Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP040.19/LBP050

Topic: F.05. Brain-Machine Interface

Support: Meta (Imperial-Meta Wearable Neural Interfaces Research Centre)
Inbrain Neuroelectronics

Title: Multidimensional motoneuron control using intramuscular microelectrode arrays in tetraplegic spinal cord injury

Authors: *A. GRISON[1], C. GIBBS[1], V. RAWJI[2], L. VILA[3], I. SZCZECH[2], R. VARGHESE[2], P. BRYAN[2], A. KUNDU[2], X. YANG[2], J. GALLEGO[1], D. FARINA[1];
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Abstract: Loss of hand function after spinal cord injury (SCI) severely impairs independence and quality of life[1]. While residual muscle activity recorded on the skin can provide intuitive control signals, in SCI it is often limited by low amplitude and poor signal-to-noise ratio. Here, we show that these limitations can be overcome by implanting 40-channel microelectrode arrays directly into forearm muscles.

To evaluate this approach, we first tested whether individual motoneuron activity could be detected in muscles with minimal or no visible contraction. Participants attempted flexion and extension of individual fingers, the thumb, and the wrist during ultrasound recordings of forearm muscles. Residual fibre contraction regions were identified, allowing strategic array placement so that all channels lay within contracting muscles (participant one: two arrays in extensors; participant two: one in a flexor, one in an extensor).

Using blind source separation methods[2], we detected up to 73 simultaneously active spinal motoneurons during attempted movements in two tetraplegic participants. Motoneurons were spatially distributed across the array according to their action potential waveforms. Even in the presence of spasticity or complete paralysis, both participants successfully modulated the firing rate of a single motoneuron to track trapezoidal and dynamic profiles. They combined these strategies to play Pong[3], controlling a paddle's vertical position via a single motoneuron. Both participants could switch between control strategies to move the vertical paddle and hold it in place to score points. Having identified pairs of independent motoneurons, we mapped two units to 2D cursor movements, enabling participant one to perform 2D navigation and reach targets.

As restoring voluntary hand use is a primary goal in SCI rehabilitation[4], we next mapped motoneuron activity to control a wearable soft exoskeleton that flexed fingers via motors and wires. By reassigning motoneurons to different motors, participant one performed distinct fingers and grasp types, enabling volitional grasp of objects such as a sponge and a pen using a tripod grip.

Our findings demonstrate the feasibility of an implantable microelectrode array system that uses residual motoneuron activity for control in SCI, with the potential to improve the quality of life for individuals with paralysis.

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[3] Pong - Wikipedia. https://wikipedia.org/wiki/Pong.
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Late-Breaking Poster

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Program #/Poster #: LBP040.20/LBP051

Topic: F.05. Brain-Machine Interface

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NSF CRCNS IIS-2113271

Title: A nonlinear dynamical model for optimal regulation of neural states

Authors: *D. TYULMANKOV[1], M. HEIDARI SORKHEHDIZAJ[1], E. BILGIN[2], E. ERTURK[2], M. M. SHANECHI[3];
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Abstract: Closed-loop regulation of neural activity can both help study causal interactions across brain networks and develop brain-computer interfaces for closed-loop neuromodulation in neurological and neuropsychiatric disorders. However, closed-loop regulation of neural states is hindered by the complexity of neural population dynamics and their response to external inputs. Thus far, closed-loop control methods have focused on simple approaches such as those based on linear models because developing controllers for nonlinear models can be challenging. However, linear models may not capture sufficient complexity for accurate control. Here, we develop a nonlinear encoding model of neural population activity that can describe neural dynamics in tractable form and thus could allow for developing a closed-loop controller.
We validate our model and controller in a variety of simulated benchmark systems. In each case, our model successfully achieves its control objective of stabilizing the system at a desired target setpoint, and outperforms other baseline models. Overall, our method shows significant promise as a model-based controller for nonlinear systems, particularly well-suited for real-time control of neural dynamics.

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Location: SDCC Hall B

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

Program #/Poster #: LBP040.21/LBP052

Topic: F.05. Brain-Machine Interface

Title: Assist-as-needed exoskeleton training to enhance motor unit recruitment and sensorimotor feedback in people with spinal cord injury

Authors: *K. KACKER[1], C. WALSH[2], J. SHULGACH[1], Z. KUSHNIR[1], E. MCMAHON[1], X. TANG[1], D. J. WEBER[1];
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Abstract: Robotic exoskeletons can be used to assist motor function after spinal cord injury. While externally applied torque enables movement, the control of exoskeletons often bypasses residual volitional drive, limiting opportunities for adaptive reorganization of spared neural circuits.
We introduce an assist-as-needed (AAN) paradigm designed to actively engage residual capacity while modifying sensorimotor feedback at the boundary of volitional range. Participants initiate

movement to their maximum voluntary angle, after which the exoskeleton applies additional torque to reach the full range of motion (ROM) while preserving volitional intent. By intervening only at the volitional limit, the system extends motion into regions otherwise inaccessible, with the goal of modulating sensorimotor feedback to recruit additional motor units and promote neuroplastic adaptations.
We developed a lightweight 3D-printed robotic exoskeleton worn as a glove, enabling wrist and finger flexion/extension under EMG-based or predefined command control. Participants were fitted with 128-channel high-density EMG grids (64 flexors, 64 extensors), while inertial sensors defined volitional and passive ROM. Experimental tasks included dynamic isokinetic flexion/extension at different speeds, isometric ramp-and-hold contractions at 10% and 30% MVC, and AAN trials. During AAN, participants moved to their volitional limit within one second, after which the exoskeleton applied assistive torque to complete the motion into the passive ROM.
Motor unit decomposition during isokinetic and isometric tasks confirmed that the same units could be detected and tracked reliably across different wrist angles and contraction levels, establishing a basis for interpreting changes during AAN.The AAN task was evaluated in one participant with SCI (ASIA B), where two key effects were observed: (i) an increase in firing rates of motor units already active during volitional effort, and (ii) recruitment of previously inactive motor units once the exoskeleton extended the joint into the passive range of motion. These results suggest that assistance at the volitional boundary not only augments residual drive but also expands motor pool engagement by reshaping the sensorimotor environment.
AAN exoskeleton training shows promise as more than a compensatory tool. By combining volitional effort with targeted torque application, this approach may facilitate adaptive reorganization, improve motor control, and provide mechanistic insights into upper-limb rehabilitation for individuals with SCI.

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Late-Breaking Poster

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Program #/Poster #: LBP040.22/LBP053

Topic: F.05. Brain-Machine Interface

Title: Toward rapid calibration of compact neural network decoders for multi-effector brain-computer interfaces

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Abstract: Brain-computer interfaces (BCIs) show promise for restoring motor function and communication. Only recently have BCIs been used to decode individuated finger movements,

which may restore fine motor control; however, daily calibration can exceed 30 mins (Willsey 2025). While large pretrained decoders may improve maximum offline accuracy, they have not yet achieved high-performance online decoding, possibly due to the challenge of daily calibration. Here we explore rapid calibration of neural network decoders previously validated for high-performance real-time decoding, the long short-term memory (LSTM; Costello 2023) and temporal convolutional network (TCN; Willsey 2022, Willsey 2025), and examine whether pretraining and data augmentation can further reduce training time.
We evaluated these strategies with two intracortical Utah array datasets: (1) a rhesus macaque performing an offline 2-effector (2-DoF) finger task (Temmar 2025), and (2) a human participant with tetraplegia performing an offline 2-effector (4-DoF) bimanual cursor task with attempted movements (Deo 2024). Neural inputs (spiking-band power or threshold crossings) were decoded to velocities by LSTM, TCN, or ridge regression (RR). Accuracy was calculated for a single effector as a percentage of maximum correlation. Finally, we evaluated whether calibration trials could be reduced through decoder pretraining on previously collected data or augmented datasets.
In either a 1 or 2 simultaneous finger task, LSTMs and TCNs reached >70% accuracy with only 8 training trials (<15s of data), a 50x reduction compared to calibration trial counts of our prior work (Willsey 2022; Costello 2024). The NN decoders outperformed the linear RR decoder ($p < 0.01$) at 8 training trials. No significant accuracy differences were found between training with single- and multi-finger movement trials. Accuracy scaled approximately log-linearly with trial count. Pretraining finger decoders on prior data or an augmented dataset improved accuracy by 18-27% when using 2-4 trials. For comparison, when training an ipsilateral 2D cursor decoder, accuracy during combined uni- and bimanual tasks reached >50% accuracy at 50 trials, which may imply that training on attempted ipsilateral movements requires more training data.
These results suggest that small neural network models previously validated for real-time decoding can in principle be calibrated in NHPs (without deficits) with few offline trials, although more trials may be needed in people with paralysis. We are now exploring training decoders for people with paralysis and applying pre-training and augmentation in more complex real-time motor tasks.

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Late-Breaking Poster

LBP041: F.06. Posture and Gait

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Program #/Poster #: LBP041.01/LBP054

Topic: F.06. Posture and Gait

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Title: Non-invasive spatiotemporal spinal cord stimulation engaging muscle synergies during walking may improve motor control of the paretic leg in individuals post-stroke

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Abstract: Many individuals post-stroke exhibit impaired walking function, largely due to deficits in motor control of the paretic leg. Neuromodulation through spatiotemporal epidural spinal cord stimulation paired with locomotor training has shown promising improvements in walking in individuals with spinal cord injury. However, the invasive nature of epidural spinal cord stimulation limits its clinical applicability to broader patient populations, including those post-stroke. The potential of non-invasive spatiotemporal spinal cord stimulation paired with locomotor training to enhance locomotor recovery in individuals post-stroke remains poorly understood. The goal of this study was to determine whether applying non-invasive spatiotemporal spinal cord stimulation, designed to engage muscle synergies during walking, could improve motor control of the paretic leg in individuals post-stroke. Ten individuals with chronic stroke participated in this study and were tested in 4 conditions: treadmill walking without stimulation, walking with 3 phases of spatiotemporal spinal cord stimulation, walking with 2 phases of spatiotemporal stimulation, and walking with continuous stimulation. In the 3 phases stimulation condition, stimulation was delivered to L3 during early stance phase of the paretic leg (for weight acceptance and braking), to S1 during late stance (for forward propulsion and swing initiation), and to L4 during swing phase (for foot clearance and leg swing). In the 2 phases stimulation condition, the stimulation was delivered to S1 during stance and to L4 during swing phases. In the continuous condition, the stimulation was delivered to T11 throughout the whole gait cycle. Stimulation frequency was 30 Hz during stance phase to target leg extensors and 80 Hz during swing phase to target leg flexors. In the continuous condition, stimulation frequency was 30 Hz. Stimulation intensity was set to each participant's tolerance, and a carrier frequence of 9.5k Hz was used to increase comfort. Each condition lasted 1.5 minutes, with stimulation was on for 1 minute and off for the remaining 0.5 minutes. Kinematics of leg movements and EMG of 8 leg muscles, and ground reaction force were recorded during walking. We found that a greater improvement in muscle activity of TA during swing phase of gait was observed for the 3 phases of spatiotemporal spinal stimulation than the continuous stimulation. These findings suggest that applying spatiotemporal spinal cord stimulation engaging muscle synergies during walking may be more effective in improving motor control of the paretic leg in individuals post-stroke.

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Late-Breaking Poster

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Topic: F.06. Posture and Gait

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Title: Brain interactions underlying human locomotor adaptation: High-density EEG study

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Abstract: Locomotor adaptation is the process of adjusting one's gait patterns in response to changes in the internal and external environment. Recent studies have shown that multiple distinct brain regions, including the sensorimotor cortex (SMC) and posterior parietal cortex (PPC), are involved in this process. However, although interactions between different brain regions are widely believed to play a crucial role in cognitive and motor control, their contribution to locomotor adaptation remains poorly understood. This study aimed to investigate interactions between brain regions during the process of locomotor adaptation. Fifteen healthy young males performed a walking task on a split-belt treadmill, which has independently controlled belts for each leg. The walking task consisted of a 5-minute baseline period (same speed for both belts), a 15-minute adaptation period (different speeds for each belt), and a 10-minute de-adaptation period (same speed for both belts). The leg assigned to the slow belt during the adaptation period was the right leg. We measured electrocortical activity during the walking task using a 160-channel high-density electroencephalography (EEG) and also acquired each participant's magnetic resonance images (MRI) (T1- and T2-weighted). After preprocessing the measured EEG data, we identified brain components using independent component analysis. We then performed source localization by combining the identified brain components, a head model constructed from individual MRI data, and the EEG electrode location. We identified five brain regions using cluster analysis. The causal connectivity between brain regions, based on Granger causality, was calculated. The frequency bands of interest were the alpha (8-13 Hz) and beta (13-30 Hz) bands. We found that causal connectivity in the alpha band from the anterior cingulate cortex (ACC) to the left SMC significantly increased from early to late adaptation. Additionally, the bidirectional causal connectivity between the left PPC and the left SMC increased significantly during the adaptation period. These results suggest that interactions between a brain region responsible for sensorimotor processing (SMC) and brain regions involved in error detection (ACC) and sensory integration (PPC) play a role in adjusting asymmetrical gait patterns. This study will expand our current understanding of locomotor adaptation based on individual brain regions.

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Topic: F.06. Posture and Gait

Support: Summer Research Fellowship Program of Smith College (2025)

Title: Increased motor cortex activity during speaking negatively affects postural control due to dual task costs

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Abstract: Performing multiple tasks simultaneously may negatively impact an individual's performance in one or more of the tasks, i.e. dual task costs (DTC). Speaking is shown to increase postural sway (Dault et al., 2003), which may be grounded in the fact that speaking about movement increases brain activity in the motor cortex (Pulvermüller, 2005). Motor imagery training instead is shown to improve postural control (Nicholson et al., 2019) and activate fronto-parietal brain areas (Hétu et al., 2013). We therefore investigated the hypothesis that verbal descriptions of motor tasks increases postural sway which is accompanied by increased brain activity in the motor cortex when compared to motor imagery. Forty-one right-handed healthy participants (25.9 ± 6.8 years; 25 women, 16 men) controlled posture while either (I) imagining or verbally describing walking through a maze from an (II) egocentric or allocentric perspective. We recorded postural sway (m^2/s^4) with a wearable Inertial Measurement Unit (IMU) sensor. We collected brain oxygenation data using functional Near InfraRed Spectroscopy (fNIRS) above the frontal, motor, and parietal cortices of both hemispheres. We find that postural sway significantly increased during verbal descriptions (0.057 ± 0.059 m^2/s^4) when compared to imagery conditions (0.038 ± 0.024 m^2/s^4; $p < 0.001$). We also find that ΔHbO_2 significantly increased within the motor cortex during verbal descriptions when compared to imagery conditions ($p < 0.01$). Increased postural sway during verbal descriptions indicates that speaking about movement interferes with the simultaneous control of posture. The increased activity within the motor cortex accompanying verbal descriptions suggests that motor-cognitive components of postural control and speaking are processed within the motor cortex, which may induce DTC. Understanding DTC processes during multitasking is relevant in order to better comprehend the performance of motor-cognitive activities in daily life.

Disclosures: W. Lu: None. **S.R. Lifton Lewis:** None. **Z.E. Wire:** None. **I. Helmich:** None.

Late-Breaking Poster

LBP041: F.06. Posture and Gait

Location: SDCC Hall B

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

Program #/Poster #: LBP041.04/LBP057

Topic: F.06. Posture and Gait

Support: NIH Grant R21AG088600
NIH Grant T32-NS082128

Title: Spatial and temporal control of step length adaptation in Parkinson's disease

Authors: *A. S. GURRALA[1], J. WONG[2], J. T. CHOI[3];
[1]Applied Physiology and Kinesiology, University of Florida, Gainesville, FL; [2]Department of Neurology, University of Florida, Gainesville, FL; [3]Department of Applied Physiology and Kinesiology, University of Florida, Gainesville, FL

Abstract: Background: Locomotor adaptation, a fundamental form of sensorimotor learning, allows individuals to adjust walking patterns in response to environmental changes. Split belt treadmill walking is an established paradigm for studying locomotor adaptation. Previous split-belt studies have demonstrated substantial variability in locomotor adaptation across people with Parkinson's disease (PD), while some individuals adapt, others show minimal adjustment. This study aims to determine the contribution of spatial and temporal control to step length adaptation during split belt walking in PD. **Methods and Results:** Sixteen individuals (10 males and 6 females, mean age 62 ± 12 yrs) with PD participated. The split belt paradigm consists of 3 phases: baseline (tied-belt slow, fast and slow speeds, 2 minutes each), adaptation (6 minutes split belt walking), and post-adaptation (5 minutes slow tied belt walking). Step length asymmetry was calculated for the first and last 30 strides of the adaptation phase (early and late adaptation, respectively). Individuals that showed a significant change in step length asymmetry between early and late adaptation were classified as "adapters", and those with non-significant change were as "non-adapters". Step length analysis revealed that some participants adapted (n=10 adapters), while the others did not (n=6 non-adapters). Step length asymmetry during late adaptation was significantly different between adapters vs. non-adapters in the spatial component (Cohen's d = -2.1, p = 0.002), the temporal component (Cohen's d = -1.4, p = 0.02), and the velocity component (Cohen's d = 1.3, p = 0.03). The sum of the three components confirmed a significant difference in step length asymmetry between adapters vs. non-adapters (Cohen's d = -1.3, p = 0.03). **Conclusion:** Overall, both the spatial and temporal control to step length asymmetry can be adapted in individuals with PD. However, the spatial and temporal control to step length asymmetry are impaired in PD non-adapters compared to adapters.

Disclosures: A.S. Gurrala: None. **J. Wong:** None. **J.T. Choi:** None.

Late-Breaking Poster

LBP041: F.06. Posture and Gait

Location: SDCC Hall B

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

Program #/Poster #: LBP041.05/LBP058

Topic: F.06. Posture and Gait

Support: Parkinson's Foundation Postdoctoral Fellowship
Parkinson's Foundation Summer Student Fellowship

Title: Transcranial ultrasound stimulation of the pedunculopontine nucleus to address freezing of gait in parkinson's disease

Authors: *N. NASRKHANI[1], A. BHATTACHARYA[1], R. CHEN[2];
[1]Krembil Research Institute, Toronto, ON, Canada; [2]Krembil Research Institute and University of Toronto, Toronto, ON, Canada

Abstract: Freezing of gait (FOG) affects more than 60% of individuals with Parkinson's disease (PD), often resulting in falls and a diminished quality of life. Unfortunately, existing treatments, such as medication and deep brain stimulation (DBS), are invasive and have limited effectiveness. Transcranial ultrasound stimulation (TUS) is a non-invasive neuromodulation technique capable of targeting deep brain regions. The pedunculopontine tegmental nucleus (PPN), is a deep brain structure in the brainstem that plays a key role in initiating and supporting locomotion. Resting-state functional magnetic resonance imaging (rsfMRI) studies have shown reduced functional connectivity between the PPN and the cerebellum in PD patients with FOG compared to those without FOG. These findings support that the PPN may be a promising target for TUS as an approach to managing FOG. We hypothesize that TUS of the PPN will transiently normalize altered functional connectivity between the PPN and other brain structures, resulting in a transient reduction of FOG symptoms in PD patients. Data were obtained from 5 healthy subjects and 3 PD-FOG patients. The study consisted of 4 visits, where visit 1 consisted of an anatomical MRI to model the optimal location for targeting the PPN with TUS. Visits 2, 3, and 4 consisted of a pre-TUS FOG baseline assessment, rsfMRI, arterial spin labeling (ASL), TUS, and post-TUS rsfMRI, ASL, and FOG assessment. During each visit, participants received three sets of either 120 seconds of excitatory (5 Hz), inhibitory (100 Hz), or sham TUS, randomly assigned, targeting the PPN bilaterally. In healthy subjects, excitatory TUS increased PPN connectivity with the motor cortex, basal ganglia, and thalamus, as shown through rsfMRI, and increased local cerebral blood flow. Data from the PD-FOG patients showed clear post- vs. pre-differences in brain network connectivity after excitatory and inhibitory PPN stimulation. The patterns of change differed between protocols: excitatory stimulation showed more localized connectivity alterations involving basal ganglia and brainstem/cerebellar regions, while inhibitory stimulation showed more widespread distributed changes. Therefore, our findings suggest that PPN-targeted TUS can induce functional connectivity changes in healthy and PD-FOG individuals, supporting its ability to reach deep brain regions such as the PPN. While data

collection and analyses are still ongoing, these early results point to TUS as a promising non-invasive deep brain stimulation approach for addressing FOG in PD.

Disclosures: N. Nasrkhani: None. **A. Bhattacharya:** None. **R. Chen:** None.

Late-Breaking Poster

LBP041: F.06. Posture and Gait

Location: SDCC Hall B

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

Program #/Poster #: LBP041.06/Web Only

Topic: F.06. Posture and Gait

Support: ERASMUS

Title: Silencing of the Drosophila MBOAT7 Ortholog frj Reveals Locomotor Anomalies

Authors: *R. KARATEPE[1,2], A. S. THUM[2], T. OKYAY[1];
[1]University of Health Sciences, Istanbul, Turkey; [2]University of Leipzig, Leipzig, Germany

Abstract: MBOAT7 is an O-acyltransferase involved in the Lands cycle that preferentially incorporates arachidonic acid into the sn-2 position of phosphoinositides in the brain. This process regulates phospholipid remodeling and synaptic function. Mutations in MBOAT7 cause a phospholipid remodeling disorder, classified as a synaptopathy. Clinical features include global developmental delay, infantile hypotonia, spasticity, early-onset seizures, tremors, ataxic or wide-based gait, speech and language impairments, and intellectual disability. Neuroimaging studies often reveal cerebellar atrophy and folium dysgenesis. Similarly, Mboat7-deficient mice display unsteady gait, feeding difficulties, and early lethality, underscoring the enzyme's critical role in maintaining motor system integrity. While the effects of MBOAT7 on locomotor phenotypes are evident in both humans and mice, the impact of its ortholog on behavior in invertebrate models is not well understood. In *Drosophila*, although brain phosphoinositides lack arachidonic acid, the ortholog *farjavit* (*frj*) is expressed in the nervous system and shares 51% sequence similarity with mammalian MBOAT7. However, its functional role in locomotor regulation has not been investigated. In this study, we silenced *frj* in specific neuronal populations, including the mushroom body, motor neurons, and the entire brain. Locomotor phenotypes were quantified by video-recording third instar larvae and performing manual frame-based analyses. Silencing *frj* in the mushroom body resulted in unsteady locomotion and abnormal behaviors, such as transient loss of motor control and increased side-turning events. While some side-turning was occasionally observed in control larvae, it was markedly more pronounced in those with *frj* knockdown. These findings indicate that, despite the absence of arachidonic acid in the fly brain, silencing *frj* produces locomotor phenotypes similar to those seen in patients. Our research underscores *Drosophila* as a valuable model for investigating the contribution of MBOAT7 to locomotor dysfunction and synaptic pathology.

Disclosures: R. Karatepe: None. **A.S. Thum:** None. **T. Okyay:** None.

Late-Breaking Poster

LBP041: F.06. Posture and Gait

Location: SDCC Hall B

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

Program #/Poster #: LBP041.07/LBP059

Topic: F.06. Posture and Gait

Title: Changes in Spinal Control of Gait with Different Footwear Conditions

Authors: *L. R. PAROLA[1], D. SOUZA DE OLIVEIRA[2], D. J. WEBER[3];
[1]Mechanical Engineering, Carnegie Mellon University, Pittsburgh, PA; [2]Friedrich Alexander University Erlangen, Erlangen, Germany; [3]Mechanical Engineering and Neuroscience Institute, Carnegie Mellon University, Pittsburgh, PA

Abstract: Human locomotion arises from the remarkable coordination of spinal motor neurons and supraspinal inhibition, which together produce the human gait as a largely reflexive process. The Hoffmann reflex (H-reflex) is an electrically evoked reflex analogous to the spinal stretch reflex exhibited in gait. Probing the H-reflex enables us to quantify spinal control during gait and understand supraspinal inhibition under different conditions. Spinal reflexes are adjusted throughout the gait cycle, when transitioning from walking to running, and in response to induced asymmetry. However, no study has directly investigated how modifications to the foot-floor interface via changes in footwear influence spinal control throughout the gait cycle. This work aims to investigate how footwear affects spinal control of gait. In this work, we quantify and compare the H-reflex at the soleus muscle for different footwear conditions to understand how footwear influences spinal control throughout the gait cycle. We recruited participants to walk on a split-belt treadmill barefoot and in sneakers while we evoked H-reflexes in ankle extensor muscles by stimulating the tibial nerve of their dominant limb during loading, midstance, and pushoff phases of single support. Bipolar EMG electrodes (Trigno, Delsys Inc.) were placed bilaterally on the soleus, medial and lateral gastrocnemius, and tibialis anterior. Separate recruitment curves were measured for each footwear condition and gait event. From the recruitment curve, we selected the stimulation amplitude that evoked an M-wave at 10% of the maximal value. Each gait event was monitored in a separate 5-minute walking trial. Gait events were detected in real-time based on the vertical component of the ground reaction force. Stimulation was delivered every 4, 5, or 6 gait cycles at random to prevent subject anticipation. Kinematics were recorded with an 8-camera Vicon optical motion capture system. M- and H-waves were detected at each stimulation pulse and the peak-to-amplitudes were normalized to M-max. In two participants, we observed different trends in whether the H-reflex was higher in barefoot compared to shod walking. One participant's H-reflex increased more rapidly during barefoot than shod walking over 5 minutes of gait for all walking conditions, while the other showed varying effects. In both participants, however, the footwear condition that was higher relative to the other during loading and midstance became lower during pushoff. These data provide preliminary insight into how our spinal control adapts dynamically to footwear conditions, with distinct strategies emerging at different points in the gait cycle.

Disclosures: L.R. Parola: None. **D. Souza de Oliveira:** None. **D.J. Weber:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Panther Life Sciences, NeuroOne, NeuronOff, Bionic Power, Inc., Reach Neuro, Inc.

Late-Breaking Poster

LBP041: F.06. Posture and Gait

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Program #/Poster #: LBP041.08/LBP060

Topic: F.06. Posture and Gait

Support: NIH Grant R01HD100544

Title: Transspinal stimulation as a primer of locomotor training reorganizes neuronal excitability and function of inhibitory networks in human spinal cord injury

Authors: A. M. SAYED AHMAD[1], M. O. ZAAYA[2], N. Y. HAREL[3,4], ***M. KNIKOU**[5,6]; [1]Physical Therapy, City University of New York, New York, NY; [2]CUNY College of Staten Island, Staten Island, NY; [3]James J. Peters VA Medical Center, BRONX, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]City University of New York, Staten Island, NY; [6]Physical Therapy, Klab4Recovery Research Program, Staten Island, NY

Abstract: In this pilot randomized sham-controlled clinical trial, we characterized the spinal neuronal and network excitability in human spinal cord injury (SCI) when non-invasive transspinal stimulation was delivered before locomotor training within the same session. Fourteen people with chronic SCI received an average of 40 sessions with 30 Hz transspinal stimulation delivered for 30 minutes during standing (active: n= 4; sham: n= 5) or supine (active: n= 5) followed by 30-minutes of robotic assisted step training. Before and after completion of all training sessions, we assessed the amount of reciprocal and presynaptic inhibition following conditioning stimulation of the antagonistic common peroneal nerve, and the soleus H-reflex homosynaptic depression and recruitment input-output curve. Transspinal stimulation administered before locomotor training increased the amount of homosynaptic depression in the active-standing and active-supine groups, while presynaptic inhibition exerted on Ia afferent terminals increased in all study groups. Reciprocal Ia inhibition improved in the sham-standing and active-supine groups while in all groups the excitability threshold of soleus motoneurons decreased in all groups. This study demonstrated that transspinal stimulation preceding locomotor training partially restores some of the spinal inhibitory mechanisms acting presynaptic or postsynaptic, and produces network reorganization in chronic SCI. Noninvasive transspinal stimulation can increase the benefits of locomotor training, bringing spinal neuronal networks to a more functional state in chronic SCI.

Disclosures: A.M. Sayed Ahmad: None. **M.O. Zaaya:** None. **N.Y. Harel:** None. **M. Knikou:** None.

Late-Breaking Poster

LBP041: F.06. Posture and Gait

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Topic: F.06. Posture and Gait

Support: NIH/NIBIB P41EB018783
SPiRE 5I21RX004410-02
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Stratton VA Medical Center
Dorflinger Scholarship

Title: Adding Transcutaneous Auricular Vagus Nerve Stimulation (taVNS) to H-Reflex Operant Conditioning (HROC): Methods Development

Authors: *C. ROBINETT[1,2], T. M. VAUGHAN[3], J. A. BRANGACCIO[4], J. S. CARP[5]; [1]Lafayette College, Marysville, WA; [2]Lafayette College, Easton, PA; [3]National Center for Adaptive Neurotechnologies, Stratton VA Medical Center, Albany, NY; [4]Research/physical therapy, NCAN@Stratton VA Medical Center, Albany, NY; [5]National Center for Adaptive Neurotechnologies, Stratton VA Medical Center / NCAN, Delmar, NY

Abstract: Objective: Hoffmann reflex (HR) operant conditioning (HROC) promotes targeted plasticity of specific spinal reflexes that can greatly improve a skill, like walking, after neurological injury (Thompson et al, 2013). Thompson et al. (2009) reported significant between-session changes during HR down conditioning (HRDC) of healthy controls by session 12 of a 24-session conditioning protocol. Separately, vagus nerve stimulation (VNS) has been shown to enhance task-based recovery following spinal cord injury and stroke (Kilgard et al, 2025; Dawson et al, 2021). We are developing methods for adding noninvasive transcutaneous auricular VNS (taVNS) (Verna et al, 2021) to the visual feedback of HROC. We hypothesize adding taVNS will accelerate onset of between-session change.
Methods: Our HROC protocol is based on Thompson et al. (2009), modified to use a 1-Hz HR stim rate (Brangaccio et al, in press) instead of the standard 0.2-Hz rate. Participants complete 4-6 baseline sessions, followed by 12 conditioning sessions at an average of 3x/wk. During all sessions, the participant stands approximately 1m from a computer eye-level 45” monitor and maintains stable background soleus EMG while receiving stimulation on the posterior tibial nerve for 9 blocks of 75 HR trials each. The stimulation intensity is adjusted to maintain a stable direct muscle response (M wave). In baseline sessions, no feedback is provided. In conditioning sessions, feedback is provided during blocks 2-8: a visual display of the soleus EMG is coupled with 500 ms of taVNS or earlobe sham stimulation at 25 Hz (biphasic, 0.5 ms/phase) when the HR size is smaller than a criterion value. To assess between-session change, the mean normalized HR size from the first (i.e., no-feedback) trial blocks were compared between baseline and conditioning sessions by t-test.
Results: For the 7 conditioning sessions completed, the mean HR was -27%±7SE and -7%±5SE

of baseline HR ($p<0.05$ and $p>0.4$ by t-test) for 1 taVNS and 1 sham participant, respectively. To assess if the current protocols produced HR decrease sooner than the 12 days needed in Thompson et al. (2009), we determined that HR in the taVNS participant decreased more than the mean change in HR minus 2xSD reported by Thompson et al. (2009) on conditioning days 3, 5, 6, and 7, while none of the conditioning days in the sham participant met this criterion. Discussion: These early results suggest that combining HROC with taVNS is possible and has the potential to reduce HROC conditioning time. This may facilitate HROC efficacy and adoption into clinical practice. Additional data are needed to assess the efficacy of combined HROC and taVNS.

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Late-Breaking Poster

LBP042: F.07. Rhythmic Pattern Generation

Location: SDCC Hall B

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

Program #/Poster #: LBP042.01/LBP062

Topic: F.07. Rhythmic Pattern Generation

Support: R35 NS097343

Title: Thermal experience shifts the functional range and neuromodulator responses in the pyloric network of lobster, *Homarus americanus*

Authors: *S. KEDIA[1], J. RITTENBERG[2], E. E. MARDER[3];
[1]Brandeis University, Somerville, MA; [2]Brandeis University, Sharon, MA; [3]Biology, Brandeis University, WALTHAM, MA

Abstract: *H. Americanus* experience large temperature shifts in their environment between summer and winter months. All elements of their nervous machinery must continue to operate in these different regimes for the animal's survival and may need to change from season to season to allow for this. The central pattern generating pyloric networks of the stomatogastric nervous system (STNS) continuously produce rhythmic motor outputs over a wide range of temperatures. Neuromodulators maintain rhythmicity in basal conditions and can extend the thermal range over which an isolated STNS produces robust pyloric output. We tested the impact of acclimating animals at low and high (4 and 18 °C) temperatures for a period of >3 weeks on network function. Acclimation at high temperatures increases the temperature range (~7 °C increase) over which the network produces a triphasic pyloric rhythm. The role of neuromodulator driven changes was probed using multiple doses of the neuromodulator crab cardioactive peptide (CCAP) which restored a triphasic output at both 10 and 20 °C in hot acclimated animals but only did so at 10 °C in cold acclimated animals. This suggests shifts in either the intrinsic conductance expression or neuromodulator sensitivity generated by the thermal experience of the

animal which is involved in the expansion of their thermal range. These possibilities are being further explored.

Disclosures: S. Kedia: None. **J. Rittenberg:** None. **E.E. Marder:** None.

Late-Breaking Poster

LBP042: F.07. Rhythmic Pattern Generation

Location: SDCC Hall B

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

Program #/Poster #: LBP042.02/LBP063

Topic: F.07. Rhythmic Pattern Generation

Support: BBSRC EASTBIO DTP

Title: Neuromodulation of motor competition in the Drosophila larval locomotor system

Authors: W. V. SMITH, ***S. R. PULVER**;
University of St Andrews, St Andrews, United Kingdom

Abstract: Dynamic Interactions amongst competing motor programmes shape behavioural output, but relatively little is known about how competitive interactions are modulated in motor systems. Here, we explore how adrenergic-like systems modulate competition amongst central pattern generating (CPG) networks controlling locomotion in Drosophila larvae. The isolated Drosophila CNS generates multiple competing fictive motor programmes that drive forward and backward locomotion as well as direction changes. Interactions amongst these activity patterns can be monitored using calcium imaging and electrophysiology. Bath application of octopamine (OA) promoted fictive forwards locomotion, suppressed fictive backwards locomotion. OA application also induced bouts of fictive head sweeps during wash period that were proportional to the promotion of forward waves. In contrast, Tyramine (TYR), a co-transmitter also present in OA neurons, promoted collisions and overlap of motor programmes, and bouts of silence during wash periods. Dual-colour calcium imaging of OA/TYR neurons together with motor neurons revealed that most OA/TYR neurons are recruited phasically, prior to motor neurons. Optogenetic manipulation of activity in OA/TYR neurons recapitulated a subset of effects, and further revealed that activity in OA/TYR neurons is necessary and sufficient for locomotor CPG activity in the system, suggesting that OA/TYR neurons control rhythm generation in parallel to motor competition. Overall, this work provides insights into how adrenergic-like systems can modulate dynamics of competition at multiple levels within rhythmically active locomotor networks. Pulver laboratory is accredited by the Laboratory Efficiency Assessment Framework (LEAF) at Gold Level and the methods used in this work were designed to reduce waste and promote environmentally sustainable laboratory practices.

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Late-Breaking Poster

LBP042: F.07. Rhythmic Pattern Generation

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Topic: F.07. Rhythmic Pattern Generation

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Swartz Foundation Fellowship in Theoretical Neuroscience to E.T.T.A.
Shanahan Foundation Fellowship to D.T.

Title: Descending control of a central pattern generator circuit for fly walking

Authors: *G. M. CHOU[1,2], S. M. PUGLIESE[3,2,4], E. T. T. ABE[4], D. TURCU[5], B. W. BRUNTON[4], J. C. TUTHILL[2];
[1]Princeton Neuroscience Institute, Princeton University, Princeton, NJ; [2]Neurobiology and Biophysics, University of Washington, Seattle, WA; [3]Neuroscience Graduate Program, University of Washington, Seattle, WA; [4]Biology, University of Washington, Seattle, WA; [5]Studio D3, Allen Institute, Seattle, WA

Abstract: Animal locomotion relies on rhythmic body movements driven by central pattern generators (CPGs), neural circuits that produce oscillating output without oscillating input. However, the circuit structure of a walking CPG is not known in any animal. To identify the cells and synapses that underlie rhythmic leg movement in walking flies, we developed dynamic simulations of the Drosophila ventral nerve cord (VNC) connectomes. We used a computational activation screen to identify descending neurons from the brain that drives rhythmic activity in leg motor neurons, including a command neuron for walking (DNg100), which we predicted to modulate the walking CPG. To experimentally confirm this prediction, we performed optogenetic activation of DNg100 in decapitated flies and were able to drive increases in walking speed by increasing stimulus intensity. Additionally, our connectome simulations predicted that parallel descending neurons (DNb08) produces motor rhythms, which we also confirmed experimentally using optogenetics in decapitated flies to drive rhythmic leg movements resembling a foothold search behavior. By synthetic pruning of the VNC network, we identified two overlapping microcircuits that are recruited by DNg100 and DNb08 in parallel. A model of this core CPG circuit is sufficient to generate motor rhythms. Our results reveal the cellular identity and synaptic structure of a putative CPG circuit for fly walking.

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Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.01/LBP065

Topic: F.09. Motor Neurons and Muscle

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NIH R01 NS104442
Veterans Administration Gordon Mansfield Consortium for Spinal Cord Regeneration B7332R
Dr. Miriam and Sheldon G. Adelson Medical Research Foundation
NIH RO1 NS130033

Title: Thiorphan Reprograms Neurons to Promote Functional Recovery after SCI

Authors: *E. A. VANNIEKERK;
Neurosciences, UCSD, La Jolla, CA

Abstract: We previously identified an embryonic shift in the corticospinal motor neuronal transcriptome after spinal cord injury associated with successful axonal regeneration(*1*). Exploiting this transcriptional regenerative "signature", we used *in silico* screens to identify small molecules that generate similar shifts in the transcriptome, and identified Thiorphan, a neutral endopeptidase inhibitor, as a lead candidate. In a new *adult* motor cortex neuronal *in vitro* screen(*2*), Thiorphan increased neurite outgrowth 1.8-fold ($p < 0.001$). We then infused Thiorphan into the CNS beginning two weeks after severe C5 spinal cord contusions, and when combined with a neural stem cell graft, Thiorphan elicited significant improvements in forelimb function ($p < 0.005$) and corticospinal regeneration ($p < 0.05$). Extending clinical relevance, Thiorphan significantly increased neurite outgrowth in primary cortical neuronal cultures from a 56-year-old human. These findings represent a novel path for drug discovery, starting from *in silico* screens to proof-of-concept in adult human brain cultures.

Disclosures: E.A. Vanniekerk: None.

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.02/LBP066

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant HL146114
NIH Grant AG44615

Title: Circadian pattern of BDNF in the cervical spinal cord in rats

Authors: *A. PIPKINS[1], D. DASGUPTA[1], G. HERNANDEZ VIZCARRONDO[1], W.-Z. ZHAN[1], C. B. MANTILLA[2], G. C. SIECK[1];
[1]Department of Physiology & Biomedical Engineering, Mayo Clinic, Rochester, MN;
[2]Anesthesiology, Mayo Clinic, Rochester, MN

Abstract: Brain-derived neurotrophic factor (BDNF) plays a role in neuronal survival and synaptic plasticity. Previous studies have shown that there is a circadian fluctuation in BDNF mRNA and protein expression in the hippocampus and suprachiasmatic nucleus (SCN) suggesting time-of-day dependent modulation. These results indicate that neurotrophic signaling could be regulated by the circadian cycle. Previous studies have also suggested that during exercise, BDNF expression is activity dependent. However, the extent to which these results generalize across the other regions of the central nervous system (CNS)- especially regions that involve motor output- remains poorly understood. In this study, we examined the circadian regulation of BDNF and downstream TrkB signaling ($pTrkB^{Y817}$ phosphorylation) across four different timepoints (0700, 1300, 1900, 0100) in hippocampus, hypothalamus, cervical spinal cord, and lumbar spinal cord of adult female (n=3 per time point) and male (n=3 per time point) Sprage-Dawley rats. We hypothesized that BDNF levels and TrkB signaling in the four different CNS regions exhibit distinct circadian fluctuations, reflecting the combined influence of intrinsic clock genes and activity patterns. Western Blot analysis of BDNF protein levels and $pTrkB^{Y817}$ phosphorylation showed region-specific and time-of-day-dependent patterns in all four CNS regions, with the hippocampus showing higher BDNF/TrkB signaling than the other three CNS regions. Overall, our findings highlight that BDNF/TrkB signaling varies across the circadian cycle but is region-specific, emphasizing the importance of time-of-day when studying neurotrophic dynamics. Understanding the role of BDNF/TrkB signaling in the circadian cycle and its region-specific regulation may optimize timing of neurorehabilitation-based therapies by aligning them with periods of peak neuroplasticity. The clinical relevance of this study could help us gain an insight into more effective treatments for spinal cord injury by targeting the time for peak neuroplastic response.

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Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.03/LBP067

Topic: F.09. Motor Neurons and Muscle

Title: Compound muscle action potential as an early functional in vivo measure of Sarm1 inhibition after sciatic nerve transection.

Authors: *S. HUR;
Neuroscience, Genentech Inc., South San Francisco, CA

Abstract: The NADase sterile alpha and TIR motif containing 1 (Sarm1) protein drives axon degeneration after injury. Loss or inhibition of Sarm1 structurally protects axons after sciatic nerve transection (SNT) in vivo but whether Sarm1 also drives functional loss after nerve injury is less clear. We established compound muscle action potential (CMAP) as a novel functional correlate of Sarm1 activation in a SNT mouse model and evaluated its relationship with biochemical and a novel Cellpose-based histological axon detection measure. CMAP amplitudes were elicited 8h post-SNT but reached near-floor levels by 24h. Decreases in CMAP amplitude are delayed in a gene dose-dependent manner in Sarm1 knockout mice or by pharmacological Sarm1 inhibition. Myelinated axon density, the NAD hydrolysis product cyclic adenosine diphosphate ribose (cADPR), and the axon degeneration plasma biomarker neurofilament light (NfL) were all altered in a Sarm1- dependent manner. In wild type mice, axon density and NfL were altered at time points after that of cADPR and functional loss, indicating that functional deficits preceded structural deficits. We conclude that functional and structural declines after injury are delayed by Sarm1 inhibition and that CMAP measures after SNT can serve as a novel, preclinical, functional, pharmacodynamic readout for Sarm1 inhibition.

Disclosures: S. Hur: A. Employment/Salary (full or part-time); Genentech Inc..

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.04/LBP068

Topic: F.09. Motor Neurons and Muscle

Title: Outcomes of Conservative Management in Severe Traumatic Facial Paralysis: A Retrospective Analysis

Authors: *S. KIM;
DEPARTMENT OF OTORHINOLARYNGOLOGY - HEAD AND NECK SURGERY, PUSAN NATIONAL UNIVERSITY SCHOOL OF MEDIC, Yangsan, Korea, Republic of

Abstract: Study Design: Retrospective Analysis **Objective:** To evaluate the outcomes of conservative management in patients with severe facial paralysis (House-Brackmann grade V) or denervation with recommended surgery (90% or more EnoG denervation) following temporal bone fracture (TBF) who declined FN decompression surgery. **Methods:** We conducted a retrospective chart review of approximately 10 patients who presented with severe facial paralysis (House-Brackmann grade V) and 90% or more EnoG denervation following TBF. All patients had declined surgical decompression despite meeting surgical criteria. Patient

demographics, clinical presentations, radiological findings, treatment regimens, and recovery outcomes were documented. Recovery was classified as complete (House-Brackmann I-II) or partial (House-Brackmann III-IV). **Results:** Among the cohort, 70% achieved complete recovery (House-Brackmann I-II) despite severe initial presentations, while 30% demonstrated partial recovery (House-Brackmann III-IV). Analysis of clinical and radiological factors revealed that patients with delayed-onset paralysis and absence of identifiable nerve compression structures on high-resolution CT imaging demonstrated more favorable outcomes. No patients in the cohort progressed to complete non-recovery (House-Brackmann V-VI) during the follow-up period. **Conclusions:** Our findings suggest that conservative management may yield satisfactory outcomes in selected patients with severe facial paralysis following TBF, even in cases meeting traditional surgical criteria. Delayed onset of symptoms and absence of visible nerve compression on imaging appeared to correlate with better recovery patterns. These observations challenge conventional management algorithms and suggest that a subset of patients may benefit from non-surgical approaches, potentially avoiding the risks associated with surgical intervention. **Keywords:** temporal bone fracture, facial nerve palsy, conservative management, electroneurography, facial nerve recovery

Disclosures: S. Kim: None.

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.05/LBP069

Topic: F.09. Motor Neurons and Muscle

Title: A Proposed Cause, Cure, and Mechanism for Focal Task-Specific Dystonia: A Theoretical-Empirical Approach

Authors: *N. LU;
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Abstract: Focal task-specific dystonia (FTSD) reflects maladaptive neuroplasticity with motor-circuit imbalance. Prevailing accounts emphasize subcortical nuclei yet do not explain tight task-specificity. We propose the primary driver is a newly formed "dystonic synergy" in primary motor cortex (M1): excitatory synapses become adequate relative to under-strengthened inhibitory synapses, so when a skill's intensity demand exceeds the synergy's excitatory/inhibitory (E/I) capacity, involuntary contractions are triggered. Using an extensive single-case observation, we chronicle how a decade of stable piano performance deteriorated after a sudden technical change forced the finger-flexion synergy to overreach. The initial phase was dominated by "true weakness": a task-specific paresis in which the system could not generate sufficient E/I drive to match attempted speed; repeated efforts to override the limit preferentially strengthened excitatory circuits while inhibitory circuits lagged, yielding a fully formed dystonic synergy within three weeks. The maladaptive synergy then appeared in both

piano playing and typing—a related digit-based skill—severely disabling function. Once formed, the synergy remained stable but not spontaneously progressive, consistent with a saturable excitatory capacity. We further provide quantitative proof-of-concept via a spiking neural network simulation. Other structural or electrophysiological findings—basal ganglia and cerebellar changes, sensorimotor smudging in S1, impaired spinal inhibition—are reframed as secondary byproducts of chronic M1 hyperexcitation. We outline a taxonomy: (i) "typical" neuroplastic dystonias, including task-specific forms driven by repeated overreaching and synergy imbalance; (ii) atypical neuroplastic variants with strong genetic underpinnings but partial plastic compensation; and (iii) non-neuroplastic dystonias from deterministically causal gene mutations. Finally, we propose a noninvasive retraining approach for reversing FTSD: "below- or at-threshold retraining" (BATR), which methodically strengthens the inhibitory circuit of the dystonic synergy. Validated in the single-case longitudinal data and convergent studies using similar methods, BATR can rebalance the dysregulated synergy and restore normal motor function. Integrating these mechanistic and therapeutic insights, we offer a unifying framework for FTSD pathogenesis and a practical, noninvasive avenue for cure and prevention.

Disclosures: N. Lu: None.

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.06/LBP070

Topic: F.09. Motor Neurons and Muscle

Support: NIH/NINDS Grant RM1NS128775

Title: Investigating Pain-Induced Modulation of Spinal Motoneurons with the Sombrero Contraction

Authors: *B. P. BALO[1], P. YADAV[2], J. A. BEAUCHAMP[3], D. J. WEBER[4];
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Abstract: Chronic pain is a debilitating condition that disrupts motor control, driving biomechanical adaptations and maladaptive motor strategies that can worsen pain. Pain-induced motor adaptations arise through two primary mechanisms: rapid ionotropic sensory effects, often inhibitory, that filter through spinal networks onto spinal motoneurons, and slower metabotropic shifts in intrinsic motoneuron properties driven by monoaminergic brainstem inputs. Most prior research has focused on the immediate inhibitory effects of pain, while largely overlooking monoamines. This gap is critical, as monoamines set the gain state of spinal motoneurons by generating persistent inward currents (PICs) that strongly amplify and prolong excitatory inputs.

Disentangling these two mechanisms is essential for advancing understanding and creating new treatments. To address this, we conducted an exploratory study with eighteen participants (11M/7F). Participants performed novel isometric wrist flexion “sombrero” contractions while non-invasive heat pain was applied using a QST.Lab TCS II.1.b Thermode on the skin opposite the wrist flexors. The sombrero contraction quantifies PIC effects by comparing motoneuron behavior during a low-effort sustained hold (10% MVC) immediately before (Hold 1) and after (Hold 2) a linear ramp to 30% MVC. High density surface electromyography (HDsEMG) of the wrist flexors was recorded in all trials, with real time torque feedback provided to the participant. Motor units were decomposed using DEMUSE V6.1. We detected on average 22±6 motor units per participant with a pulse-to-noise ratio (PNR) of 28.9±2.1. During Hold 1 or Hold 2, participants were randomly subjected to above pain threshold heat (5.8±2.1, n = 168), below painful threshold heat (sham) (1.9±2.0, n = 168), or no heat (1.3±2.0, n = 84). HDsEMG amplitude, torque coefficient of variance, and median HDsEMG frequency were analyzed to estimate the effects of heat pain on MU behavior. Initial results show an increase in sEMG amplitude (2.6 %MVC, 95%CI: [1.3 3.8]) and torque coefficient of variance (1.5 %MVC, 95%CI: [0.84 2.2]) from Hold 1 to Hold 2, aligning with prior findings, and indicating the presence of PICs. When pain was elicited during hold 1, HDsEMG amplitudes increased and remained elevated into Hold 2, suggesting sustained motoneuron firing and likely greater PICs. In contrast, median HDsEMG frequency decreased regardless of when the painful stimulus was applied, suggesting an inhibitory induced shift in motoneuron activity. Our findings highlight the importance of considering pain-induced shifts in monoamines and their effects on spinal motoneuron behavior.

Disclosures: B.P. Balo: None. **P. Yadav:** None. **J.A. Beauchamp:** None. **D.J. Weber:** None.

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.07/LBP071

Topic: F.09. Motor Neurons and Muscle

Title: Changes in the intrinsic properties of corticomotor neurons in mice exhibiting TDP-43 accumulations associated with ALS

Authors: *R. DEBIAN;
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Abstract: Amyotrophic lateral sclerosis (ALS) is the most severe form of motor neuron (MN) disease, characterized by progressive loss of corticospinal neurons (CSNs), brainstemmotor neurons, and spinal motor neurons, resulting in sustained motor system failure and ultimately death from respiratory failure within 3-5 years of diagnosis. ALS iscurrently an incurable disease and the mechanism(s) underlying selective loss of specific cell types is not known, with 10% of the cases having a genetic cause while90% are sporadic. However, accumulating evidence

suggests that a common feature of the disease is altered MN excitability early on in the motor cortex,characterized by an imbalance between excitation and inhibition leading to reduced cortical inhibition. These altered excitability features are exhibited in all forms ofthe disease including patients with mutations in the superoxide-dismutase-1 (SOD1) gene as well as patients with TAR DNA-binding protein 43 (TDP-43) aggregations.Various studies have looked at the reasons contributing to altered neuronal synaptic activity and structure at stages prior to neuronal loss, but few have looked atchanges in intrinsic excitability.In this study, we aim to investigate the impact of TDP-43 pathology on the intrinsic properties of two major classes of projection neurons—corticospinal neurons (CSNs)and corticocortical neurons (CCNs)—within motor cortex. To induce TDP-43 pathology, we will inject L-BMAA, leading to its mislocalization and aggregation, andexamine its effects on ion channel function and neuronal excitability using whole-cell intracellular recordings. By analyzing intrinsic excitability independent of synapticinputs, we will determine whether TDP-43 dysregulation leads to upregulation or downregulation of specific ion channels, which could contribute to corticalhyperexcitability in ALS. In addition, our study aims to provide mechanistic insights into the early cortical abnormalities observed in ALS and identify novel therapeutictargets for restoring neuronal stability in the disease.

Disclosures: R. Debian: None.

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.08/LBP072

Topic: F.09. Motor Neurons and Muscle

Support: CIHR Canada Graduate Scholarship – Master's (CGSM)
McGill Innovation Fund (MIF)

Title: A preliminary EMG analysis of vibration-induced neuromodulation of human jaw muscles

Authors: *V. ASHOK KUMAR[1], P. IACONO[2], D. GRANT[2], J. COHEN-LÉVY[2], J. FUNG[3], N. REZNIKOV[2];
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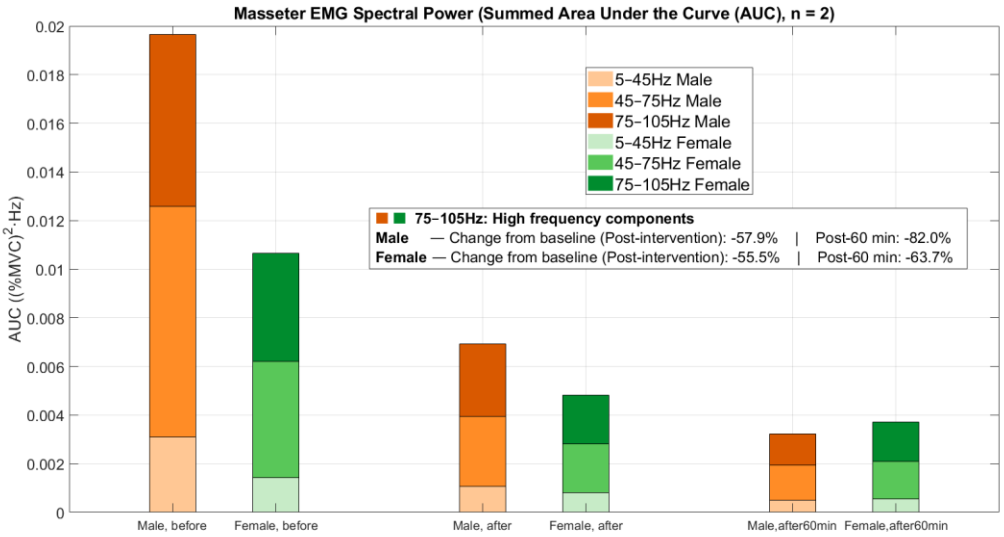
Abstract: Low-level neural activation defines muscle tone, contributing to posture and stability. During voluntary movement, muscle fiber contraction is synchronized and measurable by surface electromyography (sEMG). Suppression of high frequencies in the sEMG power spectral density (PSD) indicates fatigue and a higher synchronization threshold[1–3]. Peripheral vibration, by modulating spindle afferent drive via the tonic vibration reflex (TVR), alters motor output[4,5] and can induce excitation-frequency-dependent fatigue[6,7]. These mechanisms remain understudied in

the complex anatomy of the head and neck.This pilot study quantified the effects of targeted vibration on craniofacial muscle tone. We applied 100 Hz vibration for 3 min to the masseter and sternocleidomastoid insertions using a custom device. Two adults without orofacial pain (1F/46y, 1M/30y) underwent five experiments. Tonic contractions (3 × 5 s at 40% MVC, using the Jendrassik maneuver[8] with visual bite-force feedback) were recorded before, immediately after, and 1 h post-vibration. sEMG signals (1024 Hz) were filtered (5-105 Hz), normalized to %MVC, and analyzed for amplitude and PSD, with median frequency (MDF) extracted[2,3,9].Results showed a consistent, persistent spectral shift: high-frequency PSD and MDF decreased immediately and remained suppressed at 60 min, while sEMG amplitude was also reduced. This suggests transient de-recruitment or desynchronization of high-threshold motor units[2,6,10]. The device was well tolerated, providing foundational evidence that targeted vibration can neuromodulate craniofacial motor tone. These findings align with prior TVR and vibration-induced fatigue studies[4,7] and highlight a novel, non-invasive approach with potential therapeutic relevance for bruxism and temporomandibular disorders (TMD). Larger, controlled trials are required to establish reproducibility and long-term clinical impact[11,12].



Disclosures: V. Ashok Kumar: None. **P. Iacono:** None. **D. Grant:** None. **J. Cohen-Lévy:** None. **J. Fung:** None. **N. Reznikov:** None.

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.09/LBP073

Topic: F.09. Motor Neurons and Muscle

Support: tsqn202211226
ZR2021QH267

Title: Motor unit number estimation in Parkinson's disease based on CMAP scan

Authors: R. TIAN[1], ***Z. LU**[1], M. CHEN[1], J. CHEN[1], L. WU[1], K. LIU[2], P. ZHOU[1];
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Abstract: Background: Patients with Parkinson's disease (PD) usually have motor symptoms such as frozen gait, bradykinesia, and rigidity, which are believed to be associated with impairments of the peripheral neural system (PNS). However, PD is a typical central nervous system (CNS) disease, and few studies about the changes in motor unit number after PD have been conducted. **Objective:** To disclose alterations in motor unit number after PD, and quantify its relation with the motor symptoms. **Method:** The compound muscle action potential (CMAP) scan, which captures motor units by delivering hundreds of stimuli to the nerve, was applied in this study. Novel algorithms including step index (STEPIX) and StairFit motor unit number estimation (MUNE) were employed in order to analyze the CMAP scan data and assess the numbers of motor units. Thirteen PD patients and nineteen age-matched healthy controls were recruited. According to the dopaminergic therapy response in electronic medical record, PD subjects were subdivided into two groups, responders (PD-R, n=7) and ineffective responders (PD-I, n=6). Independent t-test was performed to investigate the motor unit number changes in the first dorsal interosseus muscle after PD. Lateral pinch and UPDRS III were also measured. **Results:** The PD subjects showed significant lower values in STEPIX and StairFit MUNE, compared to healthy controls (STEPIX: 126.38±34.56 vs. 151.16±20.98, p=0.017, StairFit MUNE: 79.46±19.06 vs. 101.74±13.19, p=0.000). In the PD subgroups, the STEPIX (110.86±19.35) and StairFit MUNE (72.14±11.13) of PD-R group were significantly lower than that of controls. Thereinto, StairFit MUNE value of PD-R was only 70% of that in PD-I. High correlations were found between STEPIX and StairFit MUNE, and also across these two parameters and lateral pinch force (PD: 9.23±5.56 Ib, controls: 18.58±5.90 Ib). **Conclusion:** This study revealed decreased motor unit number in PD patients, indicating peripheral involvement after the disease, partially contributing to motor symptoms. Moreover, motor unit loss was more prominent in those PD patients who had well levodopa response.

Disclosures: R. Tian: None. **Z. Lu:** None. **M. Chen:** None. **J. Chen:** None. **L. Wu:** None. **K. Liu:** None. **P. Zhou:** None.

Late-Breaking Poster

LBP043: F.09. Motor Neurons and Muscle

Location: SDCC Hall B

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

Program #/Poster #: LBP043.10/LBP074

Topic: F.09. Motor Neurons and Muscle

Title: Superior performance of reusable microneedle neuromuscular interfaces for lower extremity neuroprosthetic applications

Authors: J. JEONG, Y. KIM, M. KANG, J. PARK, Y. CHO, *S. LEE;
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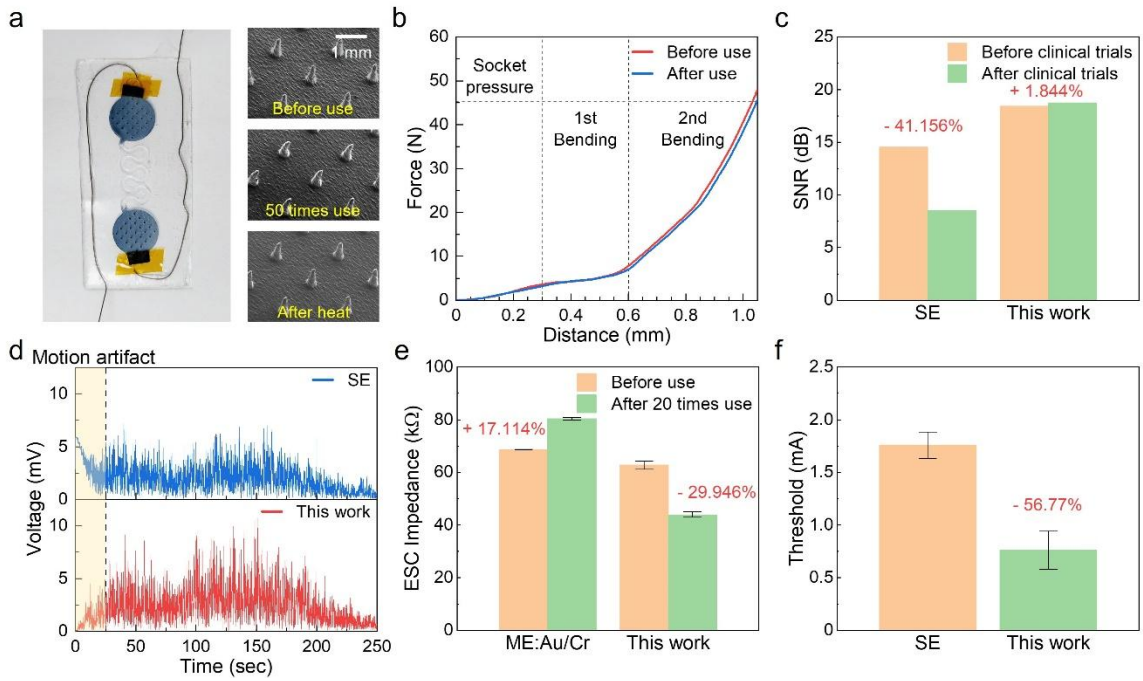
Abstract: The number of amputees is increasing due to various factors, leading to a growing demand for neuroprosthetic that can precisely reflect the user intent. To achieve this, neuroprosthetics acquire and analyze the user's bio-signals through sensors. Electromyography (EMG) is widely used to control neuroprosthetics because it enables intent decoding without surgery. However, conventional surface electrodes (SE) often provide poor quality signals due to harsh environmental conditions such as high pressure, sweat and motion artifact inside prosthetic sockets. Microneedle electrodes can overcome these limitations by providing improved recording stability and reduced sensitivity to environmental noise like motion artifact. However, their limited durability and safety hinder practical use inside sockets. To address these, we fabricated microneedles using a biocompatible shape memory polymer that softens near body temperature. The microneedles remain rigid enough to penetrate skin upon insertion, then soften with body temperature to accommodate natural tissue movement. Furthermore, we coated the microneedle with a restorable conductive polymer, maintaining stable electrical properties even after cracking the conductive layer under repeated bending. We successfully developed a reusable microneedle neuromuscular interface (RM-NI) capable of long-term EMG acquisition inside the sockets of lower limb amputees. RM-NI did not induce skin issues such as eczema during extended wear, and seven amputees reported no discomfort or pain after insertion. RM-NI also demonstrated sufficient durability for repeated use in socket environments. Compared to SE, RM-NI achieved higher signal-to-noise ratio (+24.60%), and improved AI based decoding accuracy (+4.48%). In addition, RM-NI required significantly lower current to stimulate percutaneous nerves (-56.77% vs. SE). These results highlight the superior recording and stimulation performance of RM-MI over SE (Fig. 1). Overall, RM-NI demonstrates strong potential as a next-generation EMG-based neuroprosthetic interface.



Disclosures: J. Jeong: None. **Y. kim:** None. **M. Kang:** None. **J. Park:** None. **Y. Cho:** None. **S. Lee:** None.

Late-Breaking Poster

LBP044: H.01. Fear and Aversive Learning and Memory

Location: SDCC Hall B

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

Program #/Poster #: LBP044.01/LBP075

Topic: H.01. Fear and Aversive Learning and Memory

Support: R01MH139795 (EKL)
R01MH123768 (EKL)
T32NS061788 (AJT)

Title: Sex Differences in the Dynamic Modulation of Basolateral Amygdala Microcircuitry Across Threat Memory Learning

Authors: *A. J. TELLEZ[1], B. W. HARDIN[2], N. E. BAUMGARTNER[3], P. TERAVSKIS[4], E. K. LUCAS[3];
[1]Psychiatry & Behavioral Neurobiology, UAB Neuroscience Graduate Program, Birmingham, AL; [2]Psychiatry & Behavioral Neurobiology, University of Alabama at Birmingham Chapter, Birmingham, AL; [3]Psychiatry & Behavioral Neurobiology, University of Alabama at Birmingham, Birmingham, AL; [4]University of Alabama at Birmingham, Birmingham, AL

Abstract: Across species, the basolateral amygdala (BLA) drives the encoding and retrieval of cued threat memory. While the BLA is highly influenced by fluctuations in ovarian hormones, sex differences have not been explored at the circuitry level. BLA principal neurons expressing R-spondin-2 ($Rspo2^{PN}$) are necessary and sufficient for threat memory encoding, and GABAergic interneurons expressing parvalbumin (PV^{IN}) and somatostatin (SOM^{IN}) modulate threat memory dynamics through local inhibition of principal neurons. Our single nucleus sequencing data reveal exclusive enrichment of estrogen receptor beta (ERβ) in $Rspo2^{PN}$ and, to a lesser extent, SOM^{IN} in the BLA. Given the known role of ERβ in BLA plasticity, we hypothesize that ERβ regulation of BLA microcircuitry is the underlying driver of sex differences in threat memory processing through the differential recruitment of $Rspo2^{PN}$, SOM^{IN}, and PV^{IN}. Using mouse as the model species, we combined auditory threat conditioning with fiber photometry to quantify the contributions of BLA $Rspo2^{PN}$, SOM^{IN}, and PV^{IN} in the expression and maintenance of threat memories. Subjects received bilateral infusions of adeno-associated virus in the BLA to confer expression of Ca^{2+} biosensor GCaMP6f and optic fiber implants. During threat memory acquisition, all three neuron types demonstrate distinct patterns of recruitment to both conditioned (CS; auditory tone) and unconditioned stimulus (US; footshock). $Rspo2^{PN}$ and PV^{IN} exhibit greater initial responses to the US than SOM^{IN}, with PV^{IN} recruitment decreasing across learning. Conversely, SOM^{IN} displayed a greater rate of change to the CS (versus PV^{IN}) and US (versus $Rspo2^{PN}$ and PV^{IN}) and increased recruitment across learning. While analyses of sex differences are still ongoing, the data suggest two emerging patterns during acquisition: a greater magnitude of US-recruited $Rspo2^{PN}$ and greater CS-recruited SOM^{IN} in males than females. Interestingly, stratifying the data by estrous cycle stage reveals $Rspo2^{PN}$ US recruitment in males is greater than that of proestrus, but not diestrus, females. During threat memory retrieval, we show all three cell types are reengaged to the CS and surprisingly, recruited immediately following omission of the expected US. Importantly, PV^{IN} are exclusively reengaged during the expected US. Our research of distinct cell type activity profiles exposes a dynamic and complimentary interplay between neural populations and previously unreported findings of sex-specific engagement, providing a potential mechanism for sex differences in amygdala regulation.

Disclosures: A.J. Tellez: None. **B.W. Hardin:** None. **N.E. Baumgartner:** None. **P. Teravskis:** None. **E.K. Lucas:** None.

Late-Breaking Poster

LBP044: H.01. Fear and Aversive Learning and Memory

Location: SDCC Hall B

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

Program #/Poster #: LBP044.02/LBP076

Topic: H.01. Fear and Aversive Learning and Memory

Title: Effect of detached and positive reappraisal on fear extinction and recall

Authors: *K. DAR, M. K. ASTHANA;
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Abstract: Cognitive reappraisal strategies have been recently used to enhance fear extinction. Detached and positive reappraisal are two major types of cognitive reappraisal strategies. Both strategies are known to effectively regulate negative emotion. However, previous studies have not distinguished the effect of the nature of reappraisal on fear extinction. The aim of the current study was to investigate the effect of detached and positive cognitive reappraisal on fear extinction and its recall. We used a 2-day screaming lady fear conditioning paradigm, with habituation, acquisition, and extinction occurring on day 1 and spontaneous recovery and reinstatement on day 30. We used arousal, valence, fear, expectancy ratings, and Skin Conductance Response (SCR) as subjective and physiological measures of fear. Participants were divided into three groups: detached reappraisal, positive reappraisal, and standard extinction group. Participants in the detached and positive reappraisal group were provided a pre-prepared reappraisal sentence, which they were instructed to use during extinction. 74 (Mage = 23.2, SD = 3.9; Males =37, Females = 37) participants were recruited to participate in the study. Our results showed a non-significant difference between groups during extinction in subjective arousal [$F(2,71) = 0.11$, $p = .895$, $\eta p^2 = .003$], valence [$F(2,71) = 0.87$, $p = .422$, $\eta p^2 = .024$], and fear ratings [$F(2, 71) = 0.41$, $p = .668$, $\eta p^2 = .011$]. Similarly, in UCS-expectancy ratings, we did not find any significant group difference during extinction [$F(2, 71) = 1.80$, $p = .172$, $\eta p^2 = .048$]. For SCR analysis, participants were removed if CS+ values were less than CS- values. Groups showed a non-significant difference on SCR during extinction [$F(2,45) = 2.12$, $p = .132$, $\eta p^2 = .086$]. Additionally, non-significant group differences were observed in all measures during the spontaneous recovery and reinstatement test phases. Our results imply that cognitive reappraisal did not enhance fear extinction and its recall. This suggests that not all emotion regulation strategies reliably augment extinction, and highlights the importance of considering procedural factors (e.g., timing of extinction) and the nature of the regulatory strategy (self-generated versus pre-prepared) when evaluating the efficacy of cognitive interventions in fear conditioning paradigms.

Disclosures: K. Dar: None. **M.K. Asthana:** None.

Late-Breaking Poster

LBP044: H.01. Fear and Aversive Learning and Memory

Location: SDCC Hall B

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

Program #/Poster #: LBP044.03/LBP077

Topic: H.01. Fear and Aversive Learning and Memory

Support: NIH Grant 5R01MH065961-22
NIH Grant 5R01MH117852-08

Title: Propranolol suppresses renewal of fear in male but not female rats

Authors: *A. P. ABRAMENKO[1], A. ARELLANO PEREZ[2], P. FANG[2], S. MAREN[3,2,1];
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Abstract: Exposure therapy is a widely used and effective treatment for anxiety disorders such as post-traumatic stress disorder (PTSD). A key mechanism by which anxiety is suppressed during exposure therapy is extinction learning. In the lab, extinction learning can be modeled by repeatedly presenting a stimulus (conditioned stimulus) previously paired with an aversive stimulus (unconditioned stimulus) in the absence of that aversive stimulus, resulting in the reduction of fear responding to the conditioned stimulus. However, fear often relapses when extinguished conditioned stimuli are presented outside the extinction context (renewal), limiting treatment effectiveness. In this experiment, we hypothesized the drug propranolol, a β-adrenoreceptor antagonist, would suppress relapse of fear during renewal due to its anxiolytic effects. Male and female Long Evans rats received five tone-shock pairings in context A before undergoing two days of extinction in a different context (B). Following extinction, each animal was tested in a counterbalanced order for extinction retrieval in the extinction context (B) and renewal in a novel context (C) across two days. Prior to each testing session, animals were systemically injected with either vehicle (saline) or propranolol resulting in four treatment groups. Propranolol administration selectively blocked renewal in males but not females without affecting retrieval. These data suggest that propranolol prevents renewal of fear in a sex-dependent manner.

Disclosures: A.P. Abramenko: None. **A. Arellano Perez:** None. **P. Fang:** None. **S. Maren:** None.

Late-Breaking Poster

LBP044: H.01. Fear and Aversive Learning and Memory

Location: SDCC Hall B

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

Program #/Poster #: LBP044.04/LBP078

Topic: H.01. Fear and Aversive Learning and Memory

Support: DGAPA PAPIIT grant IA206521
DGAPA PAPIIT grant IN227123

Title: Novel vs Familiar Taste: Cortical Representation and IC-BLA Connectivity

Authors: *E. RODRÍGUEZ NAVA[1,2], R. ALCANTARA RIVAS[3], V. TORRES GARCÍA[4], J.-P. MORIN[5];
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Mexico, Mexico City, Mexico; [5]Faculty of Medicine, Universidad Nacional Autonoma de Mexico, CDMX, Mexico

Abstract: Gustatory neophobia is an adaptive response to novel taste stimuli, as it is initially unknown whether the food associated with it is safe to consume. This response decreases with repeated exposures, a phenomenon known as attenuation of neophobia (AN), which has been reliably replicated in rodents under controlled laboratory conditions. There is ongoing debate as to whether this type of incidental learning involves an increase in the hedonic value of the gustatory stimulus after familiarization. To address this question, we used male Wistar rats to analyze the microstructure of licking behavior during the AN process. Additionally, we examined the neuronal activity of the insular cortex (IC)-basolateral amygdala (BLA) circuit, which has been implicated in the representation of taste valence during AN. Three experimental conditions were compared: water (A), novel saccharin (with a single exposure to the stimulus) (S1), and familiar saccharin (with five exposures to the stimulus) (S5). At the behavioral level, a significant increase in both consumption and number of licks was observed in the S5 group, confirming the attenuation of neophobia. However, the analysis of lick microstructure revealed no significant differences in the temporal organization of licks, indicating little, if any, change in palatability during familiarization. Using double immunofluorescence (IF) vs c-Fos—a marker of neuronal activity—and FluoroGold (FG) -a retrograde tracer infused into the BLA- we assessed neuronal activity in the IC after fluid ingestion in the three groups. Analysis of c-Fos expression, FG+ cells, and c-Fos+/FG+ double-labeled cells in the external (layers I-III) and internal (layers IV-VI) layers revealed no significant difference between groups. However, a significant reduction in c-Fos expression was found in the external agranular layer of familiarized animals (S5). Moreover, in the S1 group, higher activity was observed in the external layers compared to the internal ones, a difference that disappeared after familiarization. These findings suggest that, although taste familiarization does not induce global changes in the IC or its connectivity with the BLA, specific subregions -such as the external agranular insular cortex (AI)- may actively contribute to the integration or modulation of the novel gustatory stimulus.

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Late-Breaking Poster

LBP044: H.01. Fear and Aversive Learning and Memory

Location: SDCC Hall B

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

Program #/Poster #: LBP044.05/LBP079

Topic: H.01. Fear and Aversive Learning and Memory

Support: R01MH117852

Title: Locus Coeruleus-Amygdala Circuit Disrupts Prefrontal Control to Impair Fear Extinction

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Abstract: Fear suppression through extinction learning is crucial to behavioral interventions for several trauma-related disorders, such as post-traumatic stress disorder (PTSD). One of the main factors that undermines the success of fear extinction is stress, and fear often relapses under stressful conditions. The locus coeruleus (LC) is the major source of norepinephrine (NE) in the brain, and NE is known to be a key regulator of stress and extinction learning. There is evidence showing that NE release in the basolateral amygdala (BLA) impairs extinction learning, and a vast body of evidence has demonstrated that the infralimbic cortex (IL) is necessary for extinction learning. Here, we explore how LC chemogenetic stimulation leads to NE release in the BLA and suppresses IL activity to impair extinction learning. In different experiments, we used chemogenetics to activate the LC and its projections to the BLA, in combination with calcium imaging and fiber photometry to monitor activity of the IL and BLA in response to LC stimulation under different behavioral conditions. Initially, we found that LC stimulation leads to a reduction in IL spontaneous activity, in a manner that mirrors the effects of a natural stressor (i.e., foot shock). LC stimulation during extinction impaired fear extinction and disrupted IL neural dynamics during extinction and extinction retrieval. When we combined LC stimulation with intra-BLA injections of the β-adrenergic receptor blocker propranolol, we found that activation of these receptors in the BLA is necessary for the disruption of IL activity caused by LC stimulation. Additionally, we found that LC stimulation in combination with a foot shock promotes sustained activation of IL-projecting BLA neurons during an immediate extinction session. Finally, we show that activation of the LC-BLA pathway in isolation is sufficient to drive the immediate extinction deficit after a weak conditioning event. Together, our data shows that LC hyperactivity drives a heightened stress state which leads to extinction impairment. This involves activation of β-adrenergic receptors in the BLA and suppression of IL activity.

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Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP044.06/LBP080

Topic: H.01. Fear and Aversive Learning and Memory

Support: R21MH133003-02

Title: A8 dopamine neuron stimulation diminishes fear learning and supports operant responding

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Abstract: Dopamine plays a central role in reward behavior. More recently, dopamine has also been shown to modulate fear learning and expression. Most everything we know about dopamine function comes from studies centering on the ventral tegmental area (A10) and substantia nigra (A9) dopamine populations. Yet, there are many more sources of dopamine in the brain. One such source is the A8 dopamine contained within the retrorubral field. A8 dopamine neurons are positioned posterior/dorsal to the A9 dopamine neurons and have extensive projections to the forebrain. Prior work from our laboratory recorded all neuron types in the retrorubral field, finding extensive signaling of threat and aversive outcome. Here, we asked if A8 dopamine neurons modulate fear learning and if their stimulation is intrinsically rewarding. Adult TH-Cre Long Evans rats (n = 53, 30 females) received bilateral infusions of Cre-dependent channelrhodopsin into the retrorubral field, and bilateral fiber-optic ferrules implanted over A8 dopamine cell bodies. Rats were assigned to one of three behavioral conditions. The two paired groups had a 10-s tone paired with a foot shock (0.35 mA). Paired-Cue rats received 20 Hz blue-light stimulation during the cue period, while Paired-ITI rats received blue-light stimulation during the inter-trial interval (ITI). In the Unpaired-Cue group, tone and shock were presented separately, yet blue-light stimulation was administered during the cue. Extinction testing was given in the absence of blue-light illumination. Next, each rat received two optogenetic self-stimulation sessions in which a nose poke yielded a 1-s burst of 20 Hz blue-light illumination. During the patent session, blue-light entered the brain, while during the occluded session, blue-light was blocked at the ferrule. Preliminary results show that A8 dopamine stimulation reduced fear in the Paired-Cue group and supported self-stimulation across all rats (patent responding ~2x greater than occluded). A complete analysis will be presented.

Disclosures: A.M. DuBois: None. **T.B. Mazonson:** None. **P.I. Hartono:** None. **C.F. Lamberson:** None. **C.O. Bolarinwa:** None. **T.S. Lee:** None. **M.L. David:** None. **L.H. Counsman:** None. **G.E. Valvo:** None. **A.C. Fitzpatrick:** None. **S. Shen:** None. **J.B. Boyce:** None. **N.T. Gordon:** None. **S. Qian:** None. **M. Moaddab:** None. **M.A. McDannald:** None.

Late-Breaking Poster

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Location: SDCC Hall B

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

Program #/Poster #: LBP044.07/LBP081

Topic: H.01. Fear and Aversive Learning and Memory

Support: MH113053
MH117791

Title: Opposing zona incerta firing patterns to predicted threat and aversive outcome

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Abstract: Discriminating between dangerous and safe events is essential for survival. A failure to discriminate, termed fear generalization, results in treating safe stimuli as if they were dangerous. While neural circuits for fear acquisition have been extensively studied, neural circuits for fear discrimination remain unclear. Evidence suggests that the zona incerta, a subthalamic structure, contributes to fear generalization and discrimination. The goal of this study was to examine zona incerta activity while rats undergo a challenging fear discrimination procedure. Adult Long Evans rats (n = 3, 2 females) were implanted unilaterally with drivable microelectrode bundles dorsal to the zona incerta. Following recovery, we recorded zona incerta activity while rats underwent fear discrimination consisting of three 10-s auditory cues, predicting unique foot shock probabilities: danger (p = 1), uncertainty (p = 0.25), and safety (p = 0). Each session consisted of 24 trials: three danger trials, three uncertainty shock trials, nine uncertainty omission trials, and nine safety trials with an average inter-trial interval of 3.5 min. The schedule for rewarded nose poking was completely independent of cue presentation and foot shock. Conditioned suppression ratios were calculated as an indicator of fear discrimination. We recorded 158 neurons over 31 sessions from the posterior zona incerta. Rats showed complete discrimination during sessions in which zona incerta neuron activity was recorded. Zona incerta neuronal firing showed a global pattern of firing inhibition in response to threat cues (danger and uncertainty), followed by excitation after foot shock. Within this global pattern, two functional clusters were apparent. One cluster (n = 74) showed sustained inhibition during the threat cues, then sustained excitation following foot shock. A second cluster (n = 44) showed an initial inhibition to the threat cues, which was followed by ramping excitation towards cue offset and foot shock. Ramping activity in response to the danger cue was stronger and began earlier than in response to the uncertainty cue. This second cluster then showed a strong, phasic firing increase following foot shock offset, which transitioned to a lower level of sustained excitatory firing. Our complete analyses will determine if these zona incerta firing patterns reflect the rat's behavioral output, sensory responses to foot shock, or threat prediction signals that could be used to drive discrimination. We will present these results.

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Late-Breaking Poster

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Location: SDCC Hall B

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Shanghai Municipal Commission of Science and Technology Program 21dz2210100, 2021SHZDZX
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Title: Investigation of inhibitory Engrams in the basolateral amygdala for memory extinction

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Abstract: It is widely assumed that memory engrams primarily consist of excitatory neurons. Here, we investigate whether inhibitory engrams also play critical roles in memory processes. To explore putative inhibitory engrams, we employed an extinction paradigm, as extinction learning is known to involve the formation of an inhibitory memory trace. To visualize and manipulate inhibitory engrams, we developed novel immediate early gene (IEG)-based engram-tagging tools selective for inhibitory interneurons. Our key findings are as follows:

1. Extinction training activates a large, predominantly GABAergic neuronal population in the basolateral amygdala (BLA).

2. Suppressing activity-tagged GABAergic ensembles impairs extinction, leading to reactivation of the original fear-encoding engram and the return of fear behavior.

3. Extinction-tagged GABAergic ensembles comprise both parvalbumin (PV)- and somatostatin (SST)-expressing subpopulations; however, SST neurons, but not PV neurons, play a critical role in fear memory extinction.

Our results demonstrate that specific inhibitory GABAergic BLA engrams are formed during fear extinction, which interfere with existing fear memory circuits and suppress conditioned fear responses. These findings provide novel insights into the neural mechanisms of fear extinction and suggest that BLA GABAergic neurons are potential therapeutic targets for cognitive disorders, such as post-traumatic stress disorder (PTSD).

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Late-Breaking Poster

LBP045: H.02. Reward and Appetitive Learning and Memory

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

Program #/Poster #: LBP045.01/LBP083

Topic: H.02. Reward and Appetitive Learning and Memory

Support: R35NS132156-03

Title: AFD-AIY Neural Dynamics Underlying Thermotaxis Memory Retrieval in C elegans

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Abstract: C. elegans thermotaxis offers a model for studying how memory encoding and retrieval occur at the cellular level. Worms migrate toward prior training temperatures, with AFD (sensory neuron) and AIY (interneuron) playing central roles. Yet the dynamics of AFD-AIY signaling during memory retrieval and the molecular mechanisms shaping this signal remain unclear. Here, we quantify population migration kinetics under varied training regimens. Ablation of either AFD or AIY yields cryophilic movement regardless of prior training, but AFD or AIY deficient worms trained at 15 °C migrate more slowly than wildtype. In Tc20-trained worms lacking AFD, AIY calcium responses markedly decline, resembling WT responses after Tc15 training. Strikingly, enhanced AIY activity at low temperature arises both in the absence of AFD (Tc20) and in Tc15trained worms without requiring AFD function. This suggests that hyperpolarized AFD facilitates swift cryophilic migration at Tc15 and suppresses cryophilic behavior in Tc20trained animals. Thus, AIY activation might require AFD, but not its activity, to enhance cryophilic migration, while AFD dependent AIY inhibition maintains the worm's position at 20 °C. AFD is known to be glutamatergic. eat4/vGLUT mutants do not perform thermotaxis, and rescuing EAT4 expression specifically in AFD partially restores cryophilic migration in Tc15 worms, though not to wildtype performance, implying a contributory role for AFD vesicular glutamate transporter in memory encoding. Neither eat-4/vGLUT mutants nor AFD rescue strains display significant alterations in AIY activity, indicating an AIY independent cryophilic migration pathway as well. Moreover, manipulating PKC1, through constitutive activation or loss of function, elicits cryophilic or thermophilic behavior regardless of prior training. AIY responses in these pkc1 mutants are enhanced across the temperature ranges toward which worms migrate. These findings indicate that PKC1's plastic activity regulates memory retrieval by tuning AIY responses, though the downstream neurotransmission mechanisms by which PKC1 modulates AFD-AIY signaling remain unresolved.

Disclosures: X. Fu: A. Employment/Salary (full or part-time); Yale University. **J. Lee:** None. **S. Kumar:** A. Employment/Salary (full or part-time); Yale University. **D.A. Colón-Ramos:** A. Employment/Salary (full or part-time); Yale University.

Late-Breaking Poster

LBP045: H.02. Reward and Appetitive Learning and Memory

Location: SDCC Hall B

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

Program #/Poster #: LBP045.02/LBP084

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Assessing water restriction versus citric acid water to motivate sustained attention performance and their effects on astrocytic functions

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Abstract: Astrocytes regulate key processes such as glutamate and GABA recycling, glucose metabolism, and water homeostasis—functions sensitive to stress and metabolic state. Operant conditioning tasks used to study sustained attention in rodents typically rely on food or water restriction to reward correct responses. To make these rewards effective, animals often undergo food or water restriction which can lead to distress. Recent research suggests that adulterating water with low concentrations of citric acid (CA) can preserve motivation for tap water as a reward in operant tasks without restricting access. The current study tested whether Long Evans rats given ad libitum access to 2% CA water would remain motivated to perform a sustained attention task for tap water rewards (ns>8). Rats of both sexes were trained to distinguish signal (25, 100, or 500 ms light) from nonsignal trials using specific lever responses, with trials spaced at variable intervals to require sustained attention to the central panel. Task acquisition required several shaping stages from learning to press the lever to learning the signal, nonsignal response, to increasing the attentional demands by inserting a variable signal length. Rats showed similar task acquisition and weights with the water restriction and citric acid. To assess astrocyte involvement in the sustained attention task across the two methods, we used immunohistochemistry to examine glutamine synthetase (GS), a critical enzyme in astrocytic glutamate recycling at the synapse, and glial fibrillary acidic protein (GFAP), a protein which increases with stiffening of the cell linked to inflammation. We observed that GS density is significantly higher with citric acid treatment than with water restriction ($F_{1,26}$=8.20, p=0.008) while GFAP area of expression is significantly lower ($F_{1,16}$=13.70, p=0.002). This work suggests while 2% citric acid in water can motivate rats to respond for tap water rewards, there may be differences in brain chemistry as compared to water restriction that should be considered when using this paradigm.

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Late-Breaking Poster

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Program #/Poster #: LBP045.03/LBP085

Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant OD011132
Children's Marcus Autism Center

Title: Ventral hippocampus supports habitual behavior through amygdalo-striatal connections

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Abstract: Habits are familiar actions that have been repeatedly performed and rewarded, such that they have become almost automatic. The ventral hippocampus (vHC) contributes to habitual behavior, but mechanisms are still being delineated. Here we used distinct schedules of reinforcement that induce goal-sensitive or habit-like behavior in mice. Habit-like behavior was associated with dendritic spine abundance on excitatory vCA1 neurons, as well as elevated immediate-early gene (IEG) levels, a proxy for neural activity. Selectively stimulating cells containing these IEGs induced habit-like behavior in the same context in which the habit was learned, but not in a different context, suggesting that the vHC drives context-dependent habit. Chemogenetic stimulation of vHC projections to the central nucleus of the amygdala (CeA) also induced habit-like behavior, which occurred via inhibitory connections with the dorsomedial striatum (DMS), as opposed to the dorsolateral striatum. Thus, vHC-CeA-DMS connections support habit-like behavior. Notably, while stimulation of these connections prompted habit-like behavior, their inhibition did not obstruct it. Altogether, the vHC is a potent modulator of habit-like behavior via discrete amygdalo-striatal connections, even whilst it is not necessary for habitual action.

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: JSPS P23383
Kakenhi 23KF0286

Title: Increased claustrum activity coincides with the deactivation of the retrosplenial cortex during waiting for reward in mice

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Abstract: The claustrum is a thin structure densely connected with the brain. Notably, with the default mode network (DMN) it has both a strong anatomical connectivity and, during resting states, a strong functional connectivity.
Here, we observed the behaviour of the claustrum neurons and the activity of the retrosplenial cortex (RSP, an important component of the DMN) during waiting for a long period for reward. RSP is involved in either spatial-oriented functions by translating between self-perspective and allocentric perspective, or non-spatial functions by comparing perceptual input with memory. Because the claustrum targets non-spatial processing cells in RSP, we hypothesized that the behaviour of the two would be correlated during waiting for reward, when the demand for spatial information is minimum.
To this end, first we recorded with fibre photometry the activity in the RSP of 5 mice. We induced locally either the expression of GCaMP6s in most types of neurons with simultaneous retrograde Cre and AAV9.Syn.FLEX.GCaMP6s injections, or GCaMP8m expression in CaMKII positive neurons with an AAV9.CaMKII.jGCaMP8m injection. Second, in another mouse, we injected retrograde Cre in RSP and AAV9.Syn.FLEX.GCaMP6s in the claustrum, to express GCaMP6s in claustrum neurons projecting to RSP. In this case, only the claustrum was imaged, through an nVoke miniscope (Inscopix), via an implanted prism GRIN lens. All mice performed a freely-behaving, delayed-reward task. The waiting times for reward increased from session to session from 0.5 s to 20 s, some reaching up to 120 s.
The results show a strong decrease in the activity of the RSP as soon as the mouse engages in waiting at the food site. During long waiting times (> 10 s), the deactivation reaches a plateau that is maintained until the food is delivered. Then, when the food is delivered, the activity shortly increases during the consumption of the reward, followed by an even stronger decrease than during waiting for reward.
About half of the imaged claustrum cells consistently showed short firing bursts immediately before waiting or during waiting. The peak in the average activity of all the imaged claustrum cells coincides with the moment when the activity in the RSP decreases sharply. A local peak in the average activity was also present after the consumption of the reward.
The results suggest the use of the feedforward inhibition from the claustrum to RSP to switch off the spatial-processing cells and to promote the non-spatial processing cells during waiting and after reward consumption. Future optogenetic manipulations of claustrum neurons will clarify this causal relationship.

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Late-Breaking Poster

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Location: SDCC Hall B

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

Program #/Poster #: LBP045.05/LBP087

Topic: H.02. Reward and Appetitive Learning and Memory

Title: Functional MRI reveals stable sign- and goal-tracking phenotypes linked to dopaminergic modulation and psychopathology

Authors: *A. LUPO[1,2], N. SAMBUCO[2], P. SELVAGGI[2], L. A. ANTONUCCI[2], A. BERTOLINO[2], G. BLASI[2], P. DI PALO[2], R. PASSIATORE[3], A. RAIO[2], A. RAMPINO[2], M. A. MEHTA[4], G. PERGOLA[2,5];
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Abstract: Humans differ in how they process rewards and their predictive cues. This variability is relevant to psychiatric disorders such as schizophrenia, ADHD, and addiction. The Sign-Tracker/Goal-Tracker (ST/GT) model, derived from rodent studies, differentiates individuals who attribute incentive salience to reward-predictive cues (ST) from those focused on reward outcomes (GT). However, human studies replicating this model are limited, often underpowered, and focused on learning paradigms, with sparse evidence on the underlying neural processes. Here, we translated the ST/GT framework into humans via fMRI and assessed its relevance to pharmacological sensitivity and clinical status. Data from 1,203 individuals were collected across four cohorts: a Discovery sample, i.e., the third follow-up of the IMAGEN multi-site study (n = 890), a Replication (n = 245) and a Clinical (n = 34) sample from the University of Bari Aldo Moro, and a Pharmacological Challenge cohort (n = 34), recruited at the King's College London. All participants completed variants of the fMRI Monetary Incentive Delay (MID) task, which isolates reward anticipation and outcome processing without any learning component. The Pharmacological cohort received risperidone or haloperidol in a double-blind, placebo-controlled design. Hierarchical k-means clustering of BOLD activity in reward-related regions identified robust ST-GT neuroimaging profiles, reproducible across independent samples (balanced accuracy >78.7%). ST showed heightened ventral striatal activity during anticipation, while GT exhibited stronger outcome-related activation. In the Pharmacological cohort, only ST exhibited a selective response to D_2 antagonists ($p = 0.005$), with a significant reduction in anticipatory BOLD activity ($p < 0.001$) and a linear dose-dependent effect ($p = 0.009$). Finally, GT (vs. ST) patients exhibited higher negative symptom severity ($p=0.006$), which, in turn, was significantly associated with blunted ventral striatal BOLD activity ($p=0.002$) and with a greater D_2 dopaminergic affinity ($p=0.020$). These findings suggest that ST/GT neuroimaging phenotypes reflect biologically grounded individual differences in incentive salience attribution. The ST-specific dopaminergic sensitivity supports the utility of this model as a translational framework for personalized interventions in psychiatric disorders involving reward dysfunction.

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Late-Breaking Poster

LBP045: H.02. Reward and Appetitive Learning and Memory

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Topic: H.02. Reward and Appetitive Learning and Memory

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Title: State-dependent modulation of functional connectivity-timescale interactionsin the macaque brain.

Authors: C. ELORETTE[1], S. H. FUJIMOTO[1,2], P. H. RUDEBECK[1], B. E. RUSS[3], ***A. FUJIMOTO**[1,2];
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Abstract: To guide behavior, cortical and subcortical regions of the brain must coordinate by modulating both regional neural responses as well as coherence between distant areas. Such brain activity can be assessed as neural timescale and functional connectivity, representing brain's local and network-level processing, respectively. However, how those measures dynamically change from resting state to awake-behaving states, and depending on behaviorally-relevant dopaminergic manipulation, remain unknown. Macaque monkeys (N = 11, 5 females) underwent anesthetized functional MRI scans following administration of either no drug or selective dopamine receptor antagonists (D1: SCH-23390; D2: haloperidol). A subset of monkeys also underwent awake resting-state and behaving scans during a probabilistic choice task or a passive viewing task. All fMRI data were preprocessed and then submitted to whole-brain functional connectome and neural timescale analyses to assess both local and network-level brain activity across multiple scan conditions. Consistent with previous reports, neural timescales (decay constant: tau) during resting state were longer in cortical than in subcortical areas. SCH broadly decreased the amplitude parameter, whereas haloperidol predominantly increased cortical taus. In contrast, data from awake behaving scans differed substantially from resting state, showing a profound reduction of cortical taus and an increase of subcortical taus. Consequently, correlations between tau and average functional connectivity in cortical and subcortical ROIs changed dynamically across scan conditions, such that their correlation became less tight when subjects were performing a task. UMAP clustering revealed three clusters: (1) awake task scans, (2) cortical ROIs at rest, and (3) subcortical ROIs at rest. Furthermore, the awake task cluster tended to converge when subjects show greater performance in the probabilistic choice task. This pattern indicates that cortical and subcortical measures of local

and network-level activity become more closely aligned when subjects are engaged in a task. Together, we reveal the way through which cortical and subcortical areas modulate their activity depending on the state where the brains are in. These findings highlight the interaction between functional connectivity and neural timescale as a potential biomarker of cognitive engagement in primates, paving the way to understanding the organization principle of the neural dynamics across different brain states.

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Late-Breaking Poster

LBP045: H.02. Reward and Appetitive Learning and Memory

Location: SDCC Hall B

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

Program #/Poster #: LBP045.07/LBP089

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Title: Broadly-projecting mesolimbic dopamine neurons implement a distributional critic across the striatum

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Abstract: Dopamine (DA) neurons are critical for reinforcement learning and adaptive behavior, classically thought to encode a scalar reward prediction error (RPE). Recent work proposes that DA populations instead implement distributional reinforcement learning (dRL), encoding the full distribution of possible returns rather than their mean. We sought to uncover the anatomical and functional implementation of dRL in the dopamine-striatal circuit. Using Neuropixels 2.0 probes, we recorded from projection-defined DA neurons with antidromic optogenetic tagging. DA neurons projecting to the ventral striatum (VS, n=18) matched predictions from an expectile

regression code, a statistical framework for dRL coding. In contrast, dorsal striatum (DS)-projecting DA neurons (n=15) did not encode full reward distributions, suggesting they cannot implement dRL alone. Strikingly, neurons projecting to both VS and DS (n=14) most accurately represented reward distributions, with minimal error between decoded and true distributions measured via Wasserstein distance. Thus, broadly projecting mesolimbic DA neurons broadcast distributional teaching signals across the striatum. This organization matches actor-critic models, with VS as critic and DS as actor, and extends this framework to the distributional framework with the implementation of a distributional critic. To complement single-unit recordings, we developed custom multi-fiber photometry with 14 fibers spanning VS and DS (n=11 mice). Recordings showed DA axons broadcast positive RPEs across striatum, scaling with reward size and stronger to reinforced (CS+) than non-reinforced (CS−) cues. However, inhibitory CS− responses were confined to VS, suggesting ventral regions receive “cleaner” RPEs while dorsal regions carry additional information. Indeed, DS showed transient responses to state transitions and excitations to aversive cues, consistent with compartmentalized representation of outcome-specific information. Together, these findings identify VS-projecting DA neurons as the substrate to learn full reward distributions, and VS+DS-projecting DA populations as broadcasters of distributional prediction errors, while DS-only-projecting neurons lack this property. They reveal how distributional RPEs are broadcast yet interwoven with compartmentalized, non-RPE signals, establishing a new organizational principle for DA projections to the striatum and insight into how distributional coding is mechanistically implemented in brains to support continuous control in complex environments.

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Late-Breaking Poster

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Title: Exposure to the herbicide glyphosate disrupts activity in the hippocampus, but not medial prefrontal cortex, in male rats

Authors: *A. GARCÍA QUIÑONES[1], A. ADAMS[2], E. RIVERA[3], L. L. MENDEZ-SANTACRUZ[4], D. SIERRA-MERCADO[5];
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Abstract: Glyphosate, one of the most widely used herbicides, has raised concerns regarding its impact on mental health. Recent work from our lab indicates that glyphosate, even at levels considered safe by the Environmental Protection Agency (2.0 mg/kg/day), increases anxiety-like behaviors. Unfortunately, increases in anxiety may exacerbate other behaviors, such as avoidance. As part of a larger behavioral project, we are exploring how glyphosate influences the neurobiology of brain regions implicated in avoidance. Specifically, the prelimbic (PL) subregion of the medial prefrontal cortex is crucial for expression of avoidance, whereas the infralimbic (IL) subregion is thought to inhibit avoidance. Furthermore, the hippocampus is implicated in the contextual modulation of fear-related behaviors. For these reasons, we hypothesized that glyphosate exposure would disrupt activity in these brain regions. To test this idea, adult male rats (3 months of age upon commencement of experiments; Glyph: n=16; Ctrl: n=16) were exposed to glyphosate (2.0 mg/kg/day) or filtered water for controls for 12 weeks. Next, rats were sacrificed for histological analysis using c-Fos labeling. Experimenters performing data analyses were blinded to the condition of the treatment to minimize bias. We did not observe any changes in either PL (Glyph: 280 cells/cm^2; Ctrl: 220 cells/cm^22;p=0.3970, T-test) or IL (Glyph: 200 cells/cm^2; Ctrl: 200 cells/cm^2 2;=0.69, T-test). Next, we assessed four subregions of the hippocampus. Here, we observed that glyphosate increase cellular activity in the (CA1: Glyph: 75 cells/cm^2; Ctrl: 12 cells/cm^2, $p = 0.0001$, T-test), CA3 (Glyph: 50 cells/cm^2; Ctrl: 12 cells/cm^2, $p = 0.0031$, T-test) and dentate gyrus (Glyph: 65 cells/cm^2 ; Ctrl: 11 cells/cm^2, $p = 0.0001$, T-test). Contrary to this, there was no difference in activity CA2 (Glyph: 30 cells/cm^2; Ctrl: 20 cells/cm^2, $p > 0.08$). Collectively, this exploratory work suggests that glyphosate disrupts contextual modulation of fear-related behaviors thus impairing avoidance.

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Late-Breaking Poster

LBP045: H.02. Reward and Appetitive Learning and Memory

Location: SDCC Hall B

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Program #/Poster #: LBP045.09/LBP091

Topic: H.02. Reward and Appetitive Learning and Memory

Support: National Research Foundation of Korea (NRF) grant No. 2020R1A5A2019413.

Title: Chemotherapy-induced anorexia is mediated by vagal serotonin signaling to the NTS and is rescued by ginger extract

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Abstract: Background. Cisplatin is a platinum-based chemotherapeutic agent widely used in oncology, but its clinical benefit is limited by severe side effects, including anorexia. This anorexia not only reduces quality of life but also threatens treatment adherence. Recently, it has been reported that appetite loss is not a simple reflection of metabolic conditions, but rather a complex outcome of interactions among the intestine, vagus nerve, and central appetite control circuits. In particular, anorexia is associated with altered excitability in the nucleus tractus solitarius (NTS), underscoring the need to investigate mechanisms regulating this excitability. **Methods and Results.** In a cisplatin (6 mg/kg)-induced anorexia rat model, oral administration of ginger extract (100 or 500 mg/kg) significantly restored food intake, with the 100 mg/kg dose also improving body weight recovery at 48 hours. Biochemical analyses revealed that cisplatin elevated serotonin levels in both serum and nodose ganglion tissue, whereas ginger extract normalized these increases. qPCR and Western blot analyses further demonstrated that cisplatin selectively upregulated 5-HT3A and 5-HT4 receptor expression in the nodose ganglion, which were downregulated by treatment. Importantly, vagotomy abolished the anorexia-inducing effects of cisplatin, demonstrating that vagal signaling is indispensable for mediating anorexia. Moreover, pharmacological blockade of 5-HT3A or 5-HT4 receptors (Palonosetron, 0.1 mg/kg, i.p.; Piboserod, 1 mg/kg, i.p., respectively) similarly prevented cisplatin-induced anorexia. To further assess changes in NTS excitability under anorexic conditions, we measured the expression of parvalbumin (PV) and somatostatin (SST) in the NTS. **Conclusions and Significance.** Our findings demonstrate that chemotherapy-induced anorexia depends on vagal serotonin receptor signaling and, more critically, on its transmission to the NTS, where peripheral inputs are integrated into central feeding circuits. By suppressing serotonin hyperactivation and restoring vagal receptor balance, ginger extract effectively disrupts this pathological gut-vagus-NTS signaling cascade. This work highlights the vagus-to-NTS pathway as a pivotal target for therapeutic intervention and provides a foundation for further studies into neuronal dysfunction within the NTS that may exacerbate feeding suppression during chemotherapy.

Disclosures: H. Kim: None. **W. Kim:** None.

Late-Breaking Poster

LBP045: H.02. Reward and Appetitive Learning and Memory

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Topic: H.02. Reward and Appetitive Learning and Memory

Support: NIH Grant R01 DA022340-12S1

Title: CB1Rs on Septohippocampal Cholinergic Projections Regulate Reward-seeking and Spatial Working Memory

Authors: *A. D. FIGUEIREDO[1], J. F. CHEER[2];
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Abstract: ABSTRACT
Title**: CB1Rs on Septohippocampal Cholinergic Projections Regulate Reward-seeking and Spatial Working Memory**
The cholinergic medial septum-diagonal band (MSDB) projections to the hippocampus regulate effort-based motivation and spatial working memory, but the role of presynaptic cannabinoid receptor type 1 (CB1R) in modulating these processes remains unclear. We hypothesized that deleting CB1Rs selectively in MSDB cholinergic terminals projecting to the CA1 hippocampus (cKO) would enhance motivation and cognition by disinhibiting acetylcholine (ACh) release. To test this, we employed a retrograde viral strategy to delete CB1Rs in cholinergic terminals and combined chemogenetics (Gq-DREADDs) with local antagonism of muscarinic (mAChRs) and nicotinic (nAChRs) receptors to dissect circuit-specific mechanisms. Fiber photometry was integrated with behavioral assays to track real-time ACh (ACh Sensor) and endocannabinoid (eCB Sensor) signaling. The cKO mice exhibited enhanced effort-based motivation (increased Pmax, breakpoint) and spatial working memory (increase alternations). These phenotypes were replicated using a chemogenetic approach to activate MSDB cholinergic projections and abolished by intrahippocampal mAChR/nAChR antagonism, indicating both receptor subtypes critically mediate motivational outcomes. Photometry revealed that ACh signaling encodes reward-related behaviors, with, (i) anticipatory decreases preceding reward delivery, and (ii) a post-reward transient increase followed by a prolonged suppression below baseline. The duration of post-reward suppression correlated with diminishing reward demand and was attenuated in cKO mice. Similarly, latency to lever press and hippocampal ACh were inversely correlated, with elevated ACh corresponding to shorter latencies. Lastly, preliminary photometry recordings of eCB signaling revealed a transient increase post-reward, temporally overlapping with ACh suppression. This eCB signal lengthened as reward demand decreased, implicating eCBs in feedback regulation of cholinergic tone. These findings establish CB1R in MSDB cholinergic terminals as a key regulator of hippocampal ACh release, while also linking eCB-ACh signaling to motivated behavior. The distinct temporal dynamics of ACh and eCB signaling suggest a mechanism by which these systems dynamically adjust reward-seeking behaviors based on effort-outcome associations. These results advance our understanding of how neuromodulatory systems interact to shape cognitive and motivational states, with implications for disorders marked by cholinergic dysfunction.

Disclosures: A.D. Figueiredo: None. **J.F. Cheer:** None.

Late-Breaking Poster

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Title: Glyphosate exposure alters neuronal activity in the Prefrontal Cortex on female rats

Authors: *A. ADAMS[1], L. L. MENDEZ-SANTACRUZ[2], D. SIERRA-MERCADO[3];
[1]University of Puerto Rico Medical Science Campus, San Juan, PR; [2]Biology, Univ Puerto Rico Río Piedras, San Juan, Puerto Rico; [3]Anatomy & Neurobiology, Univ Puerto Rico School of Medicine, San Juan, Puerto Rico

Abstract: Glyphosate is a widely used herbicide that has been associated with increased anxiety-like behaviors. In fact, preliminary work from our lab indicates that glyphosate, even at levels considered safe by the Environmental Protection Agency (2.0 mg/kg/day), increases anxiety. Heightened anxiety may exacerbate defensive responses, such as avoidance. Avoidance is a defensive behavior in which an individual takes action to prevent potential harm. Avoidance can be modeled in rodents using platform-mediated avoidance. In this paradigm, rodents are trained to press a lever to obtain a sucrose reward. Next, rodents learn to avoid a foot shock by stepping onto a safe platform during presentation of a conditioned auditory stimulus (tone). Stepping on the platform protects the rodent from shock but eliminates access to a sucrose reward. Thus, platform-mediated avoidance creates a conflict in which rodents must choose between avoidance (no shock) and a reward (receiving sucrose pellets). The neurobiological basis of avoidance involves neuronal activity in medial prefrontal cortex, including both the prelimbic (PL) and infralimbic (IL) subregions. We hypothesized that glyphosate exposure enhances avoidance behavior and increases neuronal activity in brain regions that drive avoidance. To test our hypothesis, female rats (Sprague-Dawley, 3 months of age upon commencement of experiments) were trained in platform-mediated avoidance. Subsequently, the rats were exposed to glyphosate (2.0 mg/kg/day, n=10); or filtered water (control group, n=10) for 12 weeks. Then, the rats were euthanized and their brains were extracted for histological analysis. Finally, we used the immunofluorescence with the neuronal marker NeuN to identify neuronal populations in PL and IL. Experimenters performing data analyses were blinded to the condition of the treatment to minimize bias. Glyphosate exposure significantly decreased avoidance expression compared to controls ($p = 0.0294$). We observed that glyphosate increased neuronal count in the prefrontal

cortex of female rats ($p = 0.5922$, T-test), but not in either of the subregions individually. These exploratory findings suggest that glyphosate may modulate avoidance behavior through alterations in neuronal activity within the medial prefrontal cortex, which is implicated in decision-making and regulation of defensive responses.

Disclosures: A. Adams: None. **L.L. Mendez-Santacruz:** None. **D. Sierra-Mercado:** None.

Late-Breaking Poster

LBP045: H.02. Reward and Appetitive Learning and Memory

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Title: NAc shell Pdyn neurons' activity modulates dopamine dynamics during associative learning.

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Abstract: Dopaminergic neurons in the ventral tegmental area (VTA) and their projections to the nucleus accumbens (NAc) play a central role in encoding both rewarding and aversive experiences. These dynamics are modulated by neuropeptides such as dynorphin, which originates in the NAc predominantly from D1-type medium spiny neurons (MSNs), also called prodynorphin-expressing neurons (Pdyn), and can act via kappa opioid receptors (KORs) on VTA neurons to influence dopamine release. The NAc shell is anatomically and functionally heterogeneous, with dorsal and ventral subdivisions contributing differently to motivated behaviors. Disruptions in dynorphin and dopamine signaling in the NAc are linked to disorders such as depression and addiction. Understanding if/how dynorphin release influences dopamine

during associative learning could reveal the mechanisms behind these disorders and inform the development of new treatments.
We first monitored dynorphin release during associative learning using a genetically encoded fluorescent sensor (kLight1.3). Male and female KOR-cre mice (n=5) were subjected to the experiment. We detected dynorphin release in both dorsal and ventral NAc shell in response to reward during learning sessions. Given dynorphin's capacity to regulate VTA dopamine neurons, we next asked how Pdyn-expressing neurons influence dopamine signaling. Male and female Pdyn-cre mice (n=10) were injected with a virus expressing an axonal dopamine sensor (GRAB-DA). Using fiber photometry, we tracked dopamine dynamics simultaneously in dorsal and ventral NAc shell during learning and observed cue-reward dopamine signals. To test whether Pdyn-expressing neurons shape these dopamine responses, we optogenetically stimulated Pdyn neurons in either the dorsal or ventral shell during the Pavlovian task. Unexpectedly, stimulation in both subregions enhanced cue-evoked dopamine release. Furthermore, stimulating Pdyn terminals in the VTA produced a similar enhancement, indicating that these neurons influence dopamine both locally within the NAc and via NAc-to-VTA projections.
Altogether, our findings demonstrate that dynorphin is released in the NAc shell during associative learning and that Pdyn-expressing neurons in both dorsal and ventral NAc shell modulate dopamine dynamics. Since these neurons co-release GABA along with dynorphin, future studies will dissect the specific contribution of dynorphin/KOR signaling to these effects.

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Late-Breaking Poster

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Program #/Poster #: LBP045.13/LBP095

Topic: H.02. Reward and Appetitive Learning and Memory

Support: Reed College John Leonard Adams Fellowship

Title: The Influence of Enrichment Conditions in Ketamine use and Decision-Making

Authors: *E. MARQUARDT, D. LIEVANO, V. GONZALEZ;
Psychology, Reed College, Portland, OR

Abstract: Ketamine, a prescription anesthetic, has gained attention for its rapid-acting antidepressant effects, however concerns regarding potential abuse have prompted further research into the broader effects on behavior. Prior research has shown its ability to enhance synaptic plasticity and neuroplasticity pathways, though the impact on decision-making and its relation to anxiety is poorly understood. Environmental enrichment (EE), whether physical, social, or both, has been found to enhance cognitive and emotional behaviors, with variable outcomes depending on sex and type of EE. In this study, we investigated how physical and/or

social EE, when paired with ketamine, affects decision-making under uncertainty and anxiety-like behaviors in rats. Eighteen Long-Evans rats were assigned to one of four enrichment groups with varying social and physical enrichment and their behaviors were assessed using the Elevated Plus Maze (EPM) and an information-seeking task. In the information-seeking task, rats choose between two levers or options - the Info option, where a cue informs if there will be a delayed reward delivery or no reward; and the No Info option, where the cue does not provide information about the delayed reward. Ketamine was administered (i.p., 5 mg/kg) for five consecutive days prior to testing. Rats in paired housing without physical enrichment developed the strongest preference for the no-info option in the information-seeking task, while those in solo housing without physical enrichment developed the strongest preference for the informative option. The administered dose of ketamine did not appear to have an effect on locomotion activity or task performance. In future studies testing ketamine's effect on info-preference, ketamine should be administered at a higher dosage or for a longer duration prior to behavioral testing. Then, we can confirm whether there is a synergistic relationship between environmental enrichment and pharmacological treatment on emotional and cognitive processes.

Disclosures: E. Marquardt: None. **D. Lievano:** None. **V. Gonzalez:** None.

Late-Breaking Poster

LBP046: H.03. Motivation

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Topic: H.03. Motivation

Support: NIH Grant 1FI2GM146653-01
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Title: Loss of thalamic glis3 reveals sex-specific divergence in defensive strategies during motivational conflict

Authors: *J. O'MALLEY[1], M. YURGEL[2], Y. LENG[3], C. GAO[4], A. R. PLATT[5], M. A. PENZO[1];
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Abstract: Post-Traumatic Stress Disorder (PTSD) affects ~5% of the U.S. population, with women disproportionately impacted. A hallmark of PTSD is excessive threat avoidance, that overrides reward-seeking behaviors, biasing the balance of needs to defensive responses. The paraventricular nucleus of the thalamus (PVT) is a stress-responsive hub that integrates competing needs to guide motivated behaviors critical for homeostasis. Within the PVT,

genetically distinct neuronal populations coordinate these conflicting appetitive and aversive behaviors. Recent transcriptomic studies identified selective expression of the transcription factor *glis3* as a top marker in one of these cell types implicating a critical role for the gene. While *glis3* mainly regulates peripheral metabolic function, genome-wide association studies (GWAS) have linked *glis3* polymorphisms to PTSD suggesting a role in neurological processes linked to threat processing. Our analysis of our own PVT transcriptomic data showed a significant difference in *glis3* gene expression between male and female mice, suggesting the potential for sex-related differences. To determine the role of PVT *glis3* in threat-driven behavior, we tested conditional knockout mice in a platform-mediated avoidance conflict task (PACT). All mice learned food-reward nosepoking similarly, but introducing threat-conflicts revealed a sex-specific effect of *glis3* deletion. Male knockouts earned significantly more rewards, while female knockouts earned fewer rewards and displayed increased freezing and time on the platform. Avoidance was unaffected, indicating that *glis3* loss alters defensive strategies rather than avoidance, promoting active responding in males and passive responding in females. To assess if changes to metabolic function underly these differences we measured changes in ad lib feeding, hedonic feeding, and body weight but found no significant differences suggesting the sex dependent differences in motivated behaviors during threat processing are due to threat processing alone. However, additional behavioral assessment of locomotion suggests potential sex-dependent differences in arousal in response to stress. Future work aims to explore how arousal shapes threat-processing and to isolate how PVT *glis3* shapes threat processing independently examining active avoidance, and passive freezing responses during fear conditioned freezing. Taken together our data suggests that loss of PVT *glis3* differentially alters threat processing in a sex-dependent manner and may explain underlying sex differences in PTSD susceptibility.

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Late-Breaking Poster

LBP046: H.03. Motivation

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Topic: H.03. Motivation

Support: National Institutes of Health (NIH) Intramural Research Program (IRP)
ZIA MH002928
1ZIAMH002950

Title: A synaptic mechanism for encoding the learned value of action-derived safety

Authors: *E. E. MACDONALD[1], J. MA[2], K. YU[3], M. E. AUTHEMENT[4], Y. LENG[5], H. C. GOLDBACH[6], V. A. ALVAREZ[7], B. B. AVERBECK[8], M. A. PENZO[9];
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Mental Health, Rockville, MD; [4]National Institutes of Health, Bethesda, MD; [5]Unit on The Neurobiology and Affective Memory, Natl Inst Mental Health/NIH, Bethesda, MD; [6]NIMH, Washington, DC; [7]Laboratory on Neurobiology of Compulsive Behaviors, National Institutes of Health, Bethesda, MD; [8]NIMH/NIH, Kensington, MD; [9]National Institute of Mental Health, Bethesda, MD

Abstract: Motivated behavior is often framed in terms of biologically grounded outcomes, such as food or threat. Yet many motivated actions, like the pursuit of safety or agency, depend on outcomes that lack explicit sensory value and must instead be inferred from experience. Here, we identify a thalamostriatal circuit mechanism by which such internally constructed outcomes acquire motivational value. In mice performing an active avoidance task, neurons in the paraventricular thalamus (PVT) projecting to the nucleus accumbens (NAc) develop a safety-encoding signal that emerges following successful avoidance. This signal is experience-dependent and value-sensitive, diminishing upon devaluation of the instrumental contingency. Selective silencing of the PVT→NAc projection at safety onset disrupts avoidance persistence without impairing action-outcome learning, as confirmed by computational modeling of value updating based on prediction error. Mechanistically, PVT input recruits cholinergic interneurons (CINs) to modulate dopamine release and this influence depends on synaptic potentiation mediated by GluA2-lacking AMPA receptor insertion at PVT-CIN synapses. Disrupting this plasticity selectively impairs the avoidance response by blunting the motivational value of safety without affecting acquisition. These findings reveal how thalamic circuits assign value to abstract, internal outcomes, providing a framework for understanding how goals like safety are inferred, stabilized, and rendered behaviorally effective.

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Topic: H.03. Motivation

Title: Understanding the Benefits of Nature Exposure on Mental Health Based on NIMH's Research Domain Criteria

Authors: *H. ROSAS, J. LEE, J. LIU, J. DOAN, S. GOH, T. JAYATILAKE, A. ADDI, N. SACHS, E. BERNAT;
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Abstract: Research demonstrates that nature exposure (NE) improves stress, mood, depression, sleep, and productivity. The restorative aspects of nature have been widely discussed, yet the

underlying mechanisms remain unclear. In this study, the health-promoting effects of NE are assessed relative to three domains—Positive Valence (PV), Negative Valence (NV), and Cognitive (COG)—from the National Institute of Mental Health's Research Domain Criteria (RDoC), a framework of biobehavioral systems organized into latent factors explaining normative to psychopathological behaviors. Our preliminary work indicates that psychopathology is related to decreased PV and COG, and increased NV. We predict that NE will work to reverse this pattern. The current project aims to provide initial evidence for improved target mechanisms to understand the health-promoting effects of NE.

Thirty-two participants (15 females, 16 males, 1 non-binary) viewed two sets of NE stimuli, landscape and waterscape. Each set includes 60 still images and a five-minute Virtual Reality (VR) experience, with set order counterbalanced. Self-report measures of the RDoC domains included pre-post tests of Visual Analog Scale (VAS) for bipolar valence (Pleasantness, Unpleasantness) and the Positive and Negative Affect Schedule (PANAS) for PV and NV, and Cognitive Control and Flexibility Questionnaire (CCFQ) for COG. A Scale of Urges was also included as a secondary measure of craving for common sources of problem behavior (e.g., smoking, alcohol, cell phone usage). A Present Moment Focus (PMF, cf. mindfulness) instruction was provided to enhance participant engagement in NE.

Wilcoxon Signed-Rank Sum tests evaluated the effects of NE on PV, NV, and COG measures. The VAS significantly increased towards PV (Pleasantness) (71.9%; $Z = 3.11$, $p = 0.002$, $r = 0.555$). From the PANAS, PV (positive affect) decreased (-6.5%; $Z = -2.15$, $p = 0.032$, $r = 0.389$) and NV (negative affect) decreased (-14.5 %; $Z = -3.65$, $p < 0.01$, $r = 0.665$), where NV decreased nominally, but not significantly, more than PV. Our measure of COG (CCFQ) considerably increased (4.1%; $Z = 2.32$, $p = 0.021$, $r = 0.414$). The Scale of Urges showed a notable reduction (-32.3%; $Z = 2.51$, $p = 0.011$, $r = 0.482$).

Overall, the results supported the hypotheses, demonstrating that NE increased PV (VAS), reduced more NV than PV (PANAS), and increased COG (CCFQ). These findings motivate further investigation with physiological measures to validate whether the biological aspects of the RDoC system were modulated. Understanding the underlying mechanisms of NE in more depth can advance the development of NE for mental health interventions to improve public health.

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Late-Breaking Poster

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Support: NIH Grant 5R16GM149491-03
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Title: BDNF/TrkB Signaling Pathways in the Extinction of Morphine Place Preference

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Abstract: Opioid overdose remains a major public health crisis in the U.S., and related deaths have spiked in recent years, with prescription opioid overdose deaths increasing drastically among women. This rise, and failure of current pharmacological treatments to prevent relapse, highlights the need for novel, sex-informed approaches. Exposure-based therapies in humans aim to reduce relapse by exposing individuals to drug-associated cues in the absence of the drug. Extinction training (ET), a behavioral model simulating exposure-based therapy, involves exposure to drug-associated cues without reinforcement and has shown promise in reducing drug-seeking in preclinical models. Previously, we showed that by using conditioned place preference (CPP), ET reduced preference for the drug-paired side (DPS) accompanied by an increase in brain-derived neurotrophic factor (BDNF) expression in the hippocampus (HPC) of male rats. Similarly, females also showed significant BDNF increase in the HPC, but also in the ventral striatum/nucleus accumbens (VS/NAc), a vital region to reward and relapse. This study aimed to characterize BDNF-related signaling pathways in the HPC and the VS/NAc of female rats following ET. Adult female Sprague-Dawley rats were conditioned with morphine (5 mg/kg) for 8 days, followed by 4 days of forced extinction sessions. Our control group did not receive ET and spent this time in their home cage. Rats were euthanized post-ET, and VS/NAc and HPC tissue were analyzed by Western blot for the BDNF receptor, the phosphorylated TrkB (pTrkB). Our results showed TrkB upregulation in the VS/NAc of female rats that underwent ET and were classified in the extinction-resistant group. In the HPC, no significant changes in pTrkB were noticed although a tendency to increase in the extinction group was observed. Moreover, extinction of drug seeking was preliminarily associated with the estrus phase of the estrus cycle. Our results suggest that while ET activates BDNF pathways in females, TrkB activation may be regulated in a region-specific manner, highlighting the need for further research on hormonal modulation and sex-specific mechanisms underlying opioid abuse.

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Title: The role of the nociceptin opioid peptide in dorsal raphe nucleus on appetitive motivation

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Abstract: In the United States, approximately 59.3 million people experience mental illness across their lifetime. Many neuropsychiatric disorders are characterized by dysregulation of affective or motivated circuits in the brain. The dorsal raphe nucleus (DRN) is considered one of the most important brain regions in modulating affective and motivated behaviors. This brain region is a frequent focus of neuropsychiatric research due to its role as the primary source of serotonergic neurons. However, the DRN is not only a major serotonergic hub, but also a region with high expression of endogenous opioids, including dynorphin, enkephalin, and nociceptin. Despite the established behavioral significance of the endogenous opioid system on motivation and affect, its function within the DRN, particularly that of the nociception opioid peptide, has been largely understudied. Considering that nociceptin opioid peptide receptors are highly expressed on DRN serotonin neurons, it is likely that DRN nociceptin may play an important modulatory role on affective and motivated behaviors. To test this hypothesis, we employed a CRISPR-Cas9 approach to selectively knock down nociceptin opioid peptide in the dorsal raphe nucleus of Pnoc-cre mice and measured changes in various appetitive and motivated behaviors. Results so far suggest that CRISPR knockdown of nociceptin reduces preference for social a stimulus and for sucrose preference. By contrast, nociceptin knockdown oppositely increases progressive ratio breakpoint, perhaps suggesting divergent roles for nociceptin on affect versus motivation. Future work will continue to characterize this subpopulation and incorporate other neuronal actuators like DREADDs to dynamically modulate behavioral phenotypes. Additionally, we will employ a dual-color fiber photometry approach to simultaneously record data from nociceptin neurons (RCaMP, a calcium indicator) and nociceptin peptide (NOPLight, a nociceptin biosensor). These experiments would reveal novel, temporally descriptive information and provide insights into how this opioid peptide is recruited to modulate behavior.

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Title: Subthalamic nucleus theta oscillations track momentary happiness, not winning, after reward outcome

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Abstract: Momentary happiness is known to depend on the interplay between expected value (EV) and recent reward prediction errors (RPEs). Integrating reward expectations with real outcomes is critical to healthy decision-making, but this is altered in people who have impulse control disorders (ICDs). Crucially, up to 35% of people with Parkinson's Disease (PwPD) suffer from an ICD, where their ability to assess the value of potential and obtained rewards is impacted. In PD, treatment with DBS affords the unique opportunity to both causally stimulate and record neural activity from the value processing centers in the basal ganglia. Despite evidence of the involvement of the subthalamic nucleus (STN) and globus pallidum (GP) in value assessment, their role as well as the effects of DBS on risk/reward outcome evaluation and resulting happiness remain unclear. 20 PwPD with bilateral (n=15) or unilateral (n=5) sensing-enabled Medtronic Percept DBS (10 STN and 10 GP) completed the Rutledge forced choice gambling task in clinic while on dopaminergic medication. Participants chose between a fixed value or a gamble with 50/50 probability of success, periodically rating their happiness. Subcortical neural recordings were acquired from the STN or GP while participants completed six blocks of 30 trials alternating DBS on and off per block, counterbalanced across people. Baseline-corrected average theta (4-7Hz) power was calculated from local field potential (LFP) data 0.3 to 1.3 seconds after result outcome for gamble trials. Linear mixed-effects models (LMMs) were used to identify the strongest predictors of happiness. When DBS is off, STN theta power following the result of a gamble significantly increases as happiness increases ($p=0.013$, $\beta=0.094$). Turning DBS on significantly alters this relationship ($p=0.036$, $\beta=-0.11$), negating the positive correlation between happiness and STN theta. This effect was not seen in the GP ($p=0.23$), showing spatial selectivity of this finding. Further supporting the unique contribution of happiness over RPE, an LMM with happiness as a predictor provided a better fit to theta power than a model with RPE (lower Akaike Information Criterion (AIC): $4066.7 < 4068.3$), suggesting that happiness is a stronger predictor of theta dynamics. STN but not GP theta power increases when one is happy with a result, revealing a biomarker in PwPD that tracks momentary

happiness beyond the effects of winning or losing. This relationship disappears when DBS is turned on. Together, this work reveals an important role for theta power in the STN during happiness and reward evaluation which DBS significantly modulates.

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Title: Distinct encoding of reward and aversion by D1 cell subtypes in the nucleus accumbens

Authors: *M. B. POMRENZE, N. DENOMME, J. BAEK, G. C. TOUPONSE, M. WANG, N. ESHEL, J. M. TUCCIARONE, R. C. MALENKA;
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Abstract: The nucleus accumbens (NAc) is a key integration site for the control of motivated behaviors. Not only is diverse information routed to the NAc by glutamate and neuromodulator (i.e., dopamine (DA)) inputs, a heterogenous assortment of cell-types locally integrate and process information related to reward, aversion, and motivation. Canonical models of the NAc describe two major medium spiny neuron subtypes, expressing DA D1 or D2 receptors, which encode and promote reward and aversion, respectively. However, single-cell RNA sequencing has revealed numerous subpopulations within these major families. We recently identified an eccentric cell-type in the D1 family, expressing *Tshz1*, that operates distinctly from canonical D1 neurons, which express *Pdyn*. How these D1 cell subtypes modulate local NAc activity to encode reward and aversion remains incompletely understood. Optical stimulation of *Tshz1* neurons with ChRmine in the NAc medial shell produced sustained inhibition of DA release and was aversive. In contrast, stimulation of NAc *Pdyn* neurons transiently increased DA release and was reinforcing. Stimulation of *Tshz1* neurons also generated sustained inhibition of neighboring *Pdyn* and ChAT neurons, but less so in D2 or PV- and SST-expressing interneurons. Light offset triggered an excitatory response in SST interneurons. Stimulation of *Pdyn* neurons also inhibited ChAT neurons, but this inhibition decayed within 1-2 seconds. Both *Tshz1*- and *Pdyn*-induced inhibition of ChAT cell activity produced an excitatory rebound upon light offset. The magnitude of this rebound correlated with the magnitude of inhibition. Recordings during behavior showed increased activity in both *Tshz1* and *Pdyn* neurons during social interaction. During palatable

food intake in the home cage, *Tshz1* neurons displayed inhibition while *Pdyn* neurons were excited. ChAT neurons presented with complex waveforms during both tests. In pavlovian and operant sucrose reinforcement tasks, *Tshz1* neurons consistently showed reduced activity when sucrose was consumed while *Pdyn* neurons showed enhanced activity. ChAT neurons again displayed multi-phasic responses during sucrose cue presentation. In response to foot shocks, both *Tshz1* and *Pdyn* neurons were excited while ChAT neurons showed rapid inhibition followed by a robust rebound. We thus have identified divergent responses to appetitive and aversive stimuli in two distinct D1 neuronal populations in the NAc. Ongoing studies are dissecting how these cell subtypes interact with neuromodulatory systems (e.g., DA, opioids) to control appetitive and aversive behavioral states.

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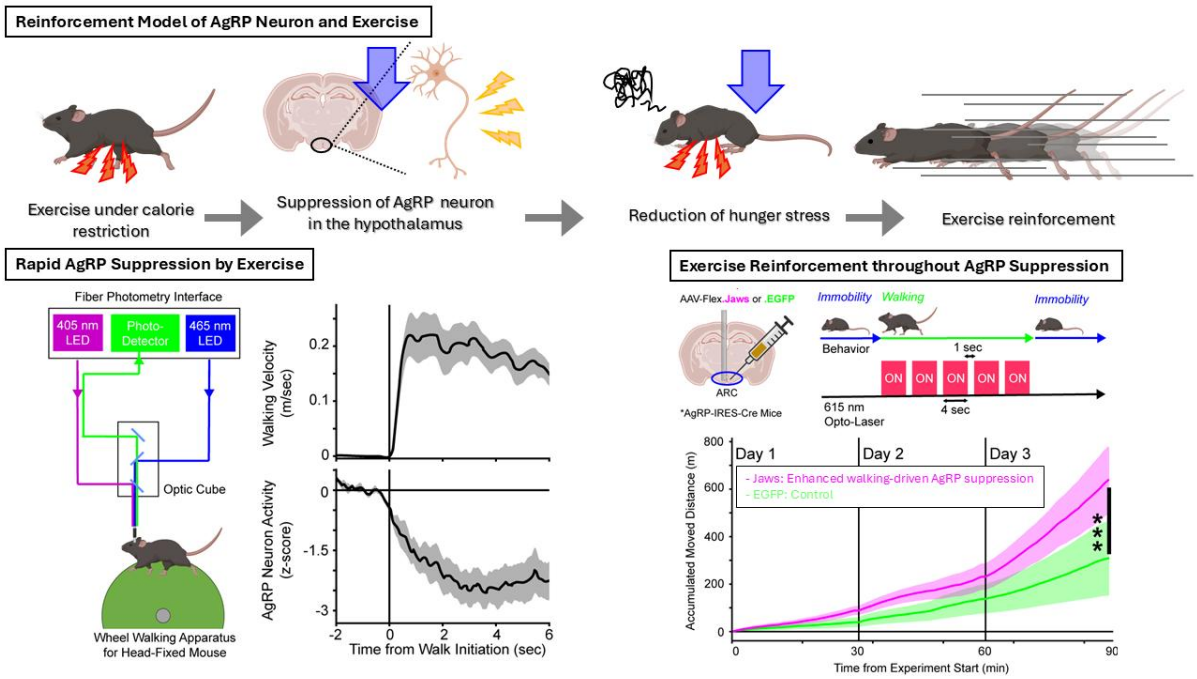
JSPS Grant JP25H02624

Title: AgRP Neuronal Suppression by Spontaneous Movement Encodes Exercise Reinforcement

Authors: *J. YOSHIDA[1], N. SUEMATSU[2], S. SOMA[2], I. LEVY[1], T. L. HORVATH[1]; [1]Department of Comparative Medicine, Yale School of Medicine, New Haven, CT; [2]Department of Molecular Cell Physiology, Kyoto Prefectural University of Medicine, Kyoto, Japan

Abstract: Hypothalamic agouti-related peptide (AgRP) neurons that drive hunger-related behaviors are activated during energy deficit, encode negative valence but can be inhibited even by perception of food without digestion. Here, we show that in head-fixed mice, discrete motor actions such as spontaneous walking and conditioned licking rapidly suppress AgRP neuron activity. This suppression persisted throughout movement and terminated upon cessation, which was independent of food perception or conditioned cues. The degree of suppression was positively correlated with movement vigor. While optogenetic enhancement of AgRP neuron suppression did not initiate movement, it promoted reinforcement of concurrent walking behavior. These findings unmask that spontaneous, low intensity physical activity can reduce AgRP neuron activity reinforcing concurrent movement/exercise with implications for systemic health benefits.



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Title: CRF-Mediated Plasticity in the VTA-NAc Circuit Underlies Stress-Induced Changes in Social Attachment

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Abstract: Social stress reshapes neural circuits involved in reward and attachment, often in sex-specific ways. In prairie voles (Microtus ochrogaster), social defeat (SD) induces social avoidance and alters partner preference, disrupting pair bonding in males while accelerating it in females. Prior work from our lab identified corticotropin-releasing factor (CRF) as a key modulator of these effects, but the impact on mesolimbic dopamine circuits remains unclear. To investigate this, we assessed molecular changes in CRF and dopamine signaling in the nucleus accumbens (NAc) and ventral tegmental area (VTA), regions critical for reward and pair bonding. Western blot and ELISA analyses revealed sex-specific changes in CRF levels and CRF and dopamine receptor expression in NAc following SD and pairing. Notably, CRF R1 levels increased in the VTA of both sexes after SD, implicating this receptor in stress-induced modulation of dopamine. Pharmacological manipulation in the VTA confirmed that CRF R1 activation promotes partner preference in stress-naïve voles, but blocks bonding in defeated males. Immunohistochemical data in the VTA showed increased activity of GABAergic neurons expressing CRF R1 in defeated subjects. Interestingly, defeat increased GABA expression in the VTA of males while not in females. Finally, preliminary photometry analysis of CRF in the VTA and dopamine in the NAc suggests sex-specific and stress-dependent transient changes during social investigation. These data provide mechanistic insight into how social stress disrupts bonding through sex-specific effects on CRF-dopamine interactions in mesolimbic circuits.

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Topic: H.03. Motivation

Title: Investigating Molecular Orchestrators of Sexually Dimorphic Ethanol Reward Behavior

Authors: *A. MARINI-DAVIS;
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Abstract: Investigating Molecular Orchestrators of Sexually Dimorphic Ethanol Reward BehaviorAntonio Marini-Davis, Ryan Oliver[1,2], Bailey Godwin[1], Sera Chase[1], Ziam Khan[1,3], Fernando J. Vonhoff[1]Reward behavior encompasses a range of vital behaviors and organism must have to ensure survival and eventual propagation of its species. The first step in encoding a reward response is to associate a stimulus with a desirable outcome. However, in *innate* reward responses, the organism does not need to make this association before encoding a stimulus as rewarding. Instead, the organisms internal state can develop a reward response over its lifetime,

as is the case with sexual rewards. In our work, we investigate potential molecular forces driving the salience of one such innate rewards: ethanol. In drosophila, ethanol can trigger an innate reward response as it signifies fermenting food in nature, or a possible sterile environment for egg laying. However, there has been conflicting observations between several studies investigating innate ethanol reward response in drosophila, with some studies suggesting an innate repulsion, and some suggesting an innate attraction, depending on sex. We observe that ethanol reward response depends on the sex, mating status and age of the animal, with young virgin males being the only group innately attracted to ethanol. We identify several potential molecular forces driving this attraction: neuropeptide F (NPF), Corazonin (Crz), and apontic (Apt). While strong effects of manipulating these proteins were observed only in males, we identified juvenile hormone (JH3)—an analog of thyroid hormone in mammals—acting within the nervous system to influence innate ethanol preference in both sexes, regardless of mating status. Additionally, we observe that JH3 has an effect on ethanol reward that is unique to ethanol and not other rewarding or repulsive substances. [1]Department of Biological Sciences, University of Maryland Baltimore County, Baltimore, MD, U.S.A. [2] Current address: Department of Biological Sciences, University of Delaware, Newark, DE. [3] Current address: University of Maryland School of Medicine, Baltimore, MD, U.S.A.

Disclosures: A. Marini-Davis: None.

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Support: NIDA, R01DA044315

Title: Neurokinin B expressing dopamine cells exhibit extended activity following appetitive outcomes and stress relief

Authors: *D. C. M. YEATES[1], M. N. NIX[2], L. S. ZWEIFEL[3];
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Abstract: The neuropeptide neurokinin B (NkB) potently increases the activity of dopamine (DA) neurons in the ventral tegmental area (VTA) and mediates numerous behavioral changes following chronic social isolation. Only a subset of VTA DA neurons express the receptor for NkB, *Tacr3,* but what functionally distinguishes DA cells that express *Tacr3* (DA:Tacr3+) from DA cells that lack *Tacr3* (DA:Tacr3-) is not known. To begin to address this, we examined dynamic calcium activity using fiber photometry in *Tacr3* Cre; *Th* Flp male and female mice, with Cre-on/Flp-on GCaMP6m expressed in the DA:Tacr3+ population and Cre-off/Flp-on

GCaMP6m in the DA:Tacr3- population. Using multiple headfixed behavioral paradigms, we find that the DA:Tacr3+ population has distinct activity patterns compared to the DA:Tacr3- population. DA:Tacr3+ neurons respond with moderate phasic calcium responses during consumption of varying sucrose solutions (0% to 30% sucrose), but remain active for up to 15 seconds following the termination of sucrose access. In contrast, DA:Tacr3- neurons show strong phasic responses to sucrose that quickly fall to baseline following access termination. Pavlovian conditioning with three auditory cues that predict different reward probabilities (100%, 50%, and 0%) revealed that DA:Tacr3+ neurons show moderate calcium responses to cues and exhibit extended post consumption activity, but with limited reward expectation induced activity scaling. The DA:Tacr3- population shows classical reward prediction error scaling with strong phasic responses. Following outcome devaluation, DA:Tacr3+ phasic activity almost entirely disappeared while the DA:Tacr3- population had reduced but still significant responses. Functionally, CRISPR mutagenesis of *Tacr3* in VTA DA cells decreased the total number of licks during reward consumption periods. Similar to reward consumption, release from acute restraint stress resulted in phasic increase in dopamine in both DA:Tacr3+ and DA:Tacr3- neurons, but the duration of the activation was larger and more sustained in the DA:Tacr3+ population across different restraint lengths. Finally, social isolation resulted in faster reaction times to reward predictive cues, with a corresponding increase in phasic calcium rise during reward consumption in both DA:Tacr3+ and DA:Tacr3- populations. Collectively, these results demonstrate that the DA:Tacr3+ population differentially encodes reward- and stress-related information, and activation of the Tacr3 receptor is linked to the vigor of reward responding.

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Support: NIDA Grant DA047976
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NIMH Grant MH129310

Title: Cerebellar circuits mediating social craving

Authors: *Z. HUANG[1], A. PACHECO-SPIEWAK[1], C. LIS[2], K. PAPASTRAT[1], N. KANG[3], S. J. WEBER[4], C. LÉNA[5], L. A. RAMSEY[6], M. VENNIRO[7];
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Paris, France; [6]NIDA IRP, Baltimore, MD; [7]Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD

Abstract: Background: Social interactions are highly rewarding, and periods of social isolation amplify the motivation to socially engage in humans. Here, we developed a rat model to mimic social craving. We also identified a novel role for cerebellar circuits in mediating social craving during periods of social isolation. **Methods**: First, we trained male and female rats for food (2h/d, 6d) and social (2h/d, 12d) self-administration. Next, we assessed social craving following 1 and 14 days of social isolation. During late craving test on Day 15, we identified brain-wide social craving-activated brain regions using neuronal activity marker Fos. Next, using DREADD-based chemogenetic inhibition, we investigated the roles of cerebellar circuits during social craving. Lastly, we used *ex vivo* brain slice electrophysiology to examine glutamatergic synaptic plasticity following social isolation. **Results**: Regardless of sex, social craving was higher after 14 days of social isolation than after 1 day, demonstrating enhanced social craving after social deprivation. Social craving was associated with activation of the deep cerebellar nuclei (DCN), upstream cerebellar Vermis and Crus, and downstream ventromedial thalamus (VML). Chemogenetic inhibition of DCN, Crus, VML and a selective inhibition of DCN◊VML decreased social craving following 14 days of isolation. Using *ex vivo* brain slice electrophysiology, we found that social isolation reduced AMPA/NMDA receptor current ratio at DCN◊VML synapses. **Conclusion**: We introduced a novel social craving rat model and identified novel roles of the DCN, upstream input from Crus, and downstream projection to VML in increased motivation to seek social interaction during periods of social deprivation.

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Topic: H.03. Motivation

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BBRF Young Investigator Grant 28897

Title: Sociosensory mechanisms mediating cocaine craving

Authors: *K. PAPASTRAT[1], A. C. PUCHE[2], L. A. RAMSEY[3], M. VENNIRO[2], D. CAPRIOLI[4], C. LIS[5];
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Abstract: Title: Sociosensory mechanisms mediating cocaine craving
Authors: Kimberly M. Papastrat[1,2], Cody A. Lis[3], Daniele Caprioli[4,5], Adam C. Puche[1,2], Leslie A. Ramsey[6], Marco Venniro[1,2,7]* **Affiliations**:[1]Department of Neurobiology, University of Maryland School of Medicine, Baltimore, USA[2]Program in Neuroscience, University of Maryland School of Medicine, Baltimore, USA[3]Department of Integrative Physiology and Neuroscience, Washington State University, Washington, USA[4]Department of Physiology and Pharmacology, Sapienza University of Rome, Rome, Italy[5]Santa Lucia Foundation (IRCCS Fondazione Santa Lucia), Rome, Italy[6]Intramural Research Program, NIDA, NIH, Baltimore, USA[7]Department of Psychiatry, University of Maryland School of Medicine, Baltimore, USA **Background**: Social interactions are inherently rewarding and provide protection against substance use disorders. However, it remains unclear which components of the complex multisensory social experience drive these effects. In this study, we investigated the role of olfaction in shaping social interaction, social preference over cocaine, cocaine craving in rats, and the associated socio-related physiological responses during cocaine craving.**Methods:** We performed bulbectomy in male and female rats to test the necessity of olfaction for volitional social interaction and choice between social interaction and cocaine. To further probe olfactory contributions, we trained rats to self-administer the odor of a social partner, examined their preference for partner-associated social odors over cocaine to model voluntary abstinence, and assessed incubation of cocaine craving. Finally, we used NeuroLux mechano-acoustic devices to measure physiological responses during cocaine craving.**Results**: Independent of sex, rats with intact olfactory systems preferred social interaction over cocaine, while rats with impaired olfaction showed preference for cocaine. Providing access to a partner odor in a choice paradigm led to cocaine abstinence, preventing incubation of cocaine craving, in contrast to forced abstinence or non-contingent reward exposure. NeuroLux recordings provided insight into changes in physiological parameters during social volitional abstinence and cocaine craving. **Conclusion**: Our findings show that olfaction is essential for volitional social reward and that preference for partner-associated odors can buffer cocaine craving. These results highlight the potential of odor-based social sensory interventions for treating substance use disorders and provide new insight into the physiological responses underlying cocaine craving.

Disclosures: K. Papastrat: None. **A.C. Puche:** None. **L.A. Ramsey:** None. **M. Venniro:** None. **D. Caprioli:** None. **C. Lis:** None.

Late-Breaking Poster

LBP046: H.03. Motivation

Location: SDCC Hall B

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

Program #/Poster #: LBP046.14/LBP109

Topic: H.03. Motivation

Support: NIDA DA047976
NIDA DA056440
NIMH MH129310

Title: The impact of autism spectrum disorder models on motivated social interactions

Authors: *N. KANG[1], A. PACHECO-SPIEWAK[2], K. PAPASTRAT[2], H. HARONY-NICOLAS[3], M. VENNIRO[4];
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Abstract: Background: Autism spectrum disorder (ASD) is a neurodevelopmental disorder that impacts social interaction. Here, we investigated how mutations in four commonly associated genes (SHANK3, FMR1, GRIN2B, and NRXN1) affect volitional social interactions in rat models. Method: We trained wild-type and heterozygous SHANK3, FMR1, GRIN2B, and NRXN1 rats for food self-administration (2 h/d, 5 d). Next, we trained them for social self-administration under increasing effort requirements (2 h/d, 15 sessions). The schedule included Fixed Ratio (FR)1, FR2, and FR4 (5 sessions each), followed by Progressive Ratio (PR) tests (3 sessions). Subsequently, we trained the rats to a mutually exclusive choice between social interaction and food (3 h/d, 20 sessions). Once a stable preference was established, we increased the effort requirement for the preferred option (food) to assess the magnitude of preference shifting. Results: FMR1 homozygous knockout rats show social deficits at higher FR or effort requirement relative to wild-type rats. Critically, they reliably performed food self-adminstration at lower FR. For all other groups, we did not observe any differences regardless of sex, age, or FR requirements. Additionally, all groups consistently preferred food over social interaction. However, when the effort required for obtaining food was progressively increased, all groups shifted their preference to social interaction. Conclusion: Our data suggest that heterozygous SHANK3, FMR1, GRIN2B, and NRXN1 rats do not exhibit social deficits in motivated social interactions compared to wild-type rats. The current project is investigating the impact of homozygous FMR1 and NRXN1 mutations on volitional social interaction.

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Topic: H.03. Motivation

Support: NIDA K99 DA045662-01
NARSAD Young Investigator Award
NIDA T32

Title: A whole-brain network gating appetitive female aggression

Authors: *N. L. GOODWIN[1], M. JIN[2], C. TODDES[3], J. NAVARRETE[4], V. TSAI[5], Y. ZHANG[6], P. ANUMOLU[7], S. HUSARIK[8], S. R. NILSSON[9], M. HESHMATI[10], S. A. GOLDEN[6];
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Abstract: Aggression is a highly conserved behavior and exists along a spectrum from adaptive to maladaptive. Adaptive aggression can serve to protect mates, territory, and resources. Maladaptive aggression, however, can present as escalated and uncontrolled, and can occur comorbid with neuropsychiatric disorders including autism spectrum disorders, post-traumatic stress disorder, and intermittent explosive disorder. Inappropriate aggression seeking is detrimental to both individuals and society, and current treatment options are largely ineffective, or associated with significant side effects. Appetitive aggression, in which animals perform operant tasks to gain access to a partner to aggress upon, have been previously described in males. This study directly compares reactive (fight or flight) and appetitive aggression across the sexes. While both males and females both exhibit reactive aggression in resident intruder tests, males but not females show appetitive aggression. I examined the neural correlates of this behavioral sex difference using whole-brain c-fos activity mapping, identifying a potential network inhibiting appetitive aggression in females. In males, I further identified the lateral septum as a potential locus of differential control of reactive and appetitive aggression. Ultimately, this study indicates that reactive and appetitive aggression are neurally dissociable processes, with an inhibitory network in females gating appetitive aggression.

Disclosures: N.L. Goodwin: None. **M. Jin:** None. **C. Toddes:** None. **J. Navarrete:** None. **V. Tsai:** None. **Y. Zhang:** None. **P. Anumolu:** None. **S. Husarik:** None. **S.R. Nilsson:** None. **M. Heshmati:** None. **S.A. Golden:** None.

Late-Breaking Poster

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Topic: H.03. Motivation

Support: NIDA [DA047976 and DA056440]
NIMH [MH129310]

Title: Modeling social isolation in heroin dependence

Authors: *N. BAIDOO[1], C. LIS[2], M. ANFUSON[3], N. KANG[4], M. VENNIRO[5,6];
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Abstract: BACKGROUND: Social motivation is central to substance use disorders, yet its disruption by drug dependence remains understudied. We examined how heroin dependence and withdrawal affect social interaction using a mutual self-administration task and developed a model of progressive social isolation, in which partner non-engagement during drug exposure shifts residents' preference toward alternative rewards.METHODS: We trained rats for food and then mutual social self-administration (1 h/day, 5 sessions each). We induced heroin dependence in residents with osmotic minipumps (3.5 mg/kg/day) and tested its effects on volitional mutual social and food self-administration. We then examined withdrawal, precipitated with naloxone (3 mg/kg, s.c.) or spontaneous after pump removal. Finally, we developed a novel choice procedure in which partner rats could reject mutual social interaction with heroin-dependent residents, allowing residents to either persist in seeking social reward despite rejection or shift their behavior towards an alternative reward.RESULTS: We observed that heroin dependence reduced mutual social interactions, with further disruption during naloxone-precipitated withdrawal, while food self-administration remained unaffected. Mutual social behavior recovered following spontaneous withdrawal. We also found that a subset of partner rats avoided heroin-exposed residents, indicating that drug dependence disrupts both social motivation and mutual social engagement. Moreover, among rejected residents, some persisted in seeking social interaction, whereas others shifted their preference from social contact to food reward.CONCLUSION: These findings reveal how opioid dependence impairs social motivation and underscore the importance of targeting disrupted social behavior as a critical component of recovery.

Disclosures: N. Baidoo: None. **C. Lis:** None. **M. Anfuson:** None. **N. Kang:** None. **M. Venniro:** None.

Late-Breaking Poster

LBP046: H.03. Motivation

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Program #/Poster #: LBP046.17/LBP112

Topic: H.03. Motivation

Title: Effects of deep brain stimulation in Parkinson's Disease on motivation under the pressure of a deadline

Authors: *E. PEGOLO[1], S. BRENER[2], J. SUH[3], T. VOGEL[4], M. A. APPS[5,4], S. LITTLE[1]; [1]University of California San Francisco, San Francisco, CA; [2]University of California, San Francisco, Berkeley, CA; [3]UCSF, San Francisco, CA; [4]University of Birmingham, Birmingham, United Kingdom; [5]University of Oxford, Oxford, United Kingdom

Abstract: Effort-based decision-making research shows that people often avoid high effort choices, yet motivation can tip the balance when rewards are at stake or when deadlines loom. The pressure of a deadline can sharpen decision-making, pushing individuals to invest effort they would otherwise withhold. In Parkinson's disease (PD), however, motivation and decision-making are disrupted, leading to difficulties in sustaining goal-directed behavior. Deep brain stimulation (DBS) of basal ganglia structures is an established therapy for alleviating motor symptoms in PD, but its impact on cognitive and motivational processes remains less clear. This study investigates how DBS modulates effort-based decisions in PD when actions must be performed under deadline pressure. Twelve PD subjects (age = 65.3 ± 9.8 years) with DBS completed a computerized effort-reward task under deadline pressure, previously validated in healthy controls. Each trial presented a choice between two options: exerting more physical effort for less reward, or less effort for more reward, where effort and reward had 4 levels each. To secure rewards, they had to reach a cumulative effort goal within eight trials (one block), otherwise losing all accumulated credits (Figure 1a). Participants completed two sessions of 20 blocks each: one with DBS ON and one OFF. Linear mixed effects models assessed DBS effects on (i) success rate (percentage of blocks completed within the deadline), (ii) number of trials required to reach the deadline, and (iii) total credits earned. Participants were more successful in achieving their goal (Figure 1b, $\beta DBS\_ON = -5.9$, $p = 0.01$) and won more credits (Figure 1c, $\beta DBS\_ON = -64.4$, $p = 0.02$) with stimulation OFF. No significant differences were found in how quickly they reached the goal (Figure 1d, $\beta DBS\_ON = -0.03$, $p = 0.74$). These results suggest that DBS impairs performance when goals must be achieved within a deadline. These findings further our understanding of how DBS affects motivation and decision-making in PD and provide new insights into the relationship between non-motor symptoms and DBS.

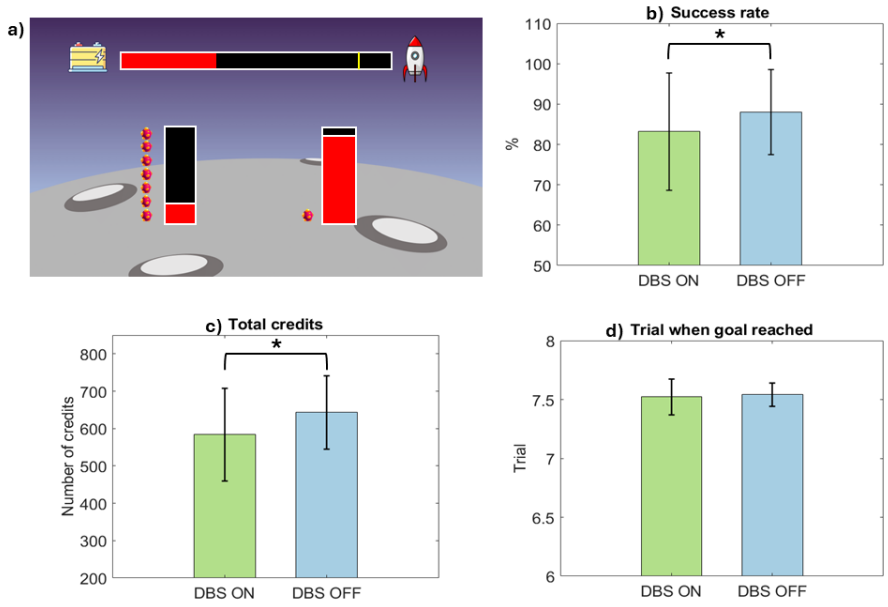

Figure 1 - Deadline paradigm (a), Success rate (b), Total credits (c), and number of trials required to reach the goal (d)

Disclosures: E. Pegolo: None. **S. brener:** None. **J. Suh:** None. **T. Vogel:** None. **M.A. Apps:** None. **S. Little:** None.

Late-Breaking Poster

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Topic: H.03. Motivation

Support: NIH U01 NS131406
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NSF CAREER IOS-2045348
NRSA NIH F30MH131300
Undergraduate Research Opportunities Program (UROP) Grant

Title: Investigating the accumbal microcircuitry underlying social attachment in prairie voles

Authors: *O. NEILLY[1], M. M. EL-KALLINY[1], J. K. KUSHNER[2], C. HOEFFER, Jr.[3], Z. R. DONALDSON[4];
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Abstract: Social attachment is a cornerstone of human behavior, as it is crucial for maintaining healthy relationships and is disrupted in psychiatric conditions. However, the underlying cellular and microcircuit mechanisms of attachment remain poorly understood. The monogamous prairie vole is a compelling model organism for examining social attachment due to their propensity to form life-long pair bonds, unlike the promiscuous mating of laboratory mice and rats. The nucleus accumbens (NAc), a region that processes reward and motivation, is important for social attachment and exhibits bond-induced changes across neuromodulatory, transcriptional, and macrocircuit levels. Here, we investigated specific components of the NAc microcircuitry and their role in bond formation. We first focused on fast spiking interneurons (FSIs), which are known to orchestrate striatal activity through feedforward inhibition. To target FSIs, we inhibited calcium permeable-AMPA receptors (CP-AMPARs). These receptors are preferentially expressed on FSIs and mediate their excitation, which we confirmed in voles via single nucleus sequencing and ex vivo electrophysiology. Hypothesizing that CP-AMPAR-mediated excitation of FSIs is necessary for pair bond formation, we bilaterally infused the CP-AMPAR antagonist IEM-1460 into the NAc of sexually naive prairie voles during pair bond formation. We found that blockade of CP-AMPARs prevented development of a partner preference, without affecting mating or total social interaction. Since CP-AMPARs are expressed at low levels and can have functional roles in other NAc cell types, we next asked if we could selectively and directly manipulate FSIs. We found enhancer-driven AAVs were selective for interneurons but not specific to FSIs, motivating us to test the necessity of interneurons more broadly in bond formation. After virally delivering an inhibitory Gi-coupled Designer Receptor Exclusively Activated by a Designer Drug (DREADD) to accumbal interneurons, we injected clozapine-N-oxide during the bond formation period to inhibit interneurons. Preliminary data shows a disruption of bond formation, suggesting a putative mechanism by which NAc FSIs, through CP-AMPAR-mediated excitation, may coordinate neural encoding of social partners. Finally, to examine neural encoding and how FSIs dynamically coordinate activity of local MSNs, we implanted Neuropixels probes and found that MSN neuronal ensemble activity is regulated by dynamic subsets of bursting FSIs. Our findings establish the necessity of accumbal CP-AMPARs and interneurons in social attachment and begin to elucidate their coordination of local microcircuitry.

Disclosures: O. Neilly: None. **M.M. El-Kalliny:** None. **J.K. Kushner:** None. **C. Hoeffer:** None. **Z.R. Donaldson:** None.

Late-Breaking Poster

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Topic: H.03. Motivation

Support: NIDA Grant DA047976
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NIMH Grant MH129310

Title: Social isolation alters social motivation and the peripheral immuno-transcriptome

Authors: *A. PACHECO-SPIEWAK[1], N. KANG[2], Z. HUANG[1], M. VENNIRO[3];
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Abstract: Background: Social isolation (SI) is a significant risk factor for neuropsychiatric disorders and detrimental physical health outcomes. In contrast, social connection is vital for psychological and physical well-being. Cells of the immune system are affected by SI and are thought to partially determine the associated behavioral disruptions, however the mechanism underlying this is incompletely understood. Here, we investigated the impact of SI on social motivation and the immune system. **Methods**: Male and female rats were weaned at post-natal day 21 and isolated or group-housed for three days (T1) or three-five weeks (T2). Next, we trained them to press a lever to gain access to a social partner as a measure of their social motivation. We then reversed housing conditions to determine whether the behavioral effects could be mitigated over 11 total sessions of social self-administration. In a separate cohort, we collected peripheral blood at T1 and T2 and used single-cell RNA sequencing to investigate molecular changes after acute and chronic SI. **Results**: Three weeks of SI increases male and female rats' social motivation. Additionally, reverse-housing increased social motivation in previously-group housed rats but didn't reduce social motivation in previously-isolated rats. Finally, although the overall cellularity of peripheral immune cells was unaffected by SI, 30 of the 44 single-cell clusters identified by scRNAseq showed significant changes in differential gene expression. **Conclusion**: Our findings demonstrate acute and chronic SI induce molecular and behavioral changes, suggesting a mechanistic link between underlying immune function and hyper-socialization. Furthermore, re-grouping rats after chronic isolation does not rescue typical social motivation.

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Late-Breaking Poster

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Program #/Poster #: LBP046.20/LBP115

Topic: H.03. Motivation

Support: Arnold and Mabel Beckman Foundation

Title: Determining the role of endogenous oxytocin in mediating social reward in rats

Authors: *J. STALL[1], K.-C. LEONG[2];
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Abstract: Investigating the neural mechanisms underlying social reward is important not only to further the current understanding of what drives social interaction, but also for informing potential therapeutic strategies for disorders characterized by social dysfunction. A growing body of literature suggests that the neuropeptide oxytocin (OXT) plays a critical role in modulating social behavior and may also be a necessary modulator of social reward. The present exploratory study aimed to elucidate the role of OXT in driving the rewarding effect of social interaction in Wistar rats using a social conditioned place preference (CPP) paradigm. Briefly, we employed a 10-day social conditioning paradigm, where subjects were conditioned to associate one of two distinct contexts with social interaction with a paired conspecific. In Experiment1, we demonstrated that both male and female rats spent an increased amount of time in the socially-paired chamber on test day compared to baseline relative to animals that did not receive conditioning with a conspecific. In Experiment2 to evaluate the role of OXT in driving this social preference behavior, OXT receptors (OXTR) were selectively knocked down through infusion of AAV-OXTR-shRNA in two neuroanatomical structures involved in reward processing: (1)the ventral tegmental area (VTA) and (2) the nucleus accumbens (NAc). Previous studies have demonstrated that both of these structures are implicated in social behaviors. Subjects received OXTR shRNA infusions either into the VTA or NAc and then underwent the 10-day CPP paradigm. We then evaluated the amount of time spent in the socially-conditioned chamber relative to control animals. Animals demonstrated diminished social conditioned place preference following OXTR knockdown in either VTA or NAc, as measured by a decrease in time spent in the socially-paired chamber at test. Findings from this study provide insight into the role of endogenous oxytocin receptors in either VTA or NAc in mediating social place preference behavior. This research further expands our understanding of the neural mechanisms underlying social reward.

Disclosures: J. Stall: None. **K. Leong:** None.

Late-Breaking Poster

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Support: NIH R21MH129989
NIH R01MH131053
PA CURE Grant SAP#4100085747

Title: Investigating the role of corticothalamic projection neurons in social motivation

Authors: *V. MIGOVICH[1], W.-J. GAO[2];
[1]Drexel University, Philadelphia, PA; [2]Neurobiology and Anatomy, Drexel University, Philadelphia, PA

Abstract: Social animals rely on members of their social group to survive and navigate the world. Social motivation, or the internal drive for social interaction, is disrupted in psychiatric disorders such as schizophrenia, especially for male patients. The medial prefrontal cortex (mPFC) is a central hub for processing social cues and is heavily implicated in maintaining social preference and social motivation. However, the contribution of circuit-specific mPFC subpopulations, as well as the specific dynamics of the prefrontal microcircuits engaged during the pursuit of social reward, remain unclear. The paraventricular nucleus of the thalamus (PVT) is a major target of mPFC innervation implicated in both affective and social behaviors. PVT-projecting mPFC neurons ($mPFC^{PVT}$) have been shown to modulate approach-avoidance decisions under motivational conflict, and data from our laboratory suggest that inhibition of $mPFC^{PVT}$ neurons might be necessary for maintaining social preference in male but not female mice. In this work, we manufactured an apparatus for social self-administration to quantify social drive in an operant manner for both male and female mice. We further characterize the electrophysiological properties of $mPFC^{PVT}$ neurons using circuit-specific patch clamp recording, revealing a contrasting biophysical profile between cells from male versus female mice. Finally, fiber photometry recordings were used to examine *in vivo* circuit-specific neuronal activity of $mPFC^{PVT}$ neurons during the social self-administration task. Results from this study serve to increase our understanding of the role of the mPFC-PVT circuit in social motivation, which may elucidate novel therapeutic targets in psychiatric conditions with social motivation deficits.

Disclosures: V. Migovich: None. **W. Gao:** None.

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Topic: H.03. Motivation

Support: National Institute of Mental Health Grant R00MH124435
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Klingenstein-Simons Foundation
McKnight Neuroscience Award
Simons Foundation Autism Research Initiative

Title: Social context-dependent dopamine dynamics in the medial prefrontal cortex and nucleus accumbens core during social interactions in mice

Authors: *N. JIMENEZ, A. LI, C. YE, M. CUM, S. SMITH, E. ILLESCAS-HUERTA, S. DEHAUT, M. PONDER, N. PADILLA-COREANO;
University of Florida, Gainesville, FL

Abstract: Dopamine (DA), a modulatory neurotransmitter, plays a critical role in motivated behaviors and reward responses. Given that certain social interactions are rewarding, DA is

implicated in both social behavior and decision-making (Krach et al., 2010). Recent work shows that NAcc DA encodes social novelty, motivation, and valence across diverse behaviors (Dai et al., 2022), but its role in long-term partners with established hierarchies remains unknown. The mPFC is critical for social decision-making and processes relevant social information, including social rank. Little is known about the general role of mPFC DA, but emerging evidence indicates that it responds to both positive and negative valence stimuli and signals novelty (Ellwood et al., 2017; Melugin et al., 2024). However, little is known about the circuit-specific roles of DA dynamics in social interactions. To address these gaps, we measured real-time DA signaling in the mPFC and NAcc during social interactions while systematically controlling for familiarity, hierarchy, and competition. Male C57 mice were injected with AAV-dLight1.3b and implanted with optical fibers targeting the NAcc or mPFC. DA was recorded in vivo using fiber photometry. Behavior was analyzed by hand scoring along with pose tracking for automated distance-based interaction detection. Both mPFC and NAcc DA signaled social novelty when encountering strangers, with DA levels decreasing upon repeated exposures and increasing when introduced to a new novel mouse. During interactions with different social agents: novel, short-term (10-minute prior exposure), and long-term (cagemate) familiar agent, we found no difference between responses to cagemates and strangers, suggesting that mPFC and NAcc DA signal more than social novelty. During social defeat bouts with a CD-1 aggressor, NAcc and mPFC DA show opposing DA dynamics. Examining social dominance using a trial-based social competition task, NAcc DA increased in response to signal tones during win trials than during lose trials. Interestingly, NAcc and mPFC DA increased during competitive trials compared to trials were only one animal attempted to win. Our findings suggest that DA dynamics in the NAcc and mPFC play distinct roles in regulating social behaviors in mice. NAcc DA responds to social valence, while mPFC DA is involved in multiple functions including novelty and reward modulation in social context. These findings enhance our understanding of the neural mechanisms underlying social interactions and inform future manipulation studies.

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Topic: H.03. Motivation

Support: R01 MH130941
RF1 NS132912
R01 MH132736

Title: Neural basis of cooperative behavior in mice

Authors: *M. JIANG[1,2,3], L. GU[1,2,3], J. C. KAO[4], W. HONG[5,2,3];
[1]UCLA, Los Angeles, CA; [2]Biological Chemistry, UCLA, Los angeles, CA; [3]Neurobiology, UCLA, Los angeles, CA; [4]Electrical and Computer Engineering, UCLA, Los Angeles, CA; [5]University of California, Los Angeles, Los Angeles, CA

Abstract: Cooperation—the process by which individuals work together to achieve shared goals—is fundamental to both human and animal societies. It plays a crucial role in enhancing individual fitness and promoting group survival. Notably, individuals with social-deficit disorders, such as autism spectrum disorder (ASD) and schizophrenia, often exhibit impaired cooperative behavior. Effective cooperation demands real-time communication, coordination, and decision-making based on ongoing assessment of others' actions. Despite its significance, the behavioral and neural mechanisms underlying cooperation remain poorly understood. In this study, we investigated cooperative behavior in mice, focusing on how they learn to coordinate their actions to obtain shared rewards. We identified key social behavioral strategies and decision-making processes that facilitate successful cooperation. Furthermore, we found that these processes are represented in the anterior cingulate cortex (ACC), and that ACC activity causally contributes to cooperative behavior. These findings offer important insights into the neural basis of cooperation.

Disclosures: M. Jiang: None. **L. Gu:** None. **J.C. Kao:** None. **W. Hong:** None.

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LBP046: H.03. Motivation

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

Program #/Poster #: LBP046.24/LBP119

Topic: H.03. Motivation

Title: Emergence of social deficits in a rodent model of excessive audiovisual stimulation

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[1]University of Texas at Dallas, Richardson, TX; [2]Neuroscience, University of Texas at Dallas, Richardson, TX

Abstract: In humans, excessive digital media exposure during infancy has been linked to disrupted social behavior function as well as increased risk for psychiatric disorders involving social dysfunction, such as mood and autism spectrum disorders (Sarfraz et al., 2023; Kim et al.,2023). Our group has adapted a rodent model of sensory overstimulation (SOS) that consists of exposing newborn rats to flashing lights synchronized with children's programming audio daily during postnatal days (PND) 10-40. We have previously shown that early life SOS induces a social deficit in female rats during late adolescence (PND 56) (Porras et al., 2024). However, the onset of this social deficit and its neurobiological underpinnings are unknown. To this end, we extended our prior work demonstrating SOS-induced social deficits by incorporating longitudinal social behavior assays in rats of both sexes. We report significant reductions in

juvenile social play in females at PND30 (females: CON: n=9, SOS: n=6, p= 0.001) and reductions in both sexes at PND32 (females CON: n=8, SOS: n=8, p= 0.03; males: CON: n=9, SOS: n=8, p= 0.04) and PND34 (females: CON: n=9, SOS: n=7, p= 0.04; males: CON: n=8, SOS: n=8, p= 0.02). Social motivation at PND35 was significantly reduced in both sexes (females: CON: n=9, SOS: n=8, p= 0.04; males: CON: n=9, SOS: n=8, p= 0.04), with effects persisting into adolescence only in SOS females (PND 45; females: CON: n=9, SOS: n=8, p= 0.04). Finally, we tested social recognition memory during late adolescence and found no between group differences in either sex (females: CON: n=8, SOS: n=8, p= 0.16; males: CON: n=8, SOS: n=8, p= 0.10). Taken together, these findings suggest age and sex-specific vulnerabilities in a subset of social behaviors (e.g., play, social motivation) following early life SOS. To probe neural changes associated with these effects, our lab is conducting ongoing immunohistochemistry (i.e., c-Fos) studies. We hypothesize that SOS-induced deficits in social motivation (i.e., reduced play, blunted social motivation) will be linked to altered neural activation patterns in reward-related brain regions implicated in social behavior (e.g., nucleus accumbens, ventral tegmental area). Collectively, these data highlight the need to investigate the long-term consequences of digital media exposure on reward system development and later life social behavior.

Disclosures: A. Porras: None. **M. Rincón-Cortés:** None.

Late-Breaking Poster

LBP046: H.03. Motivation

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Title: Serotonin modulates nucleus accumbens circuits to suppress aggression

Authors: Z. ZHANG, G. TOUPONSE, P. J. ALDERMAN, T. YASSINE, M. B. POMRENZE, T. HARRIS, A. SHANK, R. C. MALENKA, ***N. ESHEL**;
Stanford University, Palo Alto, CA

Abstract: Serotonin (5HT) has long been considered anti-aggressive, but the mechanisms by which 5HT regulates downstream circuits to control aggression remain unclear. Recent studies have implicated 5HT release in the nucleus accumbens (NAc) in promoting a range of prosocial behaviors, including behavioral antecedents of empathy. We therefore hypothesized that 5HT release in the NAc may also influence aggression. We first combined fiber photometry with the fluorescent sensor GRAB-5HT to measure real-time changes in 5HT levels in the NAc during aggression (N=6 mice). We found that 5HT levels were low at aggression onset, ramped up during aggression, and peaked around aggression offset. Notably, the slope of the 5HT ramp showed a strong negative correlation with aggression duration: the faster the rise in 5HT, the shorter the attack bout ($P<0.0001$). These data suggest that 5HT may be selectively engaged in mediating the termination of attacks. Next, we tested the causal role of NAc 5HT in aggressive behavior. We injected a Flp-sensitive excitatory opsin (Flp-rsChRmine) in the dorsal raphe of SERT-Flp mice and implanted optical fibers in the NAc (N = 11 mice). 5HT input activation significantly reduced the duration of attacks ($P<0.01$), without changing attack frequency or basic locomotor, social, or valence-related behaviors (P's>0.05). Finally, we sought to identify what downstream cells mediate the effects of NAc 5HT on aggression. Using a miniaturized microscope in either D1-Cre (N=8) or A2A-Cre (N=7) mice, we found that compared to D2 neurons, D1 neurons were more robustly activated by attacks ($P<0.01$), and furthermore, that D1 neuron activity correlated with aggression duration ($P<0.0001$). This suggests that D1 neuron activity, like 5HT release, may influence the length of aggressive episodes. To test this hypothesis, we injected the Cre-dependent inhibitory opsin, NpHR3.0, in the NAc of either D1 Cre (N=9) or A2A Cre (N=7) mice to optogenetically inhibit either D1 or D2 neurons during the resident-intruder test. Similar to the effect of 5HT input activation, D1 neuron (but not D2 neuron) inhibition reduced the duration of attack bouts ($P<0.05$) without influencing control behaviors (Ps>0.05). Does 5HT inhibit D1 neurons to suppress attacks? To find out, we generated double-transgenic mice allowing us to record NAc D1 activity while optogenetically stimulating 5HT release (N=6 mice). We found that 5HT release significantly suppressed the activity of the subset of D1 neurons that were normally excited during aggression ($P<0.01$). Together, our findings reveal that 5HT blunts aggression through selective inhibition of attack-promoting D1 neurons in the NAc.

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Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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Program #/Poster #: LBP047.01/Web Only

Topic: H.04. Emotion

Support: NSFC Grant 32300860

Title: Spatial frequency tuning of cortical responses to positive and negative facial expressions

Authors: *J. SHI[1], X. YAN[2];
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Abstract: Evolutionary models of threat detection posit a subcortical "low-road", wherein the amygdala rapidly processes fearful faces via coarse, low-spatial-frequency (LSF) cues. While this mechanism is well-established, it remains unclear whether this subcortical advantage for fear translates to a generalized processing priority within cortical visual pathways. Crucially, previous studies have often relied on filtered images (e.g., LSF-only vs. HSF-only), lacking a systematic manipulation of spatial frequency to precisely map its continuous influence on expression processing. To address this gap, we systematically manipulated the spatial frequency content of facial images (across a wide spectrum from 4 to 40 cycles/image in 6 discrete steps) depicting fear, anger, and happiness. We tracked the implicit neural dynamics of expression categorization under brief presentation conditions (200 ms at 5 Hz; 33 ms at 30 Hz) using high-density EEG, with a specific focus on steady-state visual evoked potentials (SSVEPs) as a robust, objective metric of cortical response strength in occipito-temporal regions. Explicit behavioral recognition was assessed post-EEG. Our results revealed a fundamental dissociation: Implicit neural responses (SSVEPs) showed remarkably similar amplitudes for fear and happiness across most spatial frequency conditions, with anger categorization yielding the weakest responses. A significant neural prioritization for fearful faces was observed only under limited conditions with blurred faces. In striking contrast, behavioral results demonstrated a clear and efficient recognition advantage for happy expressions over both fear and anger. These findings challenge the cortical threat-superiority hypothesis by demonstrating that cortical regions efficiently process both positive and negative signals, thereby offering new insights for affective neuroscience research and clinical translations in anxiety and neurodevelopmental disorders.

Disclosures: J. Shi: None. **X. Yan:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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Program #/Poster #: LBP047.02/LBP121

Topic: H.04. Emotion

Support: 1K99HD115784-01
R01MH126531

Title: Body maps of maternal inner-body sensations associated with low to high mother-child face-to-face emotional synchrony

Authors: *A. LAVALLEE, D. DUMITRIU;
Columbia University, New York, NY

Abstract: Biobehavioral synchrony, i.e., coordination of physiological, neural and behavioral interpersonal signals during reciprocal mother-child interactions, is critical for building socioemotional skills. Hypothesizing that engaging in shared emotions (emotional synchrony [ES]), may be an environmental input that promotes mother-child biobehavioral synchrony, we developed a slider scale interface that reliably quantifies the strength of ES using blind observers' own subjective feelings. Nonetheless, emotional states are notoriously difficult to access experimentally. Using methods proposed by Nummenmaa et al. in a series of PNAS papers showing that emotion-associated inner-body sensations can be topographically mapped to body areas, we tested the hypothesis that the strength of parent-child ES during face-to-face interactions is associated with distinct subjective maternal feelings. As part of the COMBO Initiative at Columbia University, 211 mothers and their 2yo child completed a video visit where they 1-interacted face-to-face for 3min without using toys, and 2-colored on a body map "where in their body they felt their emotions during the interaction". The videotaped interactions were independently coded for ES. Body maps were overlayed using imageJ to create four normalized density maps grouped based on ES score quartiles. Upon visual inspection, mothers in the lowest quartile of emotional synchrony most distinctively perceived inner-body sensations in the brain area. Mothers in the higher quartile of emotional synchrony was most distinctively perceived inner-body sensations in the chest area. The hands and gut area were uniquely colored by mothers in the higher and lower emotional synchrony quartiles. Preliminary investigation of the statistical significance of these differences suggests that there are localized differences in entropy structures across these matrices (D=0.005, p<0.001). Here, we find that inner-body sensations activate in distinct areas that may be closely aligned with low to high emotional synchrony as rated by blind observers. Specifically, mothers who exhibited higher levels of emotional synchrony with their child reported localized sensations in the chest, whereas mothers in lower synchrony quartiles more distinctly localized sensations to the brain. These results suggest that emotional synchrony may not only be observable in behavior but also embodied in mothers' own subjective experience, potentially serving as an environmental input that facilitates broader

biobehavioral synchrony. Further work investigating the statistical robustness of these findings is needed.

Disclosures: A. Lavallee: None. **D. Dumitriu:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.03/LBP122

Topic: H.04. Emotion

Title: Stability of Acquired Personality Disturbances in Patients with Focal Brain Lesions

Authors: *A. THOMAS[1], D. TRANEL[2];
[1]University of Iowa, Iowa City, IA; [2]Dept Neurol, University of Iowa, Iowa City, IA

Abstract: Acquired brain damage often causes profound personality changes, particularly following damage to the prefrontal cortex. The case of Phineas Gage illustrates vast difficulties with irritability and irascibility following severe damage to his prefrontal cortex. This landmark case study shaped the way we understand the relationship between the brain and complex behavior. However, over 100 years later, studies investigating the longevity of such personality changes at the group level are limited. Therefore, the objective of this investigation was to determine the longitudinal stability of acquired personality changes in a sample of individuals with focal brain damage. Participants were adults (100% White, 12 men and 6 women) with focal lesions from stroke (44%), benign tumor resection (28%), resection for epilepsy control (5%), and focal brain contusion (5%). Average age of lesion onset was 47 years (SD=14.5) and average education was 14 years (SD= 2.7). Personality change was assessed with the Iowa Scales of Personality Change (ISPC), a reliable and valid tool for measuring personality change after focal brain damage. Participants were assessed at two time points (T1 and T2). On average, T1 and T2 assessments were completed at 5 (SD=8) and 24 years (SD=8) post-lesion onset, respectively. Personality disturbance was captured across four dimensions and 14 personality traits according to the following established ISPC criteria: Emotional/Social (irritability, impatience, social inappropriateness, insensitivity, and inflexibility), Dysexecutive (lack of initiative, persistence, and planning), Hypoemotional (apathy, unemotional, and social withdrawal), and Distressed (anxiety, depression, easily overwhelmed). The results showed that every patient (13/13) with a personality disturbance in the Emotional/Social, Dysexecutive, or Hypoemotional dimension at T1 had persistent disturbance in the same dimensions at T2. Five patients who demonstrated personality disturbances in the Distressed dimension at T1 all improved at T2, suggesting greater instability of the traits in this dimension. These findings provide preliminary evidence for the persistence of personality disturbance decades after brain damage. The findings highlight the need for ongoing longitudinal assessment of personality beyond the acute post-injury period. Future research will examine this question in a larger sample size and explore associations with lesion location and volume.

Disclosures: A. Thomas: None. **D. Tranel:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.04/LBP123

Topic: H.04. Emotion

Title: Machine Learning Decoding of Emotional Responses to Stimuli from Intracranial Brain Signals

Authors: *M. ZHU[1], J. ZHANG[1], C. SMYTH[1], P. A. STARR[2], L. LI[3], S. LITTLE[1];
[1]University of California, San Francisco, San Francisco, CA; [2]University of California, San Francisco, Mill Valley, CA; [3]University of California, Berkeley, Berkeley, CA

Abstract: Group-level studies have identified extracranial neurophysiological correlates of emotion. However, predicting an individual's subjective experience from intracranial neural signals remains a significant challenge. We addressed this using a high-volume, within-subject machine learning approach in a single neurosurgical patient with chronic ECoG strips over bilateral sensorimotor cortices. The patient viewed and rated the emotional valence of1,200 standardized images, enabling classification of valence (positive, neutral, negative) and animacy (animate, inanimate). Spectral power features(Theta-High Gamma, 4-150 Hz), and spectral power ratios, were extracted from a1s post-stimulus window of cortical ECoG signals to train an SVM classifier for valence classification and a logistic regression classifier for stimulus animacy. Classification of emotional valence was statistically significant(mean macro F1-score = 0.368 ± 0.023; permutation test, p=0.027), while classification of stimulus animacy was not significantly above chance (mean accuracy = 0.517 ± 0.016; permutation test, p=0.291). In addition, valence decoding was significantly better for animate stimuli than for inanimate stimuli (mean F1-score 0.389 ± 0.032 vs. 0.306 ± 0.031; independent t-test, p=0.006).Across analyses, alpha, beta, and high-gamma power from the right hemisphere were consistently among the most informative features. These findings demonstrate that emotional valence is decodable from this patient's sensorimotor cortex, and furthermore, that this neural encoding is strongly modulated by stimulus category. The differential decoding for different stimuli may indicate a specialized role for the sensorimotor cortical network in processing emotional cues for animate stimuli.

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Topic: H.04. Emotion

Support: NIMH 4R00MH132873-03

Title: Amygdala-hippocampal beta burst synchrony predicts memory performance and individual differences in depressive symptoms

Authors: *R. YAMAMOTO[1], N. HERZ[2], S. E. QASIM[1];
[1]Department of Neurosurgery, Rutgers University, Robert Wood Johnson Medical School, New Brunswick, NJ; [2]Department of Neurology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA

Abstract: The oscillatory activity in the amygdala and hippocampus is involved in emotional memory. Recent work has also implicated the presence of transient beta-frequency (13-30 Hz) coherence “bursts” between these regions in anxiety. Given the intersection of emotional memory and psychiatric disorders like anxiety, we investigated whether such beta bursts predict memory performance as a function of depressive and anxiety symptoms. Intracranial EEG recordings were analyzed from 26 epilepsy patients performing a free recall task from the multi-site RAM dataset. Beta coherence was estimated using a sliding-window approach (250 ms windows, 50 ms steps), and bursts were defined as epochs exceeding 80% of trial-level maxima. Mixed-effects logistic regression models tested whether burst counts predicted subsequent recall performance, with trial-level valence and arousal included as covariates. Contralateral amygdala-hippocampal pairs showed a significant positive association between beta burst count and recall accuracy ($\beta = 0.115$, $p = 0.015$), whereas ipsilateral pairs showed no relationship ($\beta = 0.001$, $p = 0.97$). Crucially, individual differences moderated these effects: patients with higher depressive symptoms (BDI) exhibited impaired memory with greater contralateral bursting ($\beta = -0.11$, $p = 0.032$), and overall burst counts correlated positively with BDI ($r = 0.66$, $p = 0.014$). A similar negative moderation was observed for anxiety (BAI; $\beta = -0.10$, $p = 0.031$), although burst-BAI correlations were not significant. Results were robust across alternative burst-averaging methods. These findings indicate that cross-hemispheric amygdala-hippocampal beta bursts normally support memory but may become maladaptive in individuals with elevated depressive or anxiety symptoms, highlighting burst-level synchrony as a potential neural marker at the intersection of memory and affective disorders.

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Topic: H.04. Emotion

Support: Israeli Science Foundation Personal Grant 3066/24
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Title: Opposing roles of striatal-insular and fronto-insular networks in mood stability and instability

Authors: *N. DANAN[1], H. KEREN[2];
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Abstract: Mood spontaneously drifts over time even without external events, reflecting intrinsic affective dynamics that vary across individuals. These spontaneous drifts provide a window into how the brain regulates affect which may underlie differences in well-being and risk for depression. However, the neural mechanisms driving such regulation remain unknown. The fMRI resting-state paradigm can allow us to study these processes under conditions of minimal input. To address this question, we collected repeated mood ratings during resting-state fMRI to identify the neural connectivity patterns underlying spontaneous mood drifts. Healthy participants (N = 53; age 18-35, 41% female) completed a resting-state scan while rating their mood every 15 s, enabling estimation of individual mood slopes. Connectivity was assessed using ROI-to-ROI (RRC), independent component analysis (ICA), and seed-to-voxel (SBC) approaches implemented in CONN (v22a). Participants' mood drift was estimated and correlated with connectivity measures. Participants (n=44) completed a second retest scan separated by 2-6 weeks, allowing us to reproduce and validate the findings. The nucleus accumbens-insular pathway appeared as a consistent correlate in the RRC analysis, with higher connectivity corresponding to greater mood stability (less mood decline) across both scans (n=44 ; $r = 0.445$, $p = 0.002$ in 1st scan; and $r = 0.355$, $p = 0.021$, in 2nd scan; and $t = 2.75$, $p = 0.009$ when comparing connectivity between participants showing Stable vs. Falling mood patterns).SBC analysis further identified striatal clusters when seeding from the right insula (this result was significant only in the first scan, with $p < 0.001$). An ICA analysis performed on concatenated within-subject data from both sessions, identified the fronto-insular network as associated with greater mood instability, with higher connectivity corresponding to stronger mood decline (increased positive-voxel betas, $r = -0.446$, $p = 0.002$, $n = 44$). Together, these findings suggest opposing contributions of two large-scale neural networks to spontaneous mood regulation under minimal external input: enhanced connectivity in striatal-insular pathways supports mood stability, whereas greater engagement of a fronto-insular network is associated with mood instability. Thus, mood stability versus instability can be mapped onto distinct insula-centered connectivity patterns. The stability-related network, previously linked to depression, also

suggests that spontaneous mood decline may serve as a marker of well-being and a potential target for intervention or diagnosis.

Disclosures: N. Danan: None. **H. Keren:** None.

Late-Breaking Poster

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Foundation for Prader-Willi Research

Title: Central amygdala PKC-δ neurons encode eating related information in transient and persistent populations

Authors: *M. B. SCHMIT[1], C. JOHNSON[2], M. MISCEVIC[3], H. VU[4], A. NIGAM[3], W. I. SCHNAPP[3], G. OZTURK[5], K. VO[3], T. HASNEEN[3], H. CAI[3];
[1]Psychology, University of Arizona, Tucson, AZ; [2]University of Arizona, Scottsdale, AZ; [3]Neuroscience, University of Arizona, Tucson, AZ; [4]Public Health, University of Arizona, Tucson, AZ; [5]University of Illinois Champaign-Urbana, Urbana, IL

Abstract: Proper regulation of eating behaviors is critical for survival, requiring both appropriate promotion and inhibition of food intake. Protein kinase C-delta expressing neurons (PKC-δ) in the central nucleus of the amygdala (CeA) have been identified as a key mediators of anorexigenic signals.. However, without measuring their activity during eating behaviors, our ability to full understand how these neurons affected food intake was limited. Here, using *in vivo* microendoscope calcium imaging, we found that a subset of $CeA^{PKC-\delta}$ neurons show transient activation that lasts only a few seconds during food approach, even though activating this populaiton suppresses intake. This transient activation is required for normal food intake in eating bouts. In contrast to this transient activity, we also found that a subset of $CeA^{PKC-\delta}$ neurons show persistent activation that lasts many minutes in response to intraperitoneal injection of cholecystokinin (CCK). Our results showed that these two subsets of $CeA^{PKC-\delta}$ neurons with different dynamics are not more related than by chance, suggesting that transient and persistent dynamics are represented by distinct neural ensembles. Finally, we demonstrated that transient and persistent ensembles of $CeA^{PKC-\delta}$ neurons are differently regulated in two eating-related disease models, suggesting they are important for the proper regulation of eating behaviors.

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Late-Breaking Poster

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Topic: H.04. Emotion

Support: NIH Grant T32AG000037

Title: Arousal increases locus coeruleus blood flow, salience-related brain responses, and mediates negative-valence attentional biases

Authors: *A. J. KIM[1], C. ZHAO[1], F. GUO[1], I. PAPPAS[2], M. DAHL[3], H. I. JACOBS[4], D. WANG[1], M. MATHER[1];
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Abstract: Valence-specific effects are frequently reported in the affective attention literature. However, although a central node in affective networks, the amygdala exhibits largely valence-general brain responses across diverse stimulus types. Thus, we hypothesized that the locus coeruleus (LC) mediates valence-specific effects within affective networks. Using ultra-high field (7T) neuroimaging, we tested how arousal induced by isometric handgrip modulates processing of emotional faces in an oddball task across two sessions. Arousal increased LC responses to target and negative-valence stimuli, but not to positive-valence stimuli. Critically, these arousal-induced effects were absent in all subdivisions of the amygdala. Functional connectivity analyses showed reduced LC coupling with the default mode network for target and negative stimuli, but not for positive stimuli. Handgrip also modulated downstream attention networks including the salience network and visual cortex. Behaviorally, arousal enhanced recognition sensitivity for negative-valence faces but not positive-valence faces, and multivariate statistical analyses linked this behavioral performance to left LC brain activity. Finally, arterial spin labeling scans showed LC-specific increases in cerebral blood flow during the arousal induction that was not observable in any other brainstem regions. Collectively, these findings provide converging evidence that the LC serves as the primary driver of arousal-dependent modulation in affective attention networks that links physiological arousal to negative-valence attentional biases.

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Late-Breaking Poster

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Topic: H.04. Emotion

Support: NCT06194305

Title: A multimodal approach to brain-body interactions in Tourette Syndrome: Preliminary Evidence from CBIT

Authors: *S. A. ALI[1], C. CONELEA[2], D. J. GREENE[3];
[1]UCSD, San Diego, CA; [2]UMN, MN, MN; [3]Cognitive Science, University of California San Diego, San Diego, CA

Abstract: Tourette syndrome (TS) is characterized by involuntary motor and vocal tics that are often amplified by emotional arousal, yet the neural and physiological mechanisms linking emotion and motor regulation remain unclear. Behavioral therapy, such as Comprehensive Behavioral Intervention for Tics (CBIT), is effective, but the network-level changes supporting treatment response are not well understood. In this study, we investigated how CBIT shapes large-scale functional brain networks and autonomic regulation in youth with TS. Participants (n = 19 pre-CBIT, n = 17 post-CBIT; mean age = 14.2 years) completed three resting-state and one tic-suppression fMRI run (10 min each) alongside in-scanner photoplethysmography (PPG). We applied Infomap community detection to derive group-average cortical network maps and quantified within- and between-network connectivity pre- and post-CBIT. PPG data were processed to extract inter-beat intervals, from which we derived heart rate (HR) and heart rate variability (HRV; RMSSD). Preliminary results revealed strengthened coupling between the somato-cognitive action network (SCAN) and motor systems post-CBIT, consistent with improved sensorimotor integration. Default mode-frontoparietal connectivity decreased slightly, in line with reduced limbic-prefrontal interaction. Concurrently, autonomic measures indicated that while resting HR and HRV were largely unchanged, tic suppression after CBIT was marked by reduced HR and increased HRV, reflecting enhanced parasympathetic control. Together, these preliminary results suggest that CBIT supports tic regulation through coordinated changes in emotion-motor networks and autonomic regulation. Ongoing work will extend analyses to subcortical regions, examine brain-body coupling, and test whether multivariate baseline connectivity patterns predict treatment response.

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Late-Breaking Poster

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Program #/Poster #: LBP047.10/LBP129

Topic: H.04. Emotion

Title: The non-hallucinogenic psychedelic Tabernanthalog attenuates cued fear expression in rats

Authors: S. HO, *K.-C. LEONG;
Trinity University, San Antonio, TX

Abstract: Numerous anxiety-related and fear-related disorders have proven difficult to treat with standard pharmacological interventions, leading to psychedelics as an alternative therapeutic. Debate over the safety of standard psychedelics remains a concern, particularly concerning their hallucinogenic side effects, limiting its therapeutic potential. The recently developed non-hallucinogenic psychedelic, 5-HT2A receptor agonist Tabernanthalog (TBG), provides an exciting therapeutic option that overcomes these potential concerns. Here, we examined the effect of TBG on anxiety-related and fear-related behavior using an elevated plus maze and cued fear conditioning paradigm, respectively. Male and female Wistar rats underwent testing in both an elevated plus maze (EPM) and cued fear conditioning paradigm. Rats first received 15 minute sessions in a standard elevated plus maze apparatus. The following day, rats underwent a two day cued fear conditioning paradigm. During the first day of fear conditioning rats received short, intermittent shocks (0.5 mA, 1s) paired with a tone (80 dB; 20s) and tested 24 hours later. Prior to each EPM and cued fear conditioning tests, TBG (1.625 ul/side; i.c.v) or saline was infused directly into the lateral ventricles through surgically implanted cannulae (AP: -0.95; ML: +/- 2.0; DV: -3.5; 10° angle). Cannula placements were verified post-mortem through dye verification. In a separate experiment, expression of the immediate early gene c-Fos was assessed to determine whether there were TBG-induced differences in neuronal activation in various regions of interest following elevated plus maze training and cued fear expression. Our results found that TBG significantly attenuated cued fear expression, demonstrating TBG's high promise for attenuating cued fear expression and its potential for serving vulnerable populations. No effect of TBG was observed on anxiety-related behavior in the EPM paradigm. Overall, this study highlights TBG as a promising therapeutic intervention for fear-related disorders and highlights possible differences in TBG's modulation of fear and anxiety behavior.

Disclosures: S. Ho: None. **K. Leong:** None.

Late-Breaking Poster

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Program #/Poster #: LBP047.11/LBP130

Topic: H.04. Emotion

Support: NIH 5R01DA053752-04

Title: Investigating the role of the central amygdala dynorphin neurons in the sensory and affective component of pain

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Abstract: Chronic pain affects over 50 million Americans annually and is often comorbid with stress,creating a negative cycle in which stress worsens pain and pain intensifies stress, ultimatelyreducing treatment effectiveness. The central amygdala (CeA) is a critical hub for integratingpain and stress states, and dynorphin neurons within the CeA are implicated in aversiveprocessing. We hypothesized that CeA dynorphin neurons contribute to the affective dimensionof chronic pain, such that their activity is aversive and their inhibition reinforcing.Male and female transgenic mice were transfected with AAV-hSyn-DIO-hM4D-mCherry toexpress inhibitory designer receptors or with control virus, and with AAV-hSyn-DIO-ChR-YFPto express channelrhodopsin or controls. Mice then underwent chronic constriction nerve injuryor sham surgery. Two weeks later, we tested the valence of CeA dynorphin neuron activity usingchemogenetics with conditioned place preference (CPP) and optogenetics with real-time placepreference (RTPP).Chemogenetic inhibition of CeA dynorphin neurons induced place aversion in chronic pain mice,whereas optogenetic activation produced place preference. To assess whether these effectsreflected changes in sensory thresholds, von Frey testing was performed with bothmanipulations. Neither chemogenetic inhibition nor optogenetic activation altered mechanicalthresholds, indicating that the behavioral effects observed in CPP and RTPP were not due tomodulation of nociception.These results demonstrate that CeA dynorphin neuron activity regulates the emotional, but notsensory, dimension of chronic pain. Activation alleviates negative affect in chronic pain statesand is negatively reinforcing, whereas inhibition is aversive. Together, these findings identify thekappa/dynorphin system within the CeA as a potential target for treating the affective componentof chronic pain.

Disclosures: F. D'Oliveira da Silva: None. **C.M. Cahill:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.12/LBP131

Topic: H.04. Emotion

Support: Brain & Behavior Research Foundation Young Investigator Grant #30335
R00 MH121355
R00 MH121355-04S1

Title: Chemogenetic activation of ventral hippocampal parvalbumin interneurons rescues stress-induced anxiety-like behavior

Authors: *D. A. SAN MIGUEL, Jr.[1], J. PALMER[2], J. J. DONEGAN[3];
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Abstract: Chronic stress is a major risk factor for mood and anxiety disorders. The ventral hippocampus (vHipp), the rodent homolog of the anterior hippocampus, regulates emotional behavior and the neuroendocrine stress response. Hippocampal parvalbumin (PV) interneuron disruptions have been reported in both rodents exposed to stress and humans with psychiatric disorders, suggesting that disrupted inhibition contributes to circuit dysfunction. Our previous studies show that chronic unpredictable stress (CUS) increases firing of vHipp pyramidal neurons projecting to the medial prefrontal cortex (mPFC). Here, we tested the hypothesis that PV interneuron activation would attenuate stress-induced fear and anxiety-like behaviors (n=5-8/group). Briefly, adeno-associated viruses were used to express an excitatory DREADD (hM3Dq) in vHipp PV interneurons of adult male and female C57BL/6J mice. After recovery, mice underwent three weeks of CUS (14 stressors/week, two per day) before behavioral testing to assess fear and anxiety-like behavior. Prior to each behavioral task, mice were administered Compound 21 (C21, 1 mg/kg, intraperitoneally). Animals were randomly assigned to groups, balanced by sex, and experimenters were blinded during behavioral scoring and analysis. We verified PV cell activation by C21 using immunohistochemistry for the immediate early gene, cFos, which increased in animals with the Gq DREADD after C21 administration. As we have shown previously, mice exposed to CUS displayed anxiety-like behaviors, including reduced center exploration in the open field test (OFT), less time and entries into the open arms of the elevated plus maze (EPM). Here, we show that the stress effect on the OFT was abolished in mice that received PV activation (two-way ANOVA, stress × DREADD, $p<0.05$). While CUS also enhanced fear learning, this effect was not altered by PV activation. These findings suggest that PV interneuron hypoactivity may drive stress-induced anxiety-like behaviors and PV interneurons may be a potential therapeutic entry point for stress-related psychiatric disorders.

Disclosures: D.A. San Miguel: None. **J. Palmer:** None. **J.J. Donegan:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.13/LBP132

Topic: H.04. Emotion

Support: Advisor: Dr. Marika Landau-Wells

Title: Emotion Regulation in Threat-Related Traumatized Youth and Intervention: A Meta-Analysis and Conceptual Review

Authors: *X. YANG;
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Abstract: IMPORTANCE: Early-life maltreatment is linked to emotion-regulation difficulties and later psychopathology, yet neural findings during affective and executive tasks remain inconsistent. It's crucial to identify consistent association of ELA and threatening tasks with brain function in adolescence. OBJECTIVE: To investigate the association of adversity exposure with consistent alterations in brain activation during threat processing in maltreated youth and test convergence with inhibitory-control networks using Seed-based d Mapping (SdM), statistical approach for meta-analyzing studies on differences in brain activity and structure. DATA SOURCES: Systematic searches via Scopus and PubMed. Search term combinations: trauma, maltreatment, abuse, early life adversity, or stress; threat; fMRI; emotion regulation, cognitive control. DATA SELECTION: Task-based fMRI studies reporting whole-brain coordinates in MNI/Talairach space, human samples (n≥25;≥10/group for between-group contrast), English,2003-2025, in two domains: threat processing and inhibitory control. DATA SYNTHESIS: Coordinate-based meta-analyses using SDM-PSI; multimodal conjunction mapping; voxel-wise meta-regressions of age. PRISMA guidelines were followed. OUTCOMES: Peak coordinates were extracted from all studies and submitted to SdM meta-analyses. RESULTS: 22 studies (N=1,212; 686 maltreated/clinical; 526 controls) were included. During threat processing (MT>HC), maltreated youth showed hypoactivation in left inferior parietal/postcentral regions and decreases in cuneus and middle temporal cortex. During inhibitory control (MT>HC), they showed hyperactivation spanning left pons→insula/striatum/SLF III and relative decreases in right middle temporal and left orbital inferior frontal regions. Within-group inhibitory-control analyses in maltreated samples revealed robust engagement of bilateral middle/inferior frontal gyri and left insula. Multimodal conjunctions indicated overlap in cortico-subcortical-cerebellar systems and a mixed-sign cluster in left putamen/insula (threat↓∩control↑). Age meta-regressions suggested increased parietal recruitment with age for threat processing. CONCLUSIONS: Maltreatment is associated with context-dependent redeployment of regulatory control—under-recruiting posterior/prefrontal systems during threat while engaging subcortical-brainstem-cortical pathways during executive demands. Results highlight targets for interventions that train pre-stimulus engagement of cortical control in emotionally salient contexts.

Disclosures: X. Yang: None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.14/LBP133

Topic: H.04. Emotion

Support: NSF IOS Award 1755111 to SCF
Campus Grant (CSUS 122331) to SCF
CSUS Research Enhancement Award

Title: Assessing the Role of the Perirhinal Cortex in Stimulus Representation During Fear Extinction Retrieval Using Chemogenetic Silencing.

Authors: L. ROCHA, *S. C. FURTAK;
Psychology, Sacramento State, Sacramento, CA

Abstract: The perirhinal cortex (PER), a region within the hippocampal memory system, is implicated in both mnemonic and perceptual functions. However, its role in emotional learning and memory remains unclear. While the PER is well established in object recognition memory, emerging evidence suggests it may also facilitate the unitization of stimulus features across modality and time in emotional tasks. Unitization refers to the binding of multiple stimulus components into a unified representation. Previous research indicates that PER inactivation via a GABA agonist impairs fear extinction training and retrieval to a discontinuous stimulus. The current study aimed to investigate the role of PER in stimulus unitization during the retrieval of the extinction memory to a discontinuous visual stimulus. Designer receptors exclusively activated by designer drugs (DREADDs) were used to selectively silence neuronal activity in PER during fear extinction retrieval. Male Sprague-Dawley rats received bilateral PER injections of an adeno-associated virus (AAV) carrying a synthetic human muscarinic 4 receptor (hM4Gi). After a 4-week period, animals underwent a fear extinction paradigm. On day 1, Fear Acquisition, rats received five presentations of a discontinuous light (conditioned stimulus; CS) paired with a brief foot shock (unconditioned stimulus; US). On day 2, Extinction Training, rats were presented with 20 CS-alone presentations. On day 3, rats were injected intraperitoneally with either the DREADD agonist (deschloroclozapine, DCZ, experimental group; n=11) or dimethyl sulfoxide (DMSO, vehicle control group; n=10). After 30 min, rats underwent Extinction Retrieval, which included 15 CS-alone presentations. Results showed no significant group differences in freezing behavior during the retrieval of the extinction memory, suggesting that PER is not required. A Spontaneous Object Recognition task confirmed that PER inactivation impaired recognition memory, validating the effectiveness of the DREADD manipulation. These findings challenge the prediction that PER is necessary for stimulus unitization during retrieval of fear extinction and instead support a temporally specific role for

PER during earlier phases of fear learning. Further studies are necessary to parse apart PER contributions to the CS-US fear association compared to the CS-no US extinction association.

Disclosures: L. Rocha: None. **S.C. Furtak:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.15/LBP134

Topic: H.04. Emotion

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Title: GABA signaling in NG2 glia mediates empathic behavior under observational social defeat

Authors: *Y. JIAN[1,2,3], X. TONG[3,2,4];
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Abstract: Empathy, a critical component of social cognition, involves both basic emotional contagion and complex empathic behaviors, including consolation, sharing, and targeted helping. While extensive research has explored the neural mechanisms of emotional contagion and learning in the context of observing pain and fear, the impact of witnessing traumatic events on empathy-related behaviors remains poorly understood. This knowledge gap hampers insight into psychiatric disorders characterized by vicarious trauma. The medial amygdala (MeA) has emerged as a key hub for social emotional processing, with its GABAergic circuits implicated in affective regulation. Similar to interneurons, NG2 glia exhibit dynamic calcium signaling and regulate the excitation-inhibition balance, yet their functional role in social-emotional circuits remains poorly understood. Here, we first developed a mouse model of observational social

defeat (OSD) to investigate emotional resonance and empathy responses to witnessing social stress. Utilizing whole-brain c-Fos screening and fiber photometry recording, we observed that GABAergic neurons in the medial amygdala (MeA) were specifically activated during empathic allogrooming in OSD-exposed mice. Furthermore, we demonstrated that NG2 glia-GABAergic neuron interactions in the MeA form a microcircuit that initiates prosocial allogrooming after observational social defeat. Conditional knockout of *Gad1* in NG2 glia further amplified comforting-targeted allogrooming behavior. Our findings thus highlight a new role for NG2 glia-GABAergic neuron interactions in regulating empathy-related behaviors, with implications for targeting GABA signaling in NG2 glia as a potential therapeutic strategy in emotional disorders like vicarious trauma.

Disclosures: Y. Jian: None. **X. Tong:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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Program #/Poster #: LBP047.16/LBP135

Topic: H.04. Emotion

Support: RS-2025-00520820

Title: Valence-Specific behavioral and neural correlates during social affective recognition in mice

Authors: *G. KIM[1], C. CHUNG[2];
[1]Department of Biological Science, Konkuk University, Seoul, Korea, Republic of; [2]Department of Biological Sciences, Konkuk University, Seoul, Korea, Republic of

Abstract: Empathy, the ability to recognize and understand the emotional states of others, is crucial for appropriate social interactions and often impaired in psychiatric disorders. While much research has focused on negative emotions, such as fear and pain, how animals recognize a broader range of emotions, including positive ones, remains unclear. Recent studies suggest that mice can distinguish between emotional states and neutral states and that the prefrontal cortex (PFC) is involved in discriminating emotional states. However, it remains unclear whether these responses are driven merely by the detection of emotionally salient cues or whether mice can actively differentiate the emotional valence (i.e., positive vs. negative) of social targets. First, we examined whether mice respond differently at the behavioral and neural levels to stressed or relieved conspecifics in the homecage by measuring c-Fos expression after social interaction. While the total amount of active interaction was comparable, specific behaviors differed by emotional valence, and c-Fos mapping revealed distinct neural circuit recruitment depending on the emotional valence of the conspecific. To further test whether mice can discriminate between different emotional valences, we employed the emotion discrimination test (EDT). Mice preferentially investigated stressed or relieved conspecifics over neutral ones, consistent with

previous findings. When both stressed and relieved conspecifics were presented, mice approached stressed conspecifics sooner while spending a comparable amount of time with relieved conspecifics. Finally, we performed an unbiased clustering analysis of EDT behavioral data. This analysis revealed emotion-specific behavioral patterns, consistent with the discrimination of distinct emotional states. Together, these results suggest emotion-specific behavioral patterns and brain network recruitment during social affective recognition.

Disclosures: G. Kim: None. **C. Chung:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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Topic: H.04. Emotion

Support: DUCOM Deans' Fellowship 2024
NIH/NIMH R21MH129989
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PA CURE Grant SAP#4100085747

Title: Investigating the short- and long-term behavioral effects of adolescent exposure to psilocybin

Authors: *L. FLYNN[1], W.-J. GAO[2];
[1]Drexel University, philadelphia, PA; [2]Neurobiology and Anatomy, Drexel University, Philadelphia, PA

Abstract: Psychedelic compounds, including psilocybin, N,N-dimethyltryptamine (DMT), and ketamine, are increasingly being studied for their potential therapeutic effects in the treatment of numerous neuropsychiatric and substance use disorders. Much of the excitement surrounding psychedelics is derived from the rapid onset and sustained duration of their effects; however, the underlying mechanisms of action have not yet been fully elucidated. Recent research has demonstrated psychedelic-induced increases in synaptic plasticity in key brain regions implicated in neuropsychiatric disease, including the prefrontal cortex (PFC), and this plasticity-inducing effect is often posited as a key element in psychedelic-induced behavioral effects. The PFC undergoes a period of delayed maturation and enhanced synaptic plasticity during adolescence, which is also a critically important period for the development and onset of most neuropsychiatric diseases and substance abuse disorders. The adolescent onset of neuropsychiatric diseases has caused some researchers and clinicians to suggest the use of psychedelic therapy during adolescence, and indeed, adolescent recreational psychedelic use has been documented in the literature. Despite this, the effects of adolescent exposure to psychedelics are almost entirely unexplored. Most preclinical studies of psychedelic compounds have utilized adult animals, and children are excluded from psychedelic clinical trials.

Furthermore, the long-term effects of adolescent psychedelic exposure are not well characterized. Here, we investigated the dose-dependent behavioral effects of adolescent exposure to the classical serotonergic psychedelic psilocybin in C57BL/6J mice. Animals were administered saline or 0.33, 1.0, or 3.0 mg/kg psilocybin via intraperitoneal injection at approximately 4 weeks of age. Animals were then tested either 24 hours or 4 weeks later, using a battery of behavioral tasks, including the three-chamber test of social preference, the open field test of anxiety-like behavior, and the tail suspension test of despair-like behavior. Head twitch response (HTR) monitoring revealed a dose-dependent increase in twitches in animals exposed to psilocybin versus saline, despite some previous publications that suggested adolescent animals do not demonstrate the HTR. Despite the presence of a dose-dependent HTR, animals did not demonstrate lasting behavioral effects when tested 4 weeks following psilocybin administration. Future studies will examine the effects of multiple doses of psilocybin during adolescence, which may more closely resemble the patterns of use for adolescent humans.

Disclosures: L. Flynn: None. **W. Gao:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

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Topic: H.04. Emotion

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111 Project B18015
Shanghai Center for Brain Science and Brain-Inspired Technology

Title: Region-specific facial dynamics decode a two-dimensional emotional state map in mice

Authors: *Y. CHEN, R. HOU, X. XIAO;
Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China

Abstract: Emotions are complex psychophysiological states, and studying them in animal models is vital for understanding their evolution and function. While mouse facial expressions have been linked to emotions, the critical features and underlying neural mechanisms remain unclear. In laboratory settings, facial movements are subtle and rapid, making manual observation inefficient and subjective, and limiting accurate capture of fine spatiotemporal dynamics in emotional expression. To address this methodological gap, we developed a two-

dimensional framework integrating facial expression recording and fiber photometry to quantify both valence and intensity of emotional states. We established a comprehensive dataset containing behavioral videos from 10 head-fixed male C57BL/6 mice (8-12 weeks) subjected to distinct emotional stimuli—sucrose (positive) and tail shock (negative). For each stimulus type, a maximum of 5 trials per animal were recorded using a laterally positioned camera vertically aligned with the snout region to ensure consistent facial profiling. Using a high spatiotemporal resolution keypoint tracking algorithm, we quantified subtle and continuous movements across 37 facial landmarks. Keypoints from four critical regions—ears, whiskers, nose/mouth, and pupils—were used as input to a Long Short-Term Memory (LSTM)-based model. This approach revealed that among all facial regions, ear kinematics provided the most informative and reliable emotional features and remained robust even under high-motion conditions. Geometric analyses further demonstrated coordinated multi-region facial movements, with ear motion emerging as the most valence-sensitive feature—shifting forward during positive states and backward during negative states. Moreover, ear kinematics reflected emotional intensity; graded tail shocks (0.06, 0.2, and 0.4 mA) elicited precisely scaled changes in ear length, with a one-way ANOVA confirming significant differences in peak calcium signals among all intensity levels. Neural recordings in the ventral tegmental area (VTA) supported the two-dimensional model: glutamatergic neurons exhibited intensity-graded activation consistent with arousal, while dopaminergic and GABAergic neurons responded selectively to sucrose and shock, respectively, aligning with valence. Together, these behavioral and neural findings establish and validate a two-dimensional framework for quantifying mouse emotional states, highlighting ear dynamics as a robust marker of both valence and intensity, supported by distinct neural correlates within VTA subpopulations.

Disclosures: Y. Chen: None. **R. Hou:** None. **X. Xiao:** None.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.19/Web Only

Topic: H.04. Emotion

Title: Interaction of extraversion and neuroticism on emotional states

Authors: *K. KANANI[1], A. GHADERI[2];
[1]university of Isfahan, Isfahan, Iran, Islamic Republic of; [2]USC, Los Angeles, CA

Abstract: Personality is a robust predictor of emotional experiences. Extraverts are commonly considered to be assertive, outgoing and enthusiastic people. People with high level of neuroticism (N) is known for variability in mood, feeling down and a negative attitude toward the world. It is also referred to as negative emotionality. Previous studies have investigated the effects of extraversion (E) and N on the emotions separately, but the interactive effect of these traits is still unclear. This study examined how these traits interact in shaping emotional

outcomes, when one trait is dominant in personality compared to when they are equally strong? Data from 1,197 HCP Young Adults were analyzed. 17 emotion surveys and the short NEO were collected. Participants were grouped with *k*-means based on *N* and E scores, with Calinsky-Harabas optimizing cluster number. Groups were compared pairwise using permutation t-test with FDR correction to test emotional differences. Then, we examined whether personality traits could be predicted from emotional scores by machine learning approaches. In this analysis, emotional scores were considered as inputs and each personality trait modeled separately as the outcome. K-means revealed 4 groups, 1) high N/low E; 2) low N/high E; 3) relatively low N/high E; and 4) relatively high N/low E. Significant emotional differences were observed in most group comparisons. Group1 differed from all others in all scales (both gender). Similar results we found for group 2 with 3 and 4. But group 3-4 showed several non-significant results in positive and negative emotions. Machine learning approach (gaussian process regression) resulted with a validation RMSE of 4.74 for N, whereas for E, the model achieved $R2$=0.32 with an RMSE of 4.94. The study showed how N and E interact in shaping emotions. Extreme profiles (group 1; high N/low E, group 2; low N/ high E) differed strongly, while middle groups (group 3, 4) showed many nonsignificant results, suggesting trait effects may neutralize each other. This highlights trait interaction over isolated effects. The result of machine learning revealed that high N exhibits more distinct emotional patterns. In contrast, E was predicted to a limited extent from emotions, suggesting other factors, like social motivation, may play a stronger role.

Disclosures: K. Kanani: Other; Iranian neurowave lab, Isfahan, Iran, Department of psychology, faculty of education and psychology, University of Isfahan, Isfahan, Iran. **A. Ghaderi:** Other; Iranian neurowave lab, Isfahan, Iran, Centre for Affective Neuroscience, Development, Learning and Education (CANDLE), University of Southern California (USC), Los Angeles, USA.

Late-Breaking Poster

LBP047: H.04. Emotion

Location: SDCC Hall B

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

Program #/Poster #: LBP047.20/LBP138

Topic: H.04. Emotion

Support: IITP-2025-RS-2022-00156299

Title: Toward EEG-Based Image Reconstruction: Leveraging Affective Stimuli to Enhance ERP Signals

Authors: D. BAE[1], *S. DONG[2];
[1]IT Engineering, Sookmyung Women's University, Seoul, Korea, Republic of; [2]Sookmyung Women's University, Seoul, Korea, Republic of

Abstract: We present an early-stage pilot toward EEG-based image reconstruction that tests whether affectively evocative images can enhance event-related potentials (ERPs) compared with neutral stimuli, thereby improving decoding/reconstruction prospects. To maximize affect induction, we curated 20 affective exemplars and neutral controls from OASIS dataset based on our pre-screen ratings (n=14, age M=28.78, SD=2.04), prioritizing concentration near the extremes of the valence scale—high for positive and low for negative—while keeping between-subject variance small (positive M=5.84, SD=0.44; negative M=1.83, SD=0.39). EEG was recorded using a 32-channel Brain Products actiCHamp Plus during perception (viewing) and imagery (view-then-imagine) tasks for the separate five subjects (age M=28.6, SD=2.96); standard preprocessing was applied. We quantified the early posterior negativity (EPN, 200-300ms; occipito-temporal ROIs) and the late positive potential (LPP, 400-700 ms; centro-parietal region of interest (ROI)). Affective images tended to elicit stronger ERPs than neutral—most clearly larger LPPs during perception (negative > neutral: $\Delta = +5.17$ μV; $p = .079$; Holm-corrected $p = .159$; positive-neutral negligible). Imagery-evoked EPN modulations were negative-going (for negative-neutral) but nonsignificant (ps ≥ .455). These preliminary observations support the hypothesis that affect-driven imagery may yield more informative neural signals than imagery of neutral content, motivating reconstruction pipelines that prioritize affective stimuli. Future work will explicitly control arousal/valence, optimize ROIs/time windows, and increase sample size and trial counts to improve SNR, enabling direct reconstruction tests with feature-guided decoders and generative models.

Disclosures: D. Bae: None. **S. Dong:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.01/LBP139

Topic: H.05. Mood Disorders

Support: R01MH135293
K01MH123887

Title: A novel 5 day treatment for depression: Comparing the efficacy of accelerated 5x5 versus conventional repetitive transcranial magnetic stimulation (rTMS) for treatment resistant depression

Authors: *M. R. APOSTOL[1], J. CORLIER[2], T. VALLES[3], A. LEUCHTER[2];
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Abstract: Major depressive disorder (MDD) is a leading cause of disability and lost productivity worldwide. Non-invasive brain stimulation interventions, such as repetitive transcranial magnetic stimulation (rTMS), are effective, non-pharmacological treatments for MDD. rTMS employs a

time-varying magnetic field to modulate the neural circuits implicated in depression, which can promote remission in treatment-resistant patients. Recently, an accelerated rTMS protocol achieved FDA-clearance for MDD treatment, which utilizes 10 sessions of prolonged intermittent Theta Burst Stimulation (piTBS) per day for 5 days. However, it remains unclear what the ideal combination of sessions per day and pulses per session are required to achieve remission in MDD patients. Here, we compared the efficacy of an accelerated protocol consisting of five stimulation sessions per day for five days ("5x5") of either piTBS or individualized, electroencephalogram-based "resonant frequency" (RF) stimulation. Additionally, the 5x5 protocol was compared to a conventional once daily, six week rTMS protocol. Using the Patient Health Questionnaire (PHQ-9) to track MDD symptom improvement, we compared the outcomes of 1) accelerated patients (N = 40) undergoing 5x5 treatments (patients received either piTBS or RF rTMS; average age: 49.90 years; female: 22, male: 18) and 2) conventional patients (N = 135) receiving conventional once daily rTMS (average age: 46.69 years; female: 71, male: 62, non-binary: 2). Both protocols ameliorated MDD symptoms and there were no statistically significant differences in depression symptom changes ($p = .07$) between the accelerated 5x5 protocol (mean PHQ-9: pre-rTMS = 17.68, post-rTMS = 10.98) and conventional rTMS protocol (mean PHQ-9: pre-rTMS = 17.83, post-rTMS = 8.97). Furthermore, there were no significant differences in efficacy between the two accelerated 5x5 protocols, piTBS and RF ($p = 0.9$). A PHQ-9 median split of 5x5 patients indicated that, while half of the patients experienced robust depression score percent improvement (69%), the bottom half did not (8% PHQ-9 improvement). At two-to-four weeks follow up, however, the bottom half displayed significant improvement (36%), $p = 0.001$. These results suggested that an accelerated rTMS protocol of 5 sessions per day for 5 days (5x5) has similar efficacy to a conventional six week rTMS protocol, and that treatment efficacy of accelerated treatment may not be accurately measured until several weeks after the conclusion of treatment.

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Late-Breaking Poster

LBP048: H.05. Mood Disorders

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Topic: H.05. Mood Disorders

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Title: Intracranial neural correlates of depression severity in frontotemporal circuits

Authors: *S. POUYA[1], S. CHAMARTHI[2], J. XIAO[3], N. GIRIDHARAN[2], K. KABOTYANSKI[2], J. MYERS[2], R. MATHURA[2], V. GATES[2], K. BIJANKI[2], B. SHOFTY[4], S. J. MATHEW[5], W. K. GOODMAN[5], N. POURATIAN[6], E. BARTOLI[2], S. A. SHETH[2], N. R. PROVENZA[2];
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Abstract: Major depressive disorder is a leading cause of disability worldwide with a lifetime incidence of 10 to 15%. An estimated one-third of patients with major depressive disorder are treatment resistant, underlying the need to identify biomarkers that can inform therapeutic approaches. Our previous work identified a neural biomarker for increased depression severity characterized by high power in low-frequency bands and low power in high-frequency bands in regions of the frontal cortex (dorsolateral prefrontal cortex, ventromedial prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex). We replicated and extended these findings in an additional patient with treatment-resistant depression enrolled in an early feasibility trial of individualized deep brain stimulation. Participants had deep brain stimulating leads and stereoelectroencephalography (sEEG) electrodes implanted and were continuously monitored for 9 days. Depression severity was measured using the Computerized Adaptive Test-Depression Inventory at a frequency of 3-5 times per day. Spectral features were extracted from bipolar-referenced sEEG contacts across the 6 canonical frequency bands. Consistent with prior findings, we found that increased depression severity was significantly correlated with high power in lower frequency bands and low power in higher frequency bands in an additional patient ($p<0.05$). Further, we extended the analyses to include spectral data from the sEEG electrodes located in the amygdala for all patients and confirmed the same trends ($p<0.04$). These findings suggest that depression severity may not be limited to band-specific oscillations, but instead could reflect broader network-level changes in the aperiodic component of neural activity. Future work will use predictive modeling to decode depression severity from these spectral features. This understanding would allow data-driven strategies for delivering neuromodulatory therapies to dysfunctional circuits, steering them toward healthier network states.

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even if those funds come to an institution.; Boehringer-Ingelheim, Engrail Therapeutics, Merck, Neurocrine, Sage Therapeutics. F. Consulting Fees (e.g., advisory boards); Almatica Pharma, Biohaven, BioXcel Therapeutics, Boehringer-Ingelheim, Brii Biosciences, Clexio Biosciences, COMPASS Pathways, Delix Therapeutics, Douglas Pharmaceuticals, Eleusis, Engrail Therapeutics, Freedom Biosciences, Janssen, Liva Nova, Levo Therapeutics, Merck, Neumora, Neurocrine, Perception Neurosciences, Praxis Precision Medicines, Relmada Therapeutics, Sage Therapeutics, Seelos Therapeutics, Signant Health, Sunovion, Xenon Pharmaceuticals, XW Pharma. **W.K. Goodman:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); devices from Medtronic. F. Consulting Fees (e.g., advisory boards); Biohaven Pharmaceuticals. **N. Pouratian:** F. Consulting Fees (e.g., advisory boards); Abbott Laboratories, Sensoria Therapeutics. **E. Bartoli:** None. **S.A. Sheth:** F. Consulting Fees (e.g., advisory boards); Boston Scientific, NeuroPace, Abbott, Zimmer Biomet. **N.R. Provenza:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.03/LBP141

Topic: H.05. Mood Disorders

Support: Taishan Scholars Program No. tsqn 202306156
Shandong Provincial Natural Science Foundation ZR2024MC187

Title: Resting-state Aperiodic EEG as a Neural Marker of Subclinical Depressive Mood

Authors: *X. XU[1], L. S. COLZATO[2], B. HOMMEL[3];
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Abstract: Depressed mood exists on a continuum within the general population, ranging from transient emotional states to clinically significant major depression. Subclinical depression, while not meeting diagnostic thresholds, is associated with substantial societal and economic burdens, including reduced academic and occupational productivity, increased healthcare utilization, and heightened risk for progression to major depressive disorder. While previous research has established a link between aperiodic neural activity and major depression, it remains unclear whether this relationship extends to individuals in a nonclinical, preclinical population. Addressing this gap, the present study investigates whether the aperiodic component of resting-state electroencephalography (EEG) can predict depressive mood in healthy individuals, and further explores the spatial distribution of EEG signals most strongly associated with depressive symptoms. Seventy-two healthy college students participated in the study. Depressive mood was assessed using the Chinese version of the Beck Depression Inventory-II (BDI-II). Resting-state EEG was recorded using a 64-channel Neuroscan SynAmps2 system (sampling rate: 1000 Hz; electrode impedance ≤ 5 kΩ), with participants maintaining open eyes and fixating on a cross for

5 minutes. EEG data were preprocessed in EEGLAB (v2024.2, MATLAB R2022b), involving bandpass filtering (0.1-40 Hz), average referencing, down-sampling (500 Hz), segmentation (2-second epochs), and artifact removal via independent component analysis (ICA). Power spectral density (PSD) was computed, and the aperiodic exponent was extracted using the FOOOF toolbox in Python. After preprocessing, data from 69 participants (37 males; mean age = 20.25 ± 1.48 years) were included in the final analysis. Regression analysis indicated that the whole-brain aperiodic exponent significantly predicted depressive mood ($\beta = 0.26$, $p = 0.03$). Hierarchical clustering and permutation testing (Bonferroni-corrected) revealed that electrodes most significantly associated with depressive mood were primarily located in the frontal and fronto-temporal regions (Fpz, F11, F7, F8, FT11, FT12, C4, CP3; $p = 0.009$). These findings suggest that the aperiodic exponent from resting-state EEG may serve as a neural marker of subclinical depressive mood, with frontal and fronto-temporal regions showing particular relevance. Future studies should replicate these findings with larger samples to validate their generalizability.

Disclosures: X. Xu: None. **L.S. Colzato:** None. **B. Hommel:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

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Topic: H.05. Mood Disorders

Support: NIH R01MH118695
NSF 2316421
NSF 2112455

Title: Multi-Scale Neuroimaging Features Reveal Replicable Functional Patterns in Major Depression

Authors: *B. T. BAKER, V. D. CALHOUN;
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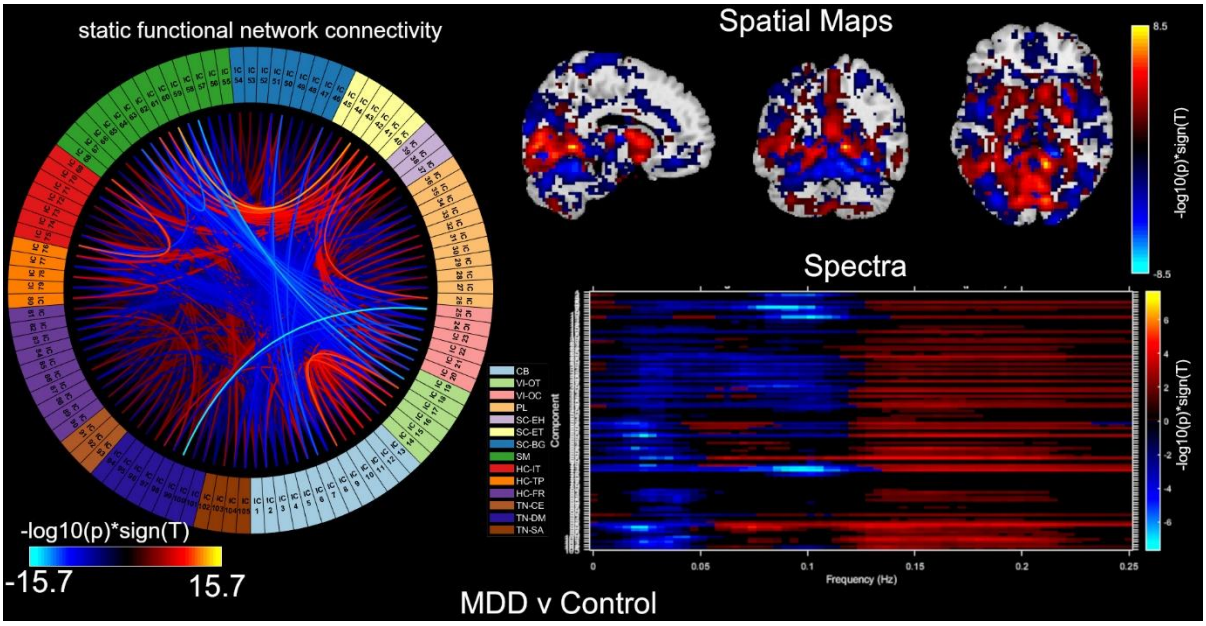
Abstract: Major depressive disorder (MDD) is a prevalent and heterogeneous mood disorder, yet replicable neuroimaging biomarkers remain elusive. We present a large-scale analysis of resting-state fMRI (rsfMRI) that identifies multi-scale functional imaging features of MDD and demonstrates their predictive value for diagnosis.
Using 2,426 scans (831 controls, 1,123 MDD) from the MDD-Direct dataset, we applied Neuromark independent component analysis (ICA) with a population-derived template (N>100k) to extract spatial maps, spectral signatures, and static functional network connectivity (sFNC). These features were tested for group differences and used in predictive modeling with deep neural networks (DNNs).

Across modalities, we observed significant alterations in MDD after multiple-comparison correction ($p<0.05$). Notably, patients exhibited systematic spectral shifts between low- and high-frequency bands, as well as connectivity changes linking the default mode and visual networks, and between somatomotor, subcortical, and visual systems. These findings highlight widespread disruptions in large-scale networks critical for affective and cognitive regulation. To assess predictive utility, we trained three DNN architectures (GRU, LSTM, Transformer) on ICA-derived features. Models achieved AUC-PR scores of 0.786 ± 0.037 (GRU), 0.778 ± 0.036 (LSTM), and 0.770 ± 0.012 (Transformer), demonstrating consistent predictive performance. In conclusion, we introduce a replicable, population-informed pipeline for deriving functional biomarkers of MDD. Our results reveal robust network- and frequency-level alterations in depression, establishing their utility for predictive modeling and providing a foundation for biomarker-driven approaches to clinical translation.



Disclosures: B.T. Baker: None. **V.D. Calhoun:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.05/LBP143

Topic: H.05. Mood Disorders

Support: Atai Life Sciences Grant

Title: fMRI-derived connectivity changes covary with symptoms in MDD patients undergoing ketamine therapy

Authors: *C. SHAFFER[1,2], A. BHATT[3,4], S. HUANG[3,4,5], C. CUSIN[2,6], S. MCEWEN[7], S. GABRIELI[3,2];
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Abstract: Ketamine, a rapid-acting antidepressant, has been shown to modulate large-scale brain networks in the 24-48 hours post-administration. However, ketamine's longitudinal effects on functional network connectivity in cortical resting state networks remain unclear. In this single-dose open-label study, we aimed to characterize whole-brain connectivity changes over time in relation to symptom reports for 20 Major Depressive Disorder (MDD) patients (M_{age}=35.45, SD_{age} = 8.16, 11 female) undergoing IV ketamine maintenance therapy. Resting-state fMRI and Hamilton Depression Rating Scale (HAM-D) scores were collected at baseline (T1), 12-24 hours post-infusion (T2), and 2-week follow-up (T3). Functional connectivity multivariate pattern analysis (fc-MVPA) identified regions where connectivity fluctuated across sessions and co-varied with symptom changes. Cluster inferences were based on Gaussian Random Field theory with voxel-wise $p < 0.001$ and FDR-corrected $p < 0.05$. Mixed-effects models assessed co-fluctuations between symptoms and connectivity from T1 to T3. Connectivity between the precuneus and primary motor cortex significantly changed over time ($p_{FDR}< .01$) and covaried with symptom changes during T2 and T3. Consistent with the treatment effects of ketamine, mean symptoms scores decreased at T2 vs. T1 ($\beta = -3.11$, $p > .005$) with a smaller, non-significant reduction at T3 vs T1 ($\beta = -1.03$, $p = .229$). While connectivity was not significantly related to symptom severity at baseline ($\beta=-8.23$, $p=0.10$), there was a significant interaction at T2 ($\beta = 23.31$, $p < 0.05$), indicating that reductions in precuneus-motor cortex connectivity at T2 was associated with lower symptom scores post-ketamine infusion. A significant interaction was also observed during T3 ($\beta =16.38$, $p <0.05$), indicating that reduced connectivity continued to be associated with lower HAM-D scores at T3. As a sensitivity check, we also report CR2 cluster-robust Wald tests (cluster = subject) to safeguard inference with our small number of clusters (n=20) and unequal residual variance across sessions, i.e., conditions under which the standard LMM covariance may be mis-specified; all key contrasts remained significant under CR2. This finding suggests that ketamine's sustained antidepressant effects may be mediated by default mode network connectivity to key motor structures. Future work will incorporate symptom-specific measures of psychomotor slowing and other relevant behavioral variables (i.e., task reaction time) to assess motor behavior across multiple dimensions.

Disclosures: C. Shaffer: Other; Atai Life Sciences PhD fellowship. **A. Bhatt:** None. **S. Huang:** 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.; Atai Life Sciences. **C. Cusin:** 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.; Atai Life Sciences. **S. McEwen:** A. Employment/Salary (full or part-time); Atai Life Sciences. **S. Gabrieli:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.06/LBP144

Topic: H.05. Mood Disorders

Support: NARSAD Young Investigator Award (BBRF)
NIH R21MH136654

Title: Leveraging supervised machine learning approaches to identify susceptible and resilient phenotypes to activity-based anorexia

Authors: *S. HEGDE, T. A. MCCORKLE, A. BELLINO, M. MCGILL, K. MENDEZ, A. K. SUTTON HICKEY;
Department of Psychology and Neuroscience, Temple University, Philadelphia, PA

Abstract: Anorexia nervosa (AN) is a life-threatening psychiatric disorder marked by severe voluntary food restriction and oftentimes a co-occurring increase in physical activity. Despite the high global mortality rate associated with AN, the neural mechanisms remain poorly understood. Preclinical studies have sought to understand these mechanisms using an activity-based anorexia (ABA) model in mice that combines limited food access with access to a voluntary running wheel, leading to hyperactivity, self-starvation, rapid weight loss, and death unless removed from the experiment. While elevated physical activity can increase the risk of developing AN, particularly when combined with food restriction, not all individuals who diet and exercise develop the disease. Similarly, a subset of rodents in the ABA paradigm are increasingly appreciated to be resistant to weight loss, typically identified based on their ability to remain on the behavioral paradigm. Yet, there are currently no phenotypic or neural indicators of ABA susceptibility prior to experimental removal, thus limiting the capability for intervention. Here, we developed a susceptibility indicator for mice on the ABA paradigm prior to severe weight loss by leveraging a comprehensive supervised machine learning pipeline that extracts distinct body weight change features like maximum weight loss, thus capturing the most severe weight drop and trajectory of the rate of weight change from longitudinal data. By first classifying animals with these computational tools, analyses are ongoing to determine the behavioral and neural read-outs underlying ABA susceptibility. Taken together, this novel quantitative framework has the potential to identify neuronal mechanisms that mediate ABA, and thus potentially AN, risk to inform early diagnosis and therapeutic strategies.

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Late-Breaking Poster

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

Program #/Poster #: LBP048.07/LBP145

Topic: H.05. Mood Disorders

Support: NIH R01 134175

Title: Evaluation of the elevated plus maze to assay risk-based decision making

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Abstract: Impaired risk-based decision-making (RBDM) is a hallmark of many psychiatric disorders but goes largely unaddressed by current pharmacotherapies. Preclinical behavioral paradigms enable study of the neural mechanisms underlying RBDM in rodents, and constitute a method to screen potential novel compounds for therapeutic potential. Development and validation of such paradigms is therefore a critical step in the development of targeted pharmacotherapies. The Elevated Plus Maze (EPM), in which rodents weigh their drive to explore their environment against their natural aversion to exposed, potentially dangerous open spaces, is typically used as an assay of anxiety-like behavior, though may also be used to measure ethologically relevant RBDM. We tested the pharmacological predictive validity of the EPM in this latter context using pramipexole, a dopamine D2/3 agonist that induces gambling disorders in humans. We hypothesized that pramipexole would increase time spent exploring the open arms of the maze, indicating elevated risk preference. We assessed male and female C57BL6/J mice (n=72; 50% female) in the EPM for 5 min following 4 consecutive days of pramipexole or vehicle administration (0.6, or 1.0 mg/kg, s.c.; between-subjects). We also conducted a separate validation study in a different cohort of mice (n=40; 50% female), using diazepam (1 mg/kg, i.p.; between-subjects) to confirm EPM pharmacological validity. Data were analyzed via two-way ANOVAs with treatment and sex as between-subjects factors. Both doses of pramipexole reduced open arm time [$F_{(2,60)}$=5.88, p=0.005], regardless of sex. Pramipexole did not significantly affect time spent in closed arms or the center zone but reduced overall locomotor activity [distance: $F_{(2,60)}$=28.15, p<0.001; velocity: $F_{(2,60)}$=27.22, p<0.001]. Diazepam increased % open arm time [$F_{(1,34)}$=12.82, p=0.001], reproducing typical EPM findings and validating our pramipexole findings. Contrary to our hypothesis, pramipexole reduced time spent in the exposed, “risky” arms of the EPM. Thus, the EPM does not measure RBDM as seen in the clinic. Clinically translatable operant paradigms (e.g., rodent Iowa Gambling Task) remain the gold standard for preclinical study of RBDM.

Disclosures: L.F. Cunningham: None. **B.Z. Roberts:** None. **J.W. Young:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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Program #/Poster #: LBP048.08/LBP146

Topic: H.05. Mood Disorders

Support: NIH Grant MH107662
Pritzker Neuropsychiatric Research Consortium
NSF Grant 1916425
NIH Grant T32GM141746

Title: Big Brother's behavioral index: profiling mouse activity and choice in a controlled environment

Authors: *A. M. ROBERTS[1], N. OGNJANOVSKI[2], K. KNOPF[3], E. GOLDIEZ[3], B. O. WATSON[4];
[1]Neuroscience, Wellesley College, Wellesley, MA; [2]Pyschiatry, University of Michigan, Ann Arbor, MI; [3]University of Michigan, Ann Arbor, MI; [4]Psychiatry, University of Michigan, Ann Arbor, MI

Abstract: While inter-individual differences in humans are often studied, many studies of animal models use population averaging, leaving individual differences less studied. Understanding stable individual differences—or "behavioral baselines"—in animal models is crucial for dissecting the neurobiological underpinnings of personality, temperament, and disease susceptibility. Recent advances in automated behavioral tracking technologies now enable previously unattainable resolution and timescales for characterizing spontaneous rodent behavior in naturalistic settings. In this work, we quantified whether individual C57 male mice showed inherent and unique behavioral predispositions that were consistent across numerous behaviors and extended periods of time. We do this by employing automated behavioral tracking in the home cage using our "Digital Home Cage" (DHC) over multiple weeks. This study employs DHCs to continuously monitor 48 individually-housed wildtype mice over a 4-week period with minimal experimenter interaction. The DHC processes multiple data streams including actigraphy, wheel running, and food and drink preference (regular or fatty food, regular or sucrose water). Behavioral data streams were processed and analyzed using dimensionality reduction (UMAP) and clustering algorithms (K-means), followed by supervised classification with machine learning, to identify and validate stable behavioral phenotypes. Importantly we quantified behaviors daily, but also by hour of the day to determine circadian patterns. Despite uniform genetic backgrounds and standardized housing, substantial inter-individual and intra-individual variability emerged, clustering mice into three distinct and reproducible behavioral phenotypes based on patterns of activity, feeding, and preference. Notably these phenotypes were stable over time. Feature importance analyses highlighted wheel running—especially during the nocturnal period—as a dominant driver of group differentiation, as well as nuanced preference for sucrose or fatty food. Similarity assessments confirmed within-mouse behavioral

stability that exceeded between-mouse similarities across days and weeks. Our study demonstrates that DHC technology combined with data-driven analytical approaches enables objective, longitudinal profiling of behavioral individuality in rodents. This work not only advances our understanding of baseline behavioral variation, but also may enhance the translational relevance and rigor of preclinical neurobehavioral research by providing richer, individualized models for studying psychiatric and neurological disease mechanisms.

Disclosures: A.M. Roberts: None. **N. Ognjanovski:** None. **K. Knopf:** None. **E. Goldiez:** None. **B.O. Watson:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.09/LBP147

Topic: H.05. Mood Disorders

Title: Modeling Social Stress Susceptibility and Resilience with Chronic Social Defeat in mice

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Abstract: Major depressive disorder (MDD) is a highly heterogeneous condition that affects more than 300 million people worldwide, making it one of the leading causes of disability. To support new drug development, preclinical models must capture this complexity to ensure translational relevance. We successfully established the chronic social defeat (CSD) paradigm in C57BL/6J mice in our laboratory, in which repeated exposure to an aggressive conspecific (older CD1 mice) over 8 days produced two distinct phenotypes: stress-susceptible (~50% of mice) and stress-resilient (~50% of mice). This natural divergence closely mirrors human variability in response to chronic psychosocial stress. Susceptible animals exhibited a marked reduction in social interaction when exposed to conspecific mice, indicating pronounced social avoidance. In addition, these animals displayed heightened anxiety-like behavior in the elevated plus maze (EPM), characterized by reduced exploration of the open arms. By contrast, resilient animals maintained normal levels of social interaction with conspecifics and showed no alterations in anxiety-like behavior. These findings confirm that the chronic social defeat paradigm captures both pathological and adaptive responses within a single framework. To further strengthen the model's translational value, additional behavioral readouts such as sucrose preference and cognitive testing will be incorporated in future studies. Our next step is to establish predictive validity by testing chronic antidepressant treatment (e.g., fluoxetine) and rapid-acting interventions (e.g., psilocybin) to reverse susceptibility-related deficits. Together, these results highlight the successful implementation of CSD in our facility and position it as a powerful platform for screening novel antidepressant compounds and investigating the mechanisms of stress vulnerability, resilience, and therapeutic response.

Disclosures: **C. Drieu La Rochelle:** A. Employment/Salary (full or part-time); BIOTRIAL PHARMACOLOGY. **F. Adraoui:** A. Employment/Salary (full or part-time); BIOTRIAL PHARMACOLOGY. **K. Carvalho:** A. Employment/Salary (full or part-time); BIOTRIAL PHARMACOLOGY.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.10/LBP148

Topic: H.05. Mood Disorders

Support: NIH Grant 1R01MH11918- 01A1
Columbia University Grant CUMCUR002883

Title: From Exploration to Adaptation: Sex-Specific Behavioral Dynamics as Predictors of Resilience in Chronic Social Defeat Stress

Authors: *P. ONTIVEROS-ANGEL;
Columbia University, New York, NY

Abstract: From Exploration to Adaptation: Sex-Specific Behavioral Dynamics as Predictors of Resilience in Chronic Social Defeat Stress
Perla Ontiveros-Ángel*[1,3], Micaela Oliveira David[2,3], Alessia Manganaro[1,3], Dani Dumitriu[1,3]
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Chronic social defeat stress (CSDS) is a validated preclinical model of vulnerability and resilience, yet sex-specific adaptations remain largely underexplored. We used a sex-inclusive 11-day CSDS paradigm in C57BL/6J mice (n=140; 70 male, 70 female) to identify behavioral predictors of susceptibility and resilience. Social interaction (SI) testing confirmed model validity, with defeated mice exhibiting reduced SI ratios relative to controls ($t(134.9) = 3.20$, $p = 0.002$). Phenotype stratification revealed 54% resilience in males versus 36% in females ($\chi^2 = 5.21$, $p = 0.022$), indicating greater female susceptibility. Two-way ANOVA revealed main effects of phenotype ($F(2,74) = 474.1$, $p < 0.0001$) and sex ($F(1,60) = 4.10$, $p = 0.047$), with a significant sex × phenotype interaction ($F(2,74) = 32.0$, $p < 0.0001$). Susceptible females displayed significantly greater corner occupancy compared to female controls ($p = 0.003$) and resilient females ($p = 0.002$), while susceptible males did not differ. Regression analyses identified angular velocity as a sex-independent predictor of SI performance (males: $R^2 = 0.157$, slope = 0.396±0.111, $p = 0.001$; females: $R^2 = 0.119$, slope = 0.345±0.114, $p = 0.003$), whereas corner ratio negatively predicted SI in both sexes (males: $p = 0.034$; females: $p = 0.002$). Distance ratio and latency to corner predicted SI in males only ($p = 0.008$ and $p = 0.011$, respectively). Longitudinal defeat-session analyses further revealed temporal and sex-dependent coping strategies. On Day 1, susceptible females exhibited greater cornering than susceptible

males; by Day 11, females increased elevated platform use and cornering, while resilient males shifted toward passive coping. Resilient females, in contrast, decreased avoidance across sessions. Together, these results establish angular velocity as a robust sex-independent marker of resilience, while avoidance metrics reveal sex-dependent vulnerabilities, advancing a quantitative temporal framework for dissecting behavioral adaptations to chronic stress.

Disclosures: P. Ontiveros-Angel: None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.11/LBP149

Topic: H.05. Mood Disorders

Support: Mayo Clinic Foundation
Ben Dov Family Luminescence Foundation
Goodman Family Foundation

Title: Psilocybin causes sex, time, and dose dependent alterations in brain signaling pathways

Authors: *J. BARNETT[1,2], K. TODD[3], J. BENETATOS[4], B. RABICHOW[2], K. OLNEY[2,3], J. D. FRYER[2,3];
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Abstract: Psilocybin is a psychedelic tryptamine that has emerged as a potential candidate for the treatment of a variety of conditions, including treatment resistant depression and post-traumatic stress disorder. Clinical trials which have assessed the efficacy of psilocybin for these conditions report a rapid and sustained improvement in patient- and clinician-rated depression scores. The established mechanism of action for psychedelics such as psilocybin is agonism of the serotonin 2A receptor ($5HT_{2A}R$), however, the downstream events that mediate their therapeutic or psychedelic effects remain uncertain. As high doses of psychedelics are known to induce strong perceptual alterations, an additional outstanding question is whether subperceptual doses induce similar molecular effects as psychoactive dosages. Here, we report dose- and sex-dependent transcriptional changes in forebrains of female and male mice at 3 timepoints (8 hours, 24 hours, and 7 days) following a single administration of psilocybin at low (0.25 mg/kg) or high (1 mg/kg) doses. Grouped analysis of both sexes demonstrated strong dose- and time-dependent transcriptomic alterations. Numerous pathways were altered depending on sex and timepoint, but common features included functions related to neuronal differentiation, neurogenesis, and changes in receptor signaling. We found more rapid transcriptional changes and attenuation of such changes in females following a single low-dose relative to males treated

identically. Females also responded more robustly to high-dose administration relative to males at 8 and 24 hours, with signal attenuation in both sexes by 7 days. A notable observation was the persistent transcriptional effect of low-dose psilocybin at 7 days, which outlasted high-dose changes in both sexes, and suggests that low doses may have prolonged biological effects. Given ongoing clinical interest in psilocybin for treating mental health disorders, our results suggest that these sexually divergent changes should be considered when weighing treatment strategies. Additional consideration should be given to temporal effects of low vs high dosages, especially when timing psilocybin with adjuvant cognitive behavioral therapy.

Disclosures: J. Barnett: None. **K. Todd:** None. **J. Benetatos:** None. **B. Rabichow:** None. **K. Olney:** None. **J.D. Fryer:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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Program #/Poster #: LBP048.12/LBP150

Topic: H.05. Mood Disorders

Title: Transcriptomic Profiling Identifies Molecular Signatures of High Fructose Corn Syrup Diet Induced Neuroadaptations in the Nucleus Accumbens

Authors: *A. CHAKRABORTI, A. AERUVA, T. J. ZAFAR, E. ABUNDIS, C. DE AVILA DAL BO, S. ZARRABIAN, J. RAMOS, J. CONTRERAS, Z. FATAHIVANANI, K. GUPTA, A. DIAZ, J. A. BIBB;
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Abstract: Diabetes and neuropsychiatric disorders are highly comorbid, with each condition exacerbating the other. The mechanisms mediating this comorbidity are poorly understood. Increased consumption of diets enriched in high-fructose corn syrup (HFCS), a common sweetener in processed foods and beverages, has been linked to both metabolic dysfunction and mood-related disturbances. To investigate the molecular underpinnings of these effects, male C57BL/6J mice were fed either a control or an HFCS-enriched diet (HFCSD) for 16 weeks (n=10/group). HFCSD mice developed metabolic impairments and displayed increased anxiety-like behavior in the elevated plus maze and open field test. Transcriptomic profiling of the nucleus accumbens (NAc), a key hub for reward and motivation, revealed 245 differentially expressed genes (153 upregulated, 92 downregulated; FDR < 0.05). Notably, immune and stress-related genes, including IL-12a, SGK1, and ADCYAP1, were significantly upregulated, whereas multiple synaptic signaling genes were downregulated. Gene set enrichment analysis (GSEA) identified coordinated alterations in gene networks involved in neuronal excitability, metabolic stress responses, and cell signaling, suggesting broad reprogramming of reward-related circuitry. Network topology analysis identified hub genes central to protein-protein interaction networks, suggesting key drivers of diet-induced neuroadaptations. Interestingly, a subset of HFCS-responsive genes and pathways overlapped with those dysregulated in the human NAc in major

depressive disorder, underscoring the translational relevance of this model. Together, these findings show that chronic HFCSD produces metabolic and behavioral alterations accompanied by robust transcriptomic remodeling of the NAc, providing mechanistic insights into how metabolic dysfunction reprograms reward circuitry and identifying molecular pathways that may serve as therapeutic targets in diabetes-psychiatric comorbidity.

Disclosures: A. Chakraborti: None. **A. Aeruva:** None. **T.J. Zafar:** None. **E. Abundis:** None. **C. de Avila Dal Bo:** None. **S. Zarrabian:** None. **J. Ramos:** None. **J. Contreras:** None. **Z. Fatahivanani:** None. **K. Gupta:** None. **A. Diaz:** None. **J.A. Bibb:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.13/LBP151

Topic: H.05. Mood Disorders

Title: Anxiolytic Effect of the δ-Opioid Receptor Agonist via Prefrontal Glutamate Modulation in Inflammatory Pain Model

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Abstract: Chronic pain is often accompanied by psychiatric comorbidities such as anxiety and depression, significantly reducing patients' quality of life. δ-opioid receptor (DOP) agonists have been shown to exert both analgesic and anxiolytic effects in rodent models. Furthermore, glutamatergic neurotransmission in the prelimbic region of the medial prefrontal cortex (PL-PFC) has been implicated in the expression of anxiety. This study aimed to investigate the effects of KNT-127, a selective DOP agonist, on pain sensitivity, anxiety-like behavior, and glutamate transmission in the PL-PFC of mice with chronic inflammatory pain. Male C57BL/6N mice (7 weeks old) were used to establish a chronic inflammatory pain model induced by complete Freund's adjuvant (CFA). Four weeks after CFA injection, KNT-127 (3 mg/kg, s.c.) was administered. Nociceptive thresholds were evaluated using the von Frey test, and anxiety-like behavior was assessed using the elevated plus maze (EPM) test. Extracellular glutamate levels in the PL-PFC were measured via in vivo microdialysis following exposure to elevated platform stress. KNT-127 produced a significant analgesic effect in CFA model mice, as indicated by increased von Frey thresholds. Additionally, KNT-127 significantly ameliorated anxiety-like behavior in the EPM test. Elevated platform stress induced a significant increase in extracellular glutamate levels in the PL-PFC, which was significantly suppressed by KNT-127 treatment.These findings suggest that DOP receptor agonists may alleviate both chronic inflammatory pain and comorbid anxiety, potentially through the modulation of glutamatergic neurotransmission in the PL-PFC. Thus, DOP agonists such as KNT-127 may represent

promising therapeutic agents for the treatment of both pain and affective symptoms in patients with chronic inflammatory conditions.

Disclosures: A. Saitoh: None. **T. Yoshioka:** None. **D. Yamada:** None.

Late-Breaking Poster

LBP048: H.05. Mood Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP048.14/LBP152

Topic: H.05. Mood Disorders

Support: The Baszucki Group
The Vulnerable Brain Project

Title: Ketamine sustains the protective effects of ketogenic diet in adult mice exhibiting anorexia-like maladaptive behavior and enhances hippocampal GABAergic inhibition

Authors: *J. WANG[1], Y. DONG[2], E. V. LEE[3], C. J. AOKI[3];
[1]New York University Washington Square Campus, New York City, NY; [2]Center for Neural Science, NYU, New York, NY; [3]Center for Neural Science, New York University, New York, NY

Abstract: Introduction: Ketogenic diet (KGD) followed by IP ketamine injections (KET) reduces anorexia-like vulnerability in an animal model of anorexia nervosa (AN), called activity-based anorexia (ABA) acutely and when ABA is repeated (ABA2), modeling relapse. By contrast, animals fed KGD without KET (KGD-noKET) lose resilience to ABA induction, when they return to standard rat chow pellet (SD). This study aimed to understand the biological bases for this difference between KGD+KET versus KGD-noKET. Prior electron microscopic analyses (EM) of animals that underwent repeated ABA indicated that enhancement of GABAergic innervation in the dorsal hippocampal CA1 contributes towards gain of resilience acutely (ABA1) and in relapses (ABA2). We hypothesized that KGD+KET enhances GABAergic innervation of the hippocampus more than following KGD-noKET. **Methods:** KGD+KET (N=7) and KGD-noKET (N=8) animals were induced to exhibit anorexia-like behavior of excessive exercise on a wheel, voluntary food restriction, enhanced anxiety-like behavior and severe (>20%) body weight (BW) loss by combining acclimation to a wheel with restricted food access (unlimited amount from 7pm-9pm only). All were fed KGD for 10 days prior to and during ABA1. KGD+KET received IP KET (30 mg/kg) on the 2nd, 3rd and 4th days of food restriction. Upon recovery from ABA1, during re-acclimation to the wheel and during ABA2, all animals were fed SD. Brain sections spanning the dorsal hippocampal CA1 were immune-labeled for GAD (glutamic acid decarboxylase) to detect GABAergic cell bodies, dendrites and axons. EM analyses was conducted while kept blind to individual differences in the above-listed ABA-like behaviors. **Results:** EM analysis revealed no group differences in lengths of GABA-immuno-labeled axons (LA) and a trend (p=.1) of increased proportion of pyramidal cell body plasma

membrane (PC) contacted by LA (% GAD). During ABA1 (acute KET), BW retention at the end of the starved hours (7 pm) and at 9 pm (end of feeding) both correlated positively with LA lengths for the KGD+KET but not the KGD-noKET. BW retention during ABA1 also correlated with LA density on PC for KGD+KET but not KGD-noKET. During ABA2 (10 days post KET), BW retention at 7 pm correlated with % GAD for the KGD+KET but not for the KGD-noKET. These positive correlations suggest that those animals with greater resilience (higher BW) acutely (ABA1) and 10 days post-KET (ABA2) were helped by the enhanced GAD innervation but only under the influence of KET. **Conclusion:** KET sustains and boosts KGD's benefits for >10 days, even when off of SD, in part by sustaining GABAergic suppression of hippocampal excitability, contributing to better weight.

Disclosures: J. Wang: None. **Y. Dong:** None. **E.V. Lee:** None. **C.J. Aoki:** None.

Late-Breaking Poster

LBP049: H.06. Anxiety Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP049.01/LBP153

Topic: H.06. Anxiety Disorders

Title: Neural Correlates of Error Processing: Predictors of Anxiety Treatment Response in Youth

Authors: *K. Y. KIM[1], S. HALLER[1], A. POE[2], E. CARDINALE[3], K. KIRCANSKI[4], D. S. PINE[1], P. KHOSRAVI[1];
[1]National Institutes of Health, Bethesda, MD; [2]Stony Brook University, Astoria, NY; [3]The Catholic University of America, Washington, DC; [4]University of Southern California, Los Angeles, CA

Abstract: Background: The ability to engage in goal-directed behavior, or inhibitory control, is mediated throughout the prefrontal cortex and striatum. Youth with anxiety disorders show maladaptive engagement; however, changes over the course of treatment remain unknown. Cognitive behavioral therapy (CBT) is the most effective treatment for anxiety in youth. Here, we examined the association between neural process of inhibitory control and anxiety treatment outcomes, evaluating the anxiety severity pre and post treatment. We hypothesize that post treatment improvement on behavioral metrics of inhibitory control is associated with decreased activity in error processing regions.
Methods: Fifty youth with anxiety disorders (age M = 14.03 +/- 2.57, male = 36%) successfully completed an inhibitory control Flanker task (4 runs) during fMRI prior to 12 sessions of CBT treatment. Sex-specific analyses were not assessed. Anxiety severity was measured at pre- and post- treatment using the Pediatric Anxiety Rating scale (PARS). We examined the association between baseline error-related activation (incongruent error - incongruent correct) and post-treatment PARS, controlling for pre-treatment PARS, age, and number of errors made. Whole-brain results were thresholded at $p < .005$, and cluster size = 56 at α; = .05. Behavioral accuracy

and reaction time (RT) during the task were analyzed using a comparable contrast and model to the brain analysis.
Results: Controlling for covariates, higher post-treatment anxiety severity was associated with greater neural activation during incongruent error trials in the left middle cingulate cortex, b=.01, t=-2.6, p=.01, right superior frontal gyrus, b=- .01, t=-3.4, p=.001, and right cuneus, b=- .01, t=-2.7, p=.009. The pattern of association was reversed for incongruent correct trials, where higher post- treatment anxiety level is associated with decreased activation. There were no behavioral associations with RT and accuracy.
Conclusions: Findings provide preliminary support for association between anxiety treatments and neural engagement during inhibitory control. The results suggest that baseline neural activation in error processing regions seems to be sensitive to anxiety severity but in task-specific conditions, indicating that neural responses to errors made compared to correct responses differentially modulate the treatment-driven changes in anxiety. There is notably a lack of behavioral-neural convergence which may reflect local neural engagement which is not evident in behavioral measures and suggests that the neural findings may be more sensitive.

Disclosures: K.Y. Kim: None. **S. Haller:** None. **A. Poe:** None. **E. Cardinale:** None. **K. Kircanski:** None. **D.S. Pine:** None. **P. Khosravi:** None.

Late-Breaking Poster

LBP049: H.06. Anxiety Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP049.02/LBP154

Topic: H.06. Anxiety Disorders

Support: R01MH123736
R01MH125198
R33MH111907
R01MH101497

Title: Altered Brain Dynamics Track Treatment Response to Cognitive Behavioral Therapy in Internalizing Psychopathologies

Authors: *K. ZHANG[1], J. JIMMY[2], B. MOALLEM[1], K. D. PHAN[2], M. MILAD[1], Z. WEN[1]; [1]University of Texas Health Science Center at Houston, Houston, TX; [2]The Ohio State University, Columbus, OH

Abstract: ABSTRACTObjective Cognitive-behavioral therapy (CBT) is effective for treating internalizing psychopathologies (IPs), but treatment response remains heterogeneous, and the underlying neural mechanisms are poorly understood. Most prior studies have relied on static brain measures, overlooking the dynamic, rapidly fluctuating nature of brain networks. Herein, we characterized fast neural dynamics in a relatively large sample of IPs, investigated their modulation by CBT, and evaluated their clinical relevance to treatment response.**Methods**A total

of 132 participants (78 IPs patients, 54 healthy controls) underwent fMRI scans before and after 12 weeks of manualized CBT (HCs received no intervention). A hidden-Markov model applied to the whole-brain time series identified eight recurrent coactivation patterns (CAPs)—momentary spatial 'snapshots' of network activity—and simultaneously estimated their temporal evolution. We quantified 4 different temporally sensitive characteristics: 1) the proportion of time networks remained in a given activity state (state occupancy rate), 2) the uninterrupted duration of a state (mean dwell time), 3) the likelihood of moving between states (transition probability), and 4) the overall predictability of state-to-state paths (trajectory entropy). Regularized canonical correlation analysis (rCCA) was used to link therapy-induced functional reorganization with multidimensional symptom change. Informed consent was obtained from all participants, and all procedures conformed to the Declaration of Helsinki.**Results**CBT significantly increased occupancy rate and dwell time of two states (CAP2 and CAP4) engaging the somatomotor and frontoparietal control networks (all FDR-corrected $p < 0.05$). The CAP2 and CAP4 states became more temporally stable after CBT treatment, as indicated by reduced transition entropy. CBT-induced whole-brain connectivity re-organization within these states significantly predicted multidimensional symptom improvement (cross-validation performance: $r = 0.27$ and 0.36, respectively, permutation tests $p<0.05$). No significant changes in brain states were observed in HCs.**Conclusions**We showed that CBT consistently redirects patients into more stable sensorimotor and cognitive-control states, which are predictive of symptom improvement. These findings position dynamic brain states as potential biomarkers for monitoring and optimizing treatment progress.

Disclosures: K. Zhang: None. **J. Jimmy:** None. **B. Moallem:** None. **K.D. Phan:** None. **M. Milad:** None. **Z. Wen:** None.

Late-Breaking Poster

LBP049: H.06. Anxiety Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP049.03/LBP155

Topic: H.06. Anxiety Disorders

Title: Preoperative anxiety in schoolchildren: the effect of a nursing intervention from Callista Roy's perspective

Authors: *J. HERNÁNDEZ-HERNÁNDEZ[1], M. SANCHEZ PADILLA[2], V. ALAMILLA[3], J. ARIAS-RICO[4], M. MONTER[5], E. RAMÍREZ MORENO[6], R. BALTAZAR TELLEZ[3], D. MOLINA AVILEZ[3];
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Abstract: Adolescence and childhood are stages highly sensitive to stress and environmental factors, and surgical procedures often generate significant preoperative anxiety. According to Callista Roy's Model of Adaptation, human well-being depends on the ability to adapt to environmental stimuli. This principle was applied to a nursing intervention designed to reduce preoperative anxiety in pediatric patients undergoing surgery at a secondary care hospital. The objective of this study was to evaluate the effectiveness of a non-pharmacological intervention based on adaptation strategies to decrease preoperative anxiety and improve coping skills in children.A quantitative, prospective, and quasi-experimental study was conducted with 30 pediatric patients (aged 2-12 years) from a secondary-level hospital, divided into an experimental group (n=15) and a control group (n=15). Preoperative anxiety was measured with the validated Spanish version of the Yale Preoperative Anxiety Scale (Cronbach's α=0.78), which assesses activity, vocalization, expressive emotion, state of excitement, and relationship with parents. Coping skills were evaluated with the Spanish version of the Coping and Adaptation Process Measurement Scale (EMPAA, Cronbach's α=0.78). The intervention included relaxation, imagination, storytelling, free drawing, and the projection of educational videos. Data analysis was performed using Student's t-test.At baseline, 100% of participants showed scores >30, indicating preoperative anxiety. After surgery, anxiety increased in the control group (2.6±0.15) but decreased significantly in the experimental group (10.9±0.17, p=0.002). The intervention was effective in reducing anxiety to mild levels in 26% of children, while 40% demonstrated high to very high coping and adaptation skills after the intervention.These findings suggest that non-pharmacological nursing interventions grounded in adaptation theory can significantly reduce preoperative anxiety in schoolchildren and promote more effective coping strategies. This highlights the importance of integrative approaches in pediatric care, with implications for improving surgical outcomes and reducing reliance on pharmacological anxiolytics.This study was approved by an Ethics Committee (Folio: CICEICB-EEP-2024-01). It was conducted without conflicts of interest or external funding.

Disclosures: J. Hernández-Hernández: None. **M. Sanchez Padilla:** None. **V. Alamilla:** None. **J. Arias-Rico:** None. **M. Monter:** None. **E. Ramírez Moreno:** None. **R. Baltazar Tellez:** None. **D. Molina Avilez:** None.

Late-Breaking Poster

LBP049: H.06. Anxiety Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP049.04/LBP156

Topic: H.06. Anxiety Disorders

Support: JSPS Research Fellowship for Young Scientists (DC2), Grant Number JP24KJ2020

Title: Inranasal administration of disulfiram in rats produces rapid and potent anxiolytic-like effects without adverse alcohol-related interactions

Authors: *A. OHTA[1,2], Y. TERASHIMA[2], D. YAMADA[1], K. NAGAI[1,2], H. KINOSHITA[3], K. MATSUSHIMA[2], A. SAITOH[1];
[1]Laboratory of Pharmacology, Faculty of Pharmaceutical Sciences, Tokyo University of Science, Tokyo, Japan; [2]Research Institute for Biomedical Sciences, Tokyo University of Science, Chiba, Japan; [3]National Research Institute of Police Science, Chiba, Japan

Abstract: The U.S. Food and Drug Administration has approved disulfiram (DSF) for the treatment of alcoholism. Recent studies revealed that DSF inhibits FROUNT, a regulator of CCR2/CCR5 signaling, and exerts anxiolytic-like and anticancer effects. DSF shows strong anxiolytic-like effects in mice without the side effects commonly associated with benzodiazepines. However, oral administration of DSF combined with alcohol can induce adverse effects such as headache, nausea, and decreased body temperature, limiting its clinical use and preventing psychotropic application. We aimed to evaluate whether intranasal administration of DSF could provide rapid anxiolytic-like effects while minimizing peripheral adverse effects. Male Wistar/ST rats were used. For intranasal administration, DSF was encapsulated with 2-hydroxypropyl-β-cyclodextrin to form an inclusion complex, which exhibited a uniform particle size suitable for intranasal delivery and ensured reproducible dispersion. Anxiolytic-like effects were assessed using the elevated plus maze (EPM) test, a well-established paradigm for measuring anxiety-related behavior. Ethanol (2,000 mg/kg, p.o.) was administered 48 h after DSF to evaluate safety. Two hours later, body temperature was measured, and blood samples were collected to quantify acetaldehyde levels with high sensitivity. Intranasal administration of DSF (1.5 mg/rat) significantly increased the time spent in the open arms of the EPM within 20 min, indicating a rapid anxiolytic-like effect. In contrast, oral administration of DSF (1,000 mg/kg) increased open-arm time 30 min after administration. Importantly, intranasal administration of DSF did not reduce body temperature or increase blood acetaldehyde levels, unlike oral administration, suggesting minimized peripheral adverse effects and improved tolerability. These findings demonstrate that intranasal administration of DSF produces rapid and potent anxiolytic-like effects at substantially lower doses than oral administration while avoiding alcohol-related side effects. Direct and efficient nose-to-brain delivery likely underlies the rapid onset and reduced systemic toxicity. Collectively, the results highlight the therapeutic potential of DSF beyond its conventional use, providing compelling preclinical evidence that intranasal delivery may represent a novel, safe, non-invasive, and fast-acting anxiolytic strategy.

Disclosures: A. Ohta: None. **Y. Terashima:** None. **D. Yamada:** None. **K. Nagai:** None. **H. Kinoshita:** None. **K. Matsushima:** None. **A. Saitoh:** None.

Late-Breaking Poster

LBP049: H.06. Anxiety Disorders

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Topic: H.06. Anxiety Disorders

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São Paulo Research Foundation (FAPESP) (2022/04387-6)
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São Paulo Research Foundation (FAPESP) 2022/06260-3

Title: Effects of oxytocin receptor ligands on anxiogenic-like effect, social avoidance and changes on medial prefrontal cortex oxytocin receptor expression evoked by chronic social defeat stress in rats

Authors: *L. C. CANTO DE SOUZA, D. B. SOUZA, C. BUSNARDO, C. CRESTANI;
Sao Paulo State University (UNESP), Araraquara, Brazil

Abstract: We investigated the effect of systemic administration of the synthetic oxytocin (OXT) analog carbetocin (CBT) and/or OXT receptor (OXTR) antagonists [atosiban (ATO) and L-368,899] on social avoidance and anxiogenic-like effect in male rats subjected to chronic social defeat stress (cSDS). Effect of cSDS and pharmacological manipulation of OXT system on expression of OXTR within the medial prefrontal cortex (mPFC) subregions [anterior cingulate (Cg), prelimbic (PL) and infralimbic (IL) cortices] was also evaluated. Our behavioral results indicated that cSDS, while not inducing social avoidance in the social interaction test, reliably induced anxiogenic-like effect as measured by the elevated plus maze test. Chronic systemic treatment with either CBT or ATO, but not L-368,899, during cSDS protocol dose-dependently prevented the anxiogenic-like effect. Both ATO and L-368,899 were able to block the anxiolytic effect of CBT in defeated animals, confirming OXTR-mediated effect. Also, cSDS increased OXTR levels within the Cg, which was inhibited by both ATO and L-368,899 treatments. Conversely, cSDS did not affect OXTR within the PL and IL. However, CBT treatment significantly increased OXTR expression within the PL and IL of defeated animals, an effect that was blocked by both ATO and L-368,899. Taken together, our study provides evidence for the critical role of the OXT system and its pharmacological manipulation in modulating anxiogenic-like effects evoked by social stress. Furthermore, the region-specific modulation of OXTR expression within the mPFC by stress and OXT system pharmacological manipulation emphasizes the complex and dynamic nature of OXTR regulation in brain regions crucial for emotional processing.

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Late-Breaking Poster

LBP049: H.06. Anxiety Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP049.06/LBP158

Topic: H.06. Anxiety Disorders

Support: NIMH: R01 MH122561

Title: Alprazolam Bidirectionally Modulates Defensive Behavior in a Sex-Dependent Manner

Authors: *C. FRIEDMAN[1], C. BORKAR[2], K. EVANS[2], J. P. FADOK[3];
[1]Tulane Brain Institute #1345 Undergraduate Neuroscience Program, New Orleans, LA; [2]Department of Psychology, Tulane University, New Orleans, LA; [3]Psychology and Tulane Brain Institute, Tulane University, New Orleans, LA

Abstract: Benzodiazepines are widely prescribed for fear- and panic-related disorders, yet their effects on the scaling of defensive responses remain unclear. We tested whether alprazolam modulates freezing, jumping, and escape in male and female C57BL/6J mice using a serial compound stimulus (SCS) fear conditioning paradigm, in which a tone is followed by white noise (WN) paired with footshock. Mice received intraperitoneal alprazolam (0.075 or 0.3 mg/kg) or saline 30 min before conditioning and again before context recall; cue recall was assessed drug-free. Two weeks later, a cue reminder was followed by perfusion for c-Fos mapping across prefrontal-limbic regions (prelimbic cortex (PL), infralimbic cortex (IL), and dorsal peduncular cortex (DP), the dorsal tenia tecta (DTT), nucleus accumbens (NAc), lateral septum (LS), central and basolateral amygdala (CeA, BLA), and dorsal/ventral bed nucleus of the stria terminalis (BNSTd/v). Across sexes, alprazolam increased freezing to the tone. Dose- and sex-specific effects emerged for responses to WN: at the lower dose (0.075 mg/kg), females—but not males—showed increased WN-evoked freezing and reductions in escape speed and jumping; at the higher dose (0.3 mg/kg), both sexes exhibited faster WN-evoked escapes, consistent with a disinhibitory action on locomotor output. In the threat context, recall induced robust tone freezing in all groups. In females, the lower dose also increased freezing and decreased WN-evoked escape speed and jumping. By contrast, recall in a neutral context reduced WN-evoked freezing in females, indicating alleviation of cue-elicited fear. C-Fos mapping revealed that low-dose alprazolam in females decreased activity in NAc, BLA, DP, DTT, BNSTd/v, and LS, while increasing activity in IL. Together, these data show that alprazolam shapes fear scaling in a sex- and dose-dependent manner: females are more sensitive to low-dose alprazolam, displaying enhanced freezing and reduced flight, accompanied by selective modification of prefrontal-limbic circuits. These findings identify circuit-level correlates of benzodiazepine effects on defensive behavior and have implications for sex-informed treatment of fear disorders.

Disclosures: C. Friedman: None. **C. Borkar:** None. **K. Evans:** None. **J.P. Fadok:** None.

Late-Breaking Poster

LBP050: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP050.01/LBP159

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: Ibogaine reshapes brain networks in the short and medium term

Authors: *K. SHINOZUKA;
Stanford University, Palo Alto, CA

Abstract: Traumatic brain injury (TBI) is a debilitating condition that affects millions of U.S. veterans and is co-morbid with other psychiatric illnesses such as post-traumatic stress disorder (PTSD), depression, and anxiety. A recent observational study in 30 veterans showed that a single dose of the atypical psychedelic drug ibogaine can be highly effective at treating TBI sequelae up to one month later. However, the neural mechanisms of ibogaine are unknown. In this exploratory analysis, we investigated whether clinical improvements on ibogaine are associated with the reorganization of certain brain networks. We applied a novel framework, FREQuency-resolved brain Network Estimation via Source Separation (FREQ-NESS), to identify frequency-specific brain networks in resting-state electroencephalography (EEG) data that was acquired at baseline, three to four days after (immediate-post), and one month after ibogaine in the aforementioned observational study. Ibogaine caused high-beta (24 and 25 Hz) networks to shift away significantly from frontal areas and significantly towards posterior regions, at both the immediate-post and 1 month-post timepoints. Furthermore, this posterior shift in the 25 Hz network was significantly correlated with improvements in PTSD symptoms one month after ibogaine. On the other hand, a standard functional connectivity measure, the weighted phase lag index, was unable to distinguish between the three timepoints at the same frequencies. Overall, our results indicate that the reconfiguration of high-beta brain networks could be a biomarker for ibogaine's therapeutic effects.

Disclosures: K. Shinozuka: None.

Late-Breaking Poster

LBP050: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP050.02/LBP160

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Title: State-dependent and behavior-specific parietal asymmetries as distinct neural biomarkers of chronic PTSD pathophysiology

Authors: *J. V. PINTO;
Univ. of Sydney, Sydney, Australia

Abstract: Parietal lobe dysfunction is postulated to underpin sensory dysregulation and body awareness disturbances in PTSD. We investigated parietal asymmetry in war refugees with chronic clinical and subclinical PTSD (PTSD, n=35) and trauma-exposed healthy controls (TEHCs, n=35) using quantitative EEG. Two biomarkers were identified: 1) Gamma asymmetry demonstrated state-dependent properties, showing significantly greater left-lateralization in PTSD versus TEHCs (FDR-corrected p=.010, d=1.12), normalizing after treatment (p<.001), and

predicting symptom improvement (p=.043). 2) Fast beta asymmetry showed trait-like prognostic value, with pre-treatment levels predicting overall treatment outcome (p= .012) and correlating with reckless behavior severity (FDR-corrected p = .030). Findings reveal distinct neural pathways: gamma reflects sensory hyperarousal pathophysiology while beta indexes behavioral inhibition deficits, providing novel biomarkers for PTSD subtyping and treatment targeting.

Disclosures: J.V. Pinto: None.

Late-Breaking Poster

LBP050: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP050.03/LBP161

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: Japan Society for the Promotion of Science (JSPS) - JP25H01314

Title: Chronic stress-induced depression alters epigenetic and transcriptomic profiles in the nucleus accumbens

Authors: *M. BILLAH[1], S. FUJII[1], M. BUNDO[1], Y. YANAGIDA[1], H. MATSUBARA[2], C. GUO[2], E. KIYOTA[1], Y. IMAMURA[1], T. FURUYASHIKI[3], Y. NAKACHI[1], K. IWAMOTO[2]; [1]Molecular Brain Science, Kumamoto University, Kumamoto, Japan; [2]Molecular Brain Science, Kumamoto Univeristy, Kumamoto, Japan; [3]Pharmacology, Institute of Science Tokyo, Tokyo, Japan

Abstract: Aberrant epigenetic alterations in the brain have been implicated in the pathophysiology of major depressive disorder (MDD). However, brain region-specific vulnerability and their regulatory mechanisms remain unclear. In this study, we profiled DNA methylation (Illumina Infinium Mouse Methylation 285K BeadChip) and mRNA expression (bulk RNA sequencing) in three brain regions: the prefrontal cortex (PFC), hippocampus (HP), and nucleus accumbens (NAc) of chronic social defeat mice. After rigorous quality assessment, normalization and statistical thresholding, we observed largest burden of differentially methylated genes (DMGs) in NAc in comparison to HP and PFC, indicating that NAc tended to be more affected by the stress. Cross-region comparison of DMGs revealed distinctions rather than overlaps, suggesting methylation-directed region-specific vulnerability to stress. We observed same scenario in case of differentially expressed genes (DEGs) analysis which confirmed larger transcriptional alterations on NAc. The direct overlaps between DMGs and DEGs were limited, occurred only in a small set of genes in NAc displaying significant correlations with behavioral traits. A subset of these genes exhibited the canonical inverse methylation-expression relationship. In the NAc, stress-responsive TFs (bZIP, bHLH), Forkhead factors, and methyl-CpG-binding (MBD) readers were enriched near DMGs. Together, our results identify NAc as the epigenetically and transcriptionally responsive region to stress where TF binding contribute with regulatory role.

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Late-Breaking Poster

LBP050: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Location: SDCC Hall B

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

Program #/Poster #: LBP050.04/LBP162

Topic: H.07. Post-Traumatic Stress Disorder and Other Psychiatric Disorders

Support: Southeast Louisiana Veterans Healthcare System Grant I01 BX005118
Catherine and Hunter Pierson Chair in Neuroscience
Tulane Brain Institute Grant

Title: Traumatic stress alters neuromodulatory regulation of basolateral amygdala parvalbumin interneurons and impairs fear extinction

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Abstract: The basolateral amygdala (BLA) plays a central role in the regulation of emotional memory formation. The BLA is regulated by neuromodulatory systems that are strongly engaged during emotional arousal and stress. Our recent studies in the mouse suggest that neuromodulation of inhibitory basket cell populations control BLA network oscillatory states and the behavioral expression of fear memory. BLA parvalbumin-expressing (PV) neurons respond to α1 adrenergic receptor, Gq-coupled 5-HT2c receptor, and Gq-coupled designer receptor (Gq-DREADD) activation with a repetitive, low-frequency bursting pattern of activity that is highly regular and long-lasting. Gq-DREADD activation of PV neurons has no effect on auditory cue-associated fear conditioning, but Gi-coupled designer receptor (Gi-DREADD) inhibition of PV neurons suppresses fear extinction, suggesting that PV neurons are maximally activated during fear extinction and facilitate extinction learning. Prior exposure of mice to a traumatic stress-with-reminders paradigm impairs fear extinction, similar to PV neuron inhibition. Traumatic stress also disrupts the Gq-coupled receptor-induced oscillatory electrical activity of BLA PV neurons recorded in ex vivo brain slices. These findings together suggest that BLA PV interneurons are critical for the extinction of fear memory and that traumatic stress alters the neuromodulator-induced induction of oscillatory electrical activity in BLA PV neurons to impair extinction memory formation. This work was supported by a grant from the Southeast Louisiana Veterans Healthcare System (I01 BX005118).

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.01/LBP163

Topic: H.08. Drugs of Abuse and Addiction

Support: TNDA T32
Amygdala kappa opioid system involvement in opioid relapse in pain states

Title: Loss of noradrenergic mu opioid receptor expression enhances opioid reward and exaggerates opioid induced withdrawal

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Abstract: Prolonged use of opioid drugs and opioid relapse is in part driven by severe withdrawal symptoms and fear of withdrawal altogether. Noradrenaline is a key neuromodulator implicated in the expression of opioid withdrawal and noradrenergic neuronal activity in the locus coeruleus is enhanced in opioid withdrawal. Noradrenaline is also important in the expression of opioid reward. However, while it is known noradrenaline release contributes to the physical withdrawal and reward, how opioids engage this monoamine system remains unclear. This study tests the hypothesis that opioid reward will be enhanced by ablation of mu opioid receptors (MORs) in noradrenergic neurons and that withdrawal will be reduced in opioid dependent states. Methods: Dopamine beta hydroxylase (DBH)-cre+ mice were bred with $MOR^{loxP/loxP}$ mice. Adult male and female DBH-cre+/floxed MOR and DBH-cre+/floxed MOR cre- littermates were used for all experiments. Mice were conditioned daily for 6 days to morphine (10 mg/kg, i.p.) and saline using an unbiased, counterbalanced conditioning paradigm (3 drug and 3 vehicle pairings) and tested for a conditioned place preference in a drug free state. To determine the effects of genotype on withdrawal and withdrawal-induced aversion, mice were administered saline or escalating doses of morphine (10-50 mg/kg, i.p.) for 5 days. Two hours after the last morphine dose, mice were injected with naloxone (2 mg/kg, i.p.) to test for physical withdrawal or subjected to a single day of conditioning where the animal withdraws in a specific context using the conditioned place preference apparatus and tested the next day in a drug free state to determine the aversion to the conditioning chamber. Data were analyzed by a t-test or 2 or 3-way ANOVA. Results: All mice showed a significant place preference for morphine. The DBH-cre+/floxed MOR cre+ mice showed a significant increase in the conditioned place preference score to morphine compared to DBH-cre+/floxed MOR cre- littermates. Naloxone-precipitated withdrawal was also enhanced in DBH-cre+/floxed MOR cre+ mice as was

naloxone-induced place aversion in both non-dependent and dependent mice. Conclusions: These data suggest that MOR on noradrenergic neurons are involved in both reward and aversive learning. Further, loss of MOR on noradrenergic neurons enhanced physical withdrawal contrary to our hypothesis. Future studies will aim to identify the circuits manipulating these withdrawal and reward behaviors by selectively targeting the MOR on noradrenaline circuits implicated in some of these behaviors.

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Late-Breaking Poster

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Program #/Poster #: LBP051.02/LBP164

Topic: H.08. Drugs of Abuse and Addiction

Support: U01 Grant 1198971 88740
MSSM Grant 1179634 96310
NIDA Grant 1153084 84320

Title: EZH2 regulation of cue-induced relapse-like behavior following heroin abstinence

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Abstract: Substance Use Disorder is defined as a chronic relapsing syndrome. It is thought that persistent transcriptional and epigenetic adaptations and modifications in the nucleus accumbens (NAc) underlie the vulnerability to drugs such as heroin. One such modifier, Enhancer of zeste homolog 2 (EZH2), the catalytic subunit of polycomb repressive complex 2 (PRC2), mediates histone H3 lysine 27 trimethylation (H3K27me3) to establish repressive chromatin states, and has been shown to be involved in long-term neuroadaptations. However, there is little information on how heroin exposure alters EZH2 function, and ultimately cue-induced relapse-like behavior remains unclear. NAc tissue from rats after long-term abstinence (AD14) from heroin self-administration had elevated *Ezh2* gene expression, accompanied by reduced EZH2-SUZ12 complex formation, and decreased H3K27me3 levels. Pharmacological inhibition of EZH2 in the NAc prior to cue-induced relapse significantly attenuated heroin-seeking behavior. We are currently in the process of additional gain of function and loss of function studies to determine the precise neurobiological targets by which EZH2 mediates cellular and behavioral plasticity. These findings identify EZH2 as a key epigenetic regulator of cue-induced relapse vulnerability in heroin addiction.

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.03/Web Only

Topic: H.08. Drugs of Abuse and Addiction

Support: DOST2020-04-A1-265

Title: Exercise decreases toluene conditioned place preference and nucleus accumbens activity

Authors: *J. ASIS[1], A. CARAMPEL[1], J. C. MUNAR[2], C. GREGORIO[3], L. DALMACIO[4], G. J. QUIRK[2], R. CENA-NAVARRO[2];
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Abstract: Chronic use of inhalants in adolescents can cause persistent behavioral impairments that need to be addressed with accessible, low-cost treatments. We recently reported that repeated inhalation of 3000 ppm toluene increased conditioned place preference (CPP) (Asis et al., 2024). Here, we assessed whether exercise could decrease toluene CPP and restore the brain to its pre-addiction state. We exposed male (n = 28) and female (n = 31) adolescent SD rats to 3000 ppm toluene vapor and assigned them to either an exercise group (Tol-Run) or a sedentary group (Tol-Sed). During the abstinence period (D1 to D7), rats in the exercise group had daily access to a movable running wheel (4 h/day), while sedentary rats were provided a fixed wheel. In toluene-exposed rats, females spent more time running than males ($t_{29} = 7.43$, $p < 0.001$). On D8 of abstinence, the CPP score was significantly correlated with total distance run in females ($p = 0.007$). Exercise prevented an increase in CPP score from D1 to D8 in females (unpaired t-test: $p = 0.036$), but not in males ($p = 0.241$). We then performed cFos immunofluorescence and found a significant decrease in cFos density in the nucleus accumbens core in females (Kruskal-Wallis $p = 0.045$, post-hoc Dunn's test Tol-Sed vs. Tol-Run $p = 0.042$), but not in males ($p = 0.337$). These data suggest that exercise attenuated preference for toluene in females by reducing activity in the reward neurocircuitry. Exercise (and also N-acetylcysteine, see Carampel et al., this conference) may be a promising intervention for preventing relapse in inhalant use disorder, similar to other substance use disorders. We are now analyzing additional cFos immunofluorescence data to identify other regions that could contribute to the decrease in toluene CPP after exercise treatment.

Disclosures: J. Asis: None. **A. Carampel:** None. **J.C. Munar:** None. **C. Gregorio:** None. **L. Dalmacio:** None. **G.J. Quirk:** None. **R. Cena-Navarro:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

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Topic: H.08. Drugs of Abuse and Addiction

Support: DOST2020-04-A1-265

Title: N-acetylcysteine decreases toluene conditioned place preference and modulates striatal activity

Authors: *A. CARAMPEL[1,2], J. ASIS[1,2], J. C. MUNAR[2], C. GREGORIO[3], P. MEDINA[4], G. J. QUIRK[2], R. CENA-NAVARRO[2];
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Abstract: Inhalant (toluene) use disorder continues to be a public health problem especially among Filipino adolescents, but no effective treatment has been reported to date. Last year at this meeting, we reported that daily injections of N-acetylcysteine (NAC; 100 mg/kg I.P.) during abstinence, but not melatonin, reduced conditioned place preference (CPP) scores of male and female adolescent Sprague-Dawley (SD) rats that have been repeatedly exposed to 3000 ppm toluene (Carampel et al., 2024). However, saline injections also significantly reduced the CPP scores of females (Carampel et al., SfN 2024), suggesting an effect of injection-induced stress. Female rats that received melatonin (10 mg/kg I.P.) did not show decreased CPP scores ($p = 0.385$) but had less anxiety-like behavior in an open field compared to saline-treated ($p = 0.012$) and NAC-treated ($p = 0.018$) females. To address the potential confounding effect of sex-specific injection-related stress on CPP results, we administered NAC via drinking water (0.9 g/L). We found that the CPP scores of toluene-exposed adolescent female SD rats decreased when they received NAC-infused water ($p = 0.022$) but not drinking water alone ($p = 0.660$). We then performed cFos immunofluorescence to determine the brain regions that are associated with toluene CPP and NAC treatment effects. We found that compared to air-exposed controls, toluene-exposed rats that were treated with saline injections had decreased cFos densities in the dorsomedial striatum (DMS; $p = 0.049$) and nucleus accumbens core (AcbC; $p = 0.064$). The cFos density in the prelimbic cortex was positively correlated with the cFos densities in the DMS ($r = 0.771$, $p < 0.001$) and AcbC ($r = 0.748$, $p < 0.001$). This suggests that prior toluene exposure may act by reducing frontal cortical modulation of the DMS and AcbC to promote drug-seeking

during abstinence. Rats receiving NAC injections did not differ from air controls in cFos densities in the DMS and AcbC ($p = 0.472$ & $p = 0.259$, respectively), consistent with NAC restoring frontal cortical control of behavior. Thus, treatment with NAC (and also exercise, see Asis et al., this conference) during the abstinence period can reverse persistent toluene-induced behavioral deficits, potentially through restoration of frontal cortical control of motivated behavior. We will perform transcriptomic analysis to determine the molecular mechanisms by which NAC can restore brain functioning to its pre-addiction state.

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant F32DA060662-01
NIH Grant T32MH065215-17
NIH Grant R01DA052317

Title: Temporal dynamics of cocaine-elicited dopamine govern how drug cues acquire value

Authors: *M. Z. LEONARD[1], T. T. CLARITY[1], A. KONOMI PILKATI[2], H. B. ELAM[1], K. C. THIBEAULT[1], E. S. CALIPARI[1];
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Abstract: The rate of cocaine delivery dramatically influences its acute reinforcing effects, and is a key determinant for the risk of developing cocaine use disorder. In preclinical models, animals preferentially respond to obtain fast drug infusions over slower administration of the same dose. Rapid cocaine infusions also selectively potentiate plasticity markers in the striatum, despite producing comparable peak drug concentrations and elicited dopamine levels. It, therefore, remains unclear how the temporal dynamics of cocaine's actions within the striatum mediate distinct neurobehavioral outcomes. Using microendoscopic and photometric imaging *in vivo*, we examine how the rate of drug administration (3.0mg/kg; delivered IV over 3, 30 or 100s) influences patterns of neural activity within the NAc of mice expressing either the genetically-encoded calcium sensor GCaMP8 or a fluorescent dopamine sensor (dLight1.2). We find that cocaine has reproducible effects on cellular activity - increasing the activity of a small population of neurons, while robustly decreasing activity in most remaining cells. While this general pattern was observed across all conditions, the time-course and number of cells that were sensitive to cocaine's effects were dynamically modulated by injection speed. DA release was also temporally defined by drug delivery rate. Rapid (3s) drug infusions elicited peak DA levels ~6-times faster than when the same dose was infused over 100s, while producing only a modest

increase in maximal DA. After repeated pairings with auditory/visual cues, stimuli associated with rapid cocaine infusion (3s-Cue) acquired more potent conditioned stimulus properties than those paired slower drug delivery (100s-Cue). 3s-Cues evoked more robust neural activation, and mice elicited more vigorous instrumental responses to produce the 3s drug-stimulus, even in the absence of cocaine itself (i.e., conditioned reinforcement) - suggesting that cues associated with rapid drug administration exert greater motivational control. Interestingly, delaying the onset of a 3s cocaine infusion was sufficient to diminish the conditioned reinforcing effects of rapid drug delivery. Collectively, these studies characterize how cocaine pharmacokinetics differentially influence neural dynamics within target striatal circuitry. Rapid drug delivery may potentiate drug-conditioned cue associations by increasing the temporal contiguity between drug-elicited DA and the actions/cues that predict it.

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

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Department of Veterans Affairs VISN1 Career Development Award
Brain & Behavior Research Foundation Young Investigator Award
American Foundation for Suicide Prevention Young Investigator Award

Title: Cell type-specific genetic regulation and differential gene expression in the central nucleus of the amygdala in alcohol use disorder

Authors: *E. N. PENICHET[1], C. LEE[2], D. MCRILEY[1], J. LEE[1], M. SKARICA[1], J. WANG[1], T. NGUYEN[1], Y. LIU[1], X. SHAN[3], H. ZHAO[3], M. J. GIRGENTI[1];
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Abstract: The central nucleus of the amygdala (CeA) regulates emotional states such as fear, anxiety, and irritability, and is thought to underlie affective symptoms of withdrawal in alcohol use disorder (AUD). Until now, knowledge of the role of the CeA in AUD has been derived from mouse studies, which are limited by differences in ethanol metabolism, immunity, and neural complexity between humans and mice. Using 174,188 nuclear transcriptomes obtained from human postmortem brain tissue, we examine cell type-specific transcriptomic alterations in the CeA between 21 AUD subjects (12 males, 9 females, mean age = 44.0 ± 12.3 years) and 27 controls (11 males, 16 females, mean age = 47.7 ± 13.0 years). To establish a baseline map of the

regulatory architecture in the CeA, we fit an eQTL regression model (adjusted for variables such as case-control status, sex, age, and genotyping principal components) to identify genetic variants associated with proximal gene expression (i.e., cis-eQTLs) in 15 cell types. We identified 49 significant ($q < .05$) variant-gene pairs (consisting of 10 eGenes) mainly concentrated in the oligodendrocyte cell lineage (88%), followed by astrocytes (10%) and inhibitory-DRD1 neurons (2%). The strongest signal was found in oligodendrocyte precursor cells (OPCs), which showed 26 variant associations with *UGT2B7*, a drug-metabolizing enzyme that had not previously been identified as an eGene in the brain. Notably, we observed a similar finding in an external dataset (ROSMAP), finding that *UGT2B7* undergoes cis-genetic regulation in OPCs in the dorsolateral prefrontal cortex. Once a baseline eQTL map in the CeA was established, we tested for variants with AUD-specific differences in genetic regulation using an interaction eQTL model. Findings showed that *PAK5*, a kinase involved in cytoskeletal remodeling, undergoes negative regulation by rs6032829 in microglia in AUD subjects. Of note, genetic regulation of *PAK5* has previously been implicated in bipolar disorder and schizophrenia. Finally, we conducted a differential gene expression analysis (while adjusting for genetic liability to problematic alcohol use) to identify transcriptomic changes in AUD likely occurring through non-heritable disease pathways. Results showed that several chemokines (CXCL1, CXCL3, CXCL8, and CXCL10) and superoxide dismutase 2 were upregulated (~100 to 600-fold increase; $q < .05$) in endothelial and mural cells in AUD subjects. In summary, the present work establishes the first cell-type resolved eQTL map of the CeA, queries differences in genetic regulation between AUD subjects and controls, and identifies a canonical NF-κB inflammatory pathway highly upregulated in AUD.

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.07/LBP166

Topic: H.08. Drugs of Abuse and Addiction

Support: Kahlert Institute for Addiction Medicine
NIDA DA047976
NIMH MH129310

Title: Central amygdala neuronal activity mediates the protective effect of social reward on the incubation of drug craving

Authors: *S. J. WEBER[1], M. VENNIRO[2];
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Abstract: Central amygdala neuronal activity mediates the protective effect of social reward on the incubation of drug craving Sophia J. Weber[1,2], Shannon E. Kirk[1], Clara J. Harvey[1], Marco Venniro[1,2,3]
Affiliations:1Department of Neurobiology, University of Maryland School of Medicine, Baltimore USA 2Kahlert Institute for Addiction Medicine, Baltimore USA 3Department of Psychiatry, University of Maryland School of Medicine, Baltimore USA
Background Relapse represents a consistent clinical problem in the treatment of substance use disorders. The incubation of drug craving model can emulate similar behavior in rodents, with rats showing elevated drug-seeking with tested after abstinence from drug self-administration. We can reduce incubated drug-seeking by allowing rats to voluntarily suppress their intake of drug in a choice paradigm because of their preference for social reward. We investigated calcium transients in the CeA during drug seeking after social-volitional abstinence.
Methods Prior to behavioral training, we injected GCaMP8s in CeA and a fiber optic cannula was implanted along with an intravenous jugular catheter. Male (M) and female (F) rats lever pressed to receive 60 s of social interaction (2 h/d x 6 d) and then intravenous methamphetamine (0.1 mg/kg/infusion; 6 h/d x 12 d). We performed drug-seeking tests on abstinence day (AD) 1 and AD15. Between these tests half of the rats were run on a choice procedure in which they were offered two levers, one for social reward and one for drug (15 trials/d X 13 d), while the other half remained in their home cage.
Results Photometry recordings during seeking tests demonstrated elevated calcium activity around the moment of active lever press on both AD1 and AD15, although this transient was not significant when assessed via bootstrapping or area under the curve (AUC) (n = 13, 4 M/9 F, within subject design).
Conclusions Our data indicates that CeA activity in response to drug-associated cues may be increased during incubated drug seeking.

Disclosures: S.J. Weber: None. **M. Venniro:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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Program #/Poster #: LBP051.08/LBP167

Topic: H.08. Drugs of Abuse and Addiction

Support: NIAAA: 5R21AA031324.

Title: Ethanol-Induced Plasticity in Sleep Genes and Circuits in Drosophila

Authors: *L. M. GARCIA[1], F. W. WOLF[1], V. SANCHEZ[2], A. R. VAN GORKOM[3];
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Abstract: Alcohol use disorder is associated with disruptions in sleep, yet the neuronal mechanisms connecting these processes remain unclear. *Drosophila* is a helpful model to dissect the genes and circuits that regulate rapid ethanol tolerance, an early form of drug-induced plasticity. We identified a functional protocircuit that integrates sleep, thermosensory, and peptidergic pathways to shape ethanol-induced behavioral plasticity. Silencing DN1a neurons, which regulate nocturnal sleep, and their TPN-II thermosensory inputs reduced rapid tolerance, revealing convergence between ethanol and temperature pathways, and potentially providing a model for tolerance to the hypothermic effect of ethanol observed in mammals. Neuropeptide manipulations uncovered an additional regulatory pathway. Knockdown of CNMa in DN1p evening neurons and the CRF/CRH-like DH44 in all neurons also decreased ethanol tolerance. CNMa in DN1p acts upstream of DH44 in the neuroendocrine pars intercerebralis to promote both wakefulness and warmth perception: CNMa-DH44 together with the DN1as emerge as two temperature pathways that are involved in sleep that regulate ethanol-induced plasticity. Manipulations of sleep neurons in the ellipsoid body (EB) navigation and orientation brain region revealed different functions. Activation of sleep-promoting EB neurons suppressed tolerance, while silencing cholinergic EB neurons, which also have a role in sleep regulation, increased tolerance. DN1 neurons project to EB neurons to form an arousal circuit, revealing a deep mechanistic parallel between sleep and ethanol responses. Together, this work defines a functional protocircuit: DN1a, TPN-II, DN1p, CNMa, DH44 and EB neurons (R3a/m/p) as critical regulators of rapid ethanol tolerance. This functional map highlights novel convergence points between sleep, circadian circuits, and ethanol responses, providing insight into how disruptions in these systems may shape vulnerability to alcohol use disorder and contribute to early stages of addiction.

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.09/LBP168

Topic: H.08. Drugs of Abuse and Addiction

Title: Cell-Type-Resolved Chromatin and Gene Expression Changes in the Central Amygdala in Alcohol Use Disorder

Authors: *C. LEE[1,2], A. HWANG[2], G. S. THIBODEAU[3], C. H. DUMAN[4], J. H. KRYSTAL[5], A. CHE[5], M. GIRGENTI[6];
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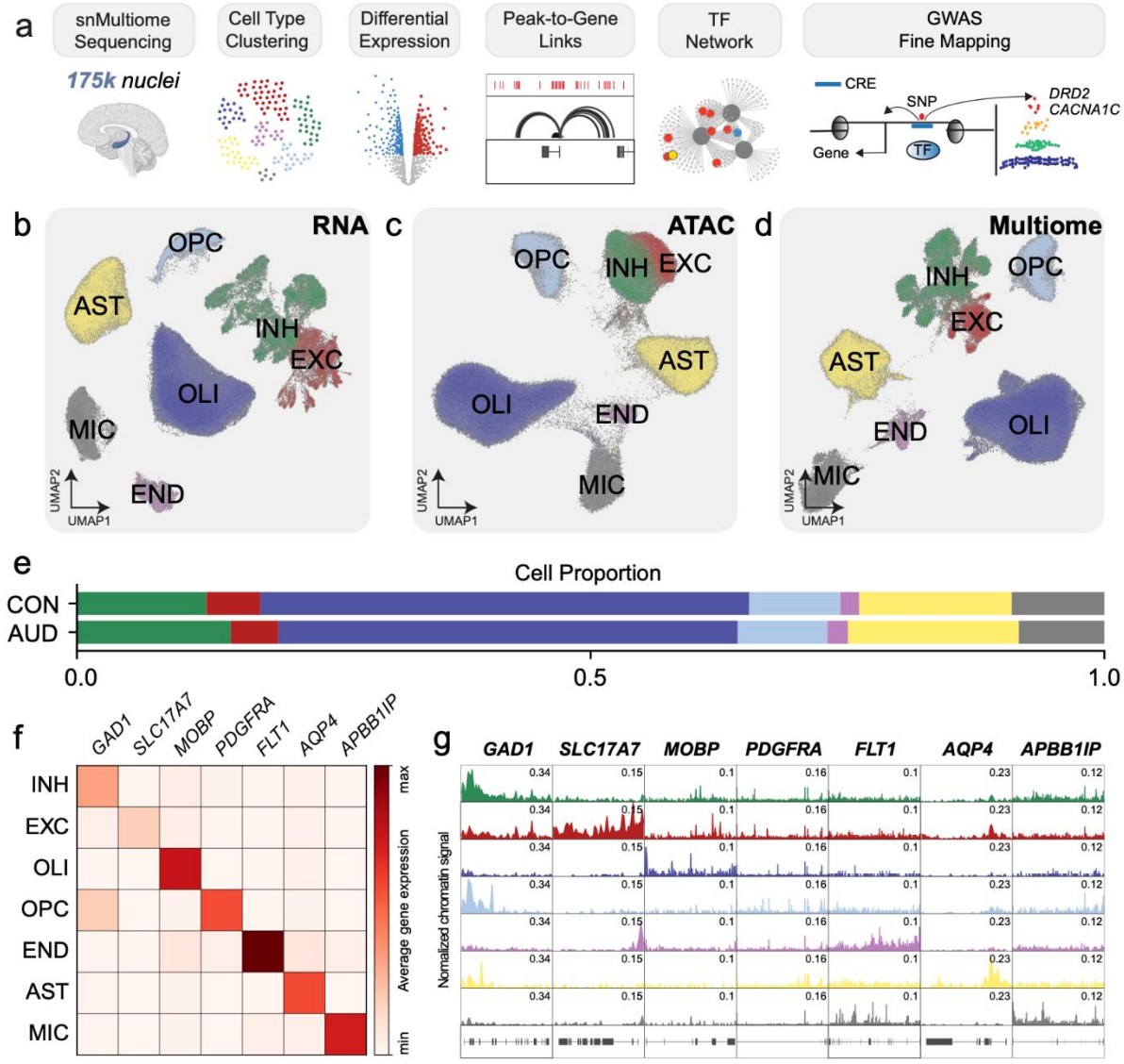
Abstract: Alcohol Use Disorder (AUD) is a leading cause of global morbidity, yet the molecular mechanisms connecting genetic risk, cell-type vulnerability, and neural circuit dysfunction remain unresolved. The central amygdala (CeA), a hub for stress and reward processing, is critical for alcohol-related behaviors, but its cell-type-specific regulatory architecture has not been systematically explored. We generated the first single-nucleus multi-omic atlas of the human CeA, profiling 174,188 nuclei from 50 postmortem donors (22 AUD, 28 controls) using snMultiome (snRNA-seq and snATAC-seq within the same nucleus). By integrating chromatin accessibility and transcriptional profiles from the same nuclei, we resolved 7 major CNS cell types and 6 inhibitory neuron (INH) subtypes. AUD profoundly reprogrammed the transcriptional landscape, with 1,805 high-confidence differentially expressed genes (DEGs)—60.6% localized to *PENK*+ INH neurons, a key opioid-modulatory population. Fluorescent in situ hybridization confirmed these cell-type-specific DEGs. Among the most dysregulated were *GABRA2*, *GRM8*, *NCAM1*, and *CALN1*, implicating disrupted neurotransmitter and calcium-dependent signaling. Integration of transcriptomic and chromatin profiles revealed 51,431 disease-linked cis-regulatory elements and 1.5M peak-to-gene links, including *CALN1*-associated chromatin loops specific to INH neurons. Transcription factor footprinting identified Kruppel-like factors (*KLF16*) as upstream regulators controlling 629 DEGs and 64 GWAS-prioritized AUD genes. Importantly, mouse snMultiome analyses after 2 g/kg EtOH exposure validated many human AUD DEG overlap and conserved KLF-driven networks. Finally, cell-type-specific fine-mapping of 131 GWAS loci uncovered 223 new credible causal variants, pinpointing credible variants at *CACNA1C*, *SEMA6D*, *PPP1R13B*, *BCL11B*, and *DRD2*. This study provides the first cell-type-resolved regulatory blueprint of the human CeA in AUD, linking genetic risk to neural circuit vulnerability.

Figure 1



Disclosures: C. Lee: None. **A. Hwang:** None. **G.S. Thibodeau:** None. **C.H. Duman:** None. **J.H. Krystal:** A. Employment/Salary (full or part-time); editor of Biological Psychiatry with income greater than $10,000.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Biohaven Pharmaceuticals Medical Sciences, Cartego Therapeutics, Damona Pharmaceuticals, Delix Therapeutics. F. Consulting Fees (e.g., advisory boards); Aptinyx, Inc. Biogen, Idec, MA, Bionomics, Limited (Australia), Boehringer Ingelheim International. **A. Che:** None. **M. Girgenti:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.10/LBP169

Topic: H.08. Drugs of Abuse and Addiction

Support: MOST 109-2320-B-002-014-MY3
NSTC 113-2410-H-002-221
NSTC 114-2410-H-002-253-MY2
Zap Surgical Systems, Inc. San Carlos, CA, USA.

Title: Non-invasive radiosurgical modulation of the nucleus accumbens reduces alcohol-craving behaviors without structural damage in miniature pigs

Authors: *C.-I. YEH[1], K.-H. CHEN[2], C.-H. LIN[1];
[1]Psychology, National Taiwan University, Taipei, Taiwan; [2]Brain Research Center, National Defense Medical Center, Taipei, Taiwan

Abstract: Approximately 10% of chronic alcohol drinkers develop Alcohol Use Disorder (AUD), a persistent public health and socioeconomic burden. Current psychological and pharmacological treatments demonstrate limited long-term efficacy, especially in severe or treatment-resistant cases. Neuromodulation targeting the nucleus accumbens (NAc) has shown promise in reducing alcohol consumption and craving, but available evidence remains limited due to the invasiveness of conventional methods. In this study, we investigated a non-invasive stereotactic radiosurgery approach to deliver low-dose focal irradiation (Dmax = 30 Gy, 5 mm collimator) bilaterally to the NAc of Lee Sung minipigs (LSPs) with prolonged voluntary alcohol consumption. Following more than two years of operant training, three alcohol-exposed LSPs (n = 3) underwent radiosurgery, while alcohol-naïve controls (n = 9) were used for comparison. Structural and functional neuroimaging (voxel-based morphometry, diffusion tensor imaging, and resting-state functional connectivity) were performed right before and every three months after the radiosurgery for one year. Postmortem analyses included cryo-sectioning and Nissl staining. Relative to controls, alcohol-exposed LSPs exhibited reduced gray matter integrity in the NAc and hippocampus, elevated fractional anisotropy in the fornix, and diminished NAc-dorsal anterior cingulate cortex (dACC) connectivity. Radiosurgery significantly reduced alcohol-craving behavior without altering NAc structure and restored NAc-dACC connectivity at 12 months. Preliminary histological findings further suggested increased cell density in both targeted and non-targeted regions of radiosurgery-treated animals. These results provide the first evidence that low-dose radiosurgery can produce sustained behavioral improvements in a large animal model of AUD without structural damage to the targeted brain region. This work establishes stereotactic radiosurgery as a promising non-invasive neuromodulation strategy, laying critical groundwork for future translational and clinical applications in the treatment of alcohol addiction.

Disclosures: C. Yeh: None. **K. Chen:** None. **C. Lin:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.11/LBP170

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01AA030272

Title: Young adult alcohol use and inter-modular organization in resting state fMRI

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Abstract: Studies using resting state fMRI (rsfMRI) have found associations in functional connectivity (FC) with alcohol use disorder (AUD). However, how young adult drinking patterns relate to FC organization is largely unknown. We use rsfMRI data (n = 244, ages 21 - 25, female = 52.48%) and test for organizational differences in FC associated with hazardous drinking behaviors, using Alcohol Use Disorders Identification Test - Consumption (AUDIT-C) scores. We applied modularity maximization to the mean FC matrix of all subjects for 5000 iterations from which we isolated a single consensus partition. We then determined the system-level representations (Yeo et al., 2011) of modules by comparing the empirical results to that of a spin-test null distribution. Next, we correlated the mean connectivity within-/between-modules with the AUDIT-C scores of subjects. We found three different modules, with the smallest (module 1) mainly including nodes in the control C, default mode (DMN) C, and visual networks; the largest (module 2) with control A, DMNb, dorsal attention, salience ventral attention, temporoparietal, and visual central networks; and module 3 with control B, DMNa and DMNc, dorsal attention B, limbic, and salience ventral attention networks. We found a significant positive correlation between module 1 and 3 connectivity with AUDIT-C scores (corrected for motion). We also found a significant negative correlation between module 1 and 2 connectivity with AUDIT-C scores (corrected for motion). These results were also replicated using Schaefer 200 parcellations. Our study investigated the association between the modular organization of rsFC and hazardous drinking behavior in young adults. The modular organization in rsfMRI may help further elucidate findings associating multiple systems in AUD, including the salience, DMN, executive, as well as sensory motor and visual networks (Vergara et al., 2017). Furthermore, differences in young adults' FC organization may become further pronounced with continued, longitudinal alcohol use, which requires future research.

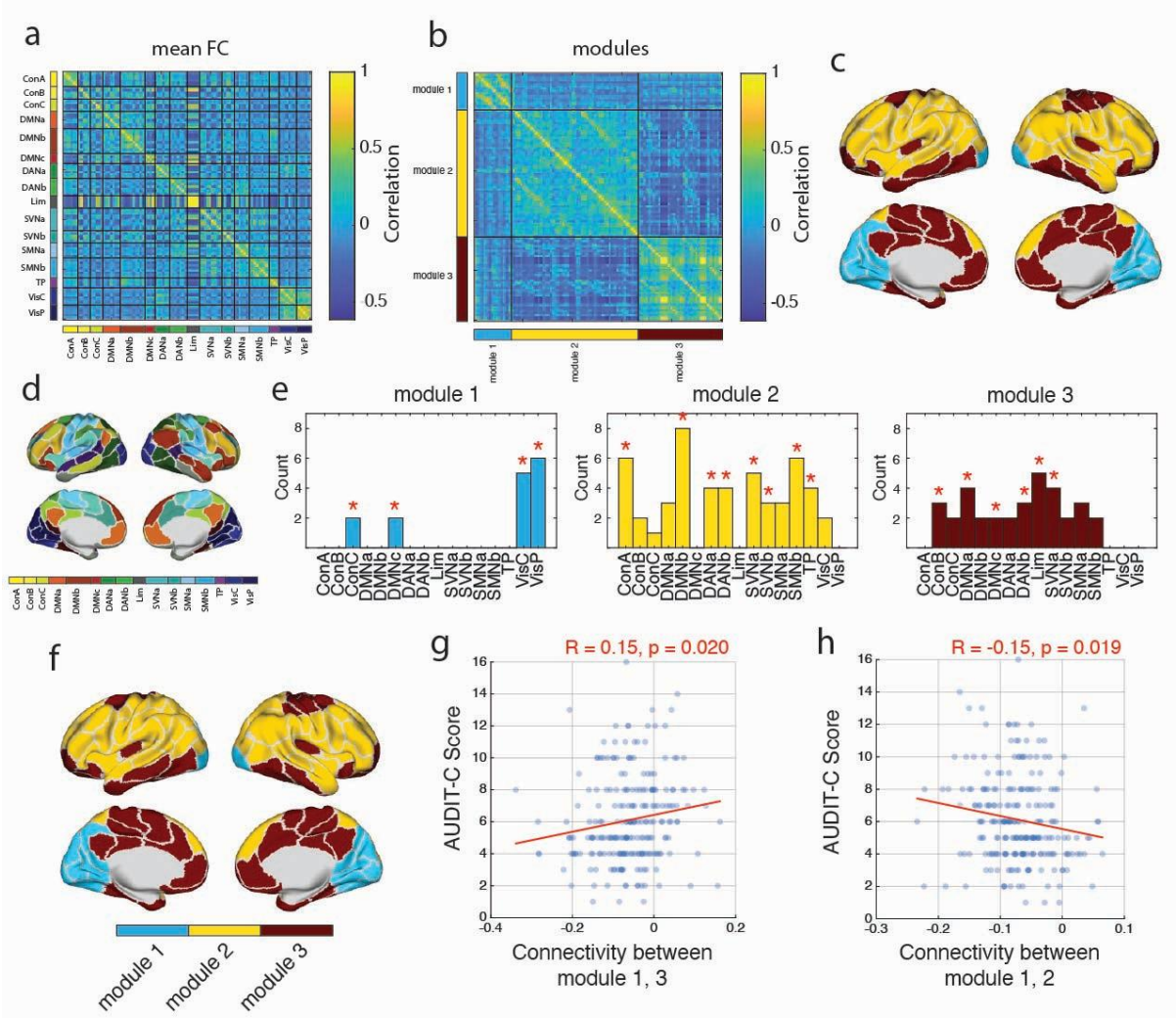

Figure 1. *Modular organization of young adults (N = 244) using resting state fMRI (rsfMRI).* (a) Mean functional connectivity of 244 subjects (b) reordered by their detected modules. Modules from (b) were plotted on the cortical surface using the Schaefer 100 parcellation. (d) Yeo 17 functional networks. (e) System-level organization of modules (Red asterisks: significantly more frequent than the spin-test null counterpart of 5000 iterations, $p < 10^{-8}$). (f) Modules detected using Schaefer 100 parcellated rsfMRI data. (g) Correlation of between module connectivity (modules 1, 3) and AUDIT-C scores (controlled for mean FD). (h) Correlation of between module connectivity (modules 1, 2) and AUDIT-C scores (controlled for mean FD).

Disclosures: Y. Jo: None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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Program #/Poster #: LBP051.12/LBP171

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA Grant R01DA056547

Title: Functional link between medullary noradrenergic neurons and methamphetamine seeking

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Abstract: The illicit use of methamphetamine (METH) has claimed thousands of lives across North America over the last several decades. Although many previous studies have emphasized a critical role of dopamine (DA) in METH use disorders, increasing evidence has suggested that METH is more potent at the norepinephrine (NE) transporter than the DA transporter. In particular, nucleus of solitary tract (NST)-NE innervation of the ventral bed nucleus of stria terminalis (vBNST) has been implicated for its role in METH-enhanced reward, withdrawal-induced aversion, and relapse vulnerability. The vBNST receives the densest NE innervation in the brain, primarily from the NST, and acts as a key stress relay center by integrating information from brainstem autonomic nuclei and limbic regions. However, it remains to be elucidated how NST-NE signaling in the vBNST promotes drug seeking and craving during abstinence and how attenuating NST-NE tone impacts stress-induced drug seeking. In this study, we characterized the effects of chemogenetic manipulations of NE neurons in the NST on (i) extinction and foot-shock induced reinstatement of METH seeking in rats that self-administered METH and (ii) NST-NE signaling in the vBNST using *in vivo* fast scan cyclic voltammetry. Our results suggest that activation of NST-NE neurons enhances drug seeking during extinction training and induces reinstatement following extinction, whereas inhibition of NST-NE during extinction led to decreased seeking of METH, highlighting NE's role in stress-induced relapse vulnerability. This research addresses a significant scientific gap in knowledge of the neurobiological mechanisms of an often-overshadowed NE pathway contributing to METH use disorders.

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.13/LBP172

Topic: H.08. Drugs of Abuse and Addiction

Title: Xylazine adulteration of heroin induces specific reward related pathways in the brain

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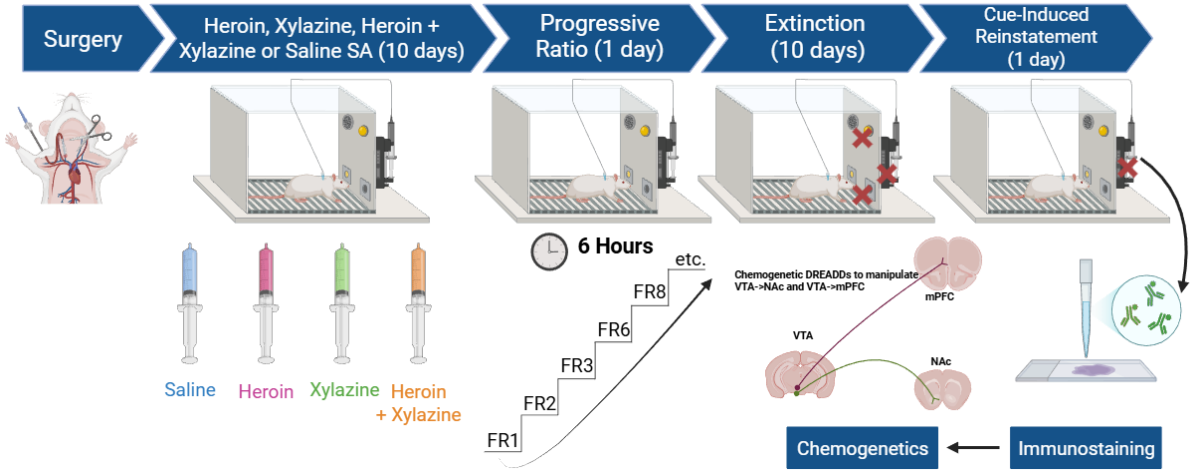
Abstract: Xylazine adulteration of heroin induces specific reward related pathways in the brainAuthors Hochstetler, M.[1], Dodge, A.[1], Chakraborty, S.[1], Jeffers, A.[1], Mallick, S.[1], Mitra, S. [12]; [1]Department of Pharmacology and Physiology, Oklahoma State University Center for Health Sciences; [2]Center for Integrative Research on Childhood Adversity, Oklahoma State University Center for Health Sciences**DisclosuresHochstetler, M.: None, Dodge, A.: None, Chakraborty, S.: None, Jeffers, A.: None, Mallick, S.: None, Mitra, S.: None**
AbstractWhile the world continues to face the growing opioid crisis, adulteration of these dangerous substances adds a new level of danger. One such adulterant, xylazine, a non-opioid sedative used in veterinary medicine, has become a subject of interest. Xylazine is not approved for human use and is associated with numerous adverse effects when consumed. Recently xylazine has been detected in the world drug supply at an alarming rate. According to the CDC, in the United States xylazine involved fatal overdoses has increased 288% since 2019. Research has primarily focused on the negative effects of xylazine adulterated fentanyl, however xylazine has also been detected in heroin world-wide. In the current study, we have shown how xylazine co-administered with heroin affects behavioral outcomes in male rats. Rats self-administered a heroin-xylazine cocktail at a significantly lower rate than heroin alone yet higher than xylazine alone. Additionally, we saw a decrease in motivation to consume during a progressive ratio test. Interestingly, following extinction there was a significant potentiation of cue-induced reinstatement behaviors in the heroin-xylazine co-administration group compared to the heroin alone group. Using immunofluorescence, we identified putative brain regions for prospective chemogenetic manipulation underlying reinstatement behavior.



Disclosures: M. Hochstetler: None. **A. Dodge:** None. **S. Chakraborty:** None. **A. Jeffers:** None. **S. Mitra:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIGMS-1R16GM149491
NIGMS-RISE-5R25GM061151
NeuroID 5R25NS080687
NIGMS G-RISE T32GM148406

Title: Low Frequency-DBS of the NAc in Morphine Spontaneous Recovery and Reinstatement

Authors: *F. I. RICARDO[1], I. BERRIOS RIVERA[2], M. E. LLORET[3], F. ROSADO[4], J. L. BARRETO ESTRADA[5];
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Abstract: Opioid addiction continues to drive the overdose crisis, with relapse rates exceeding 90% within one year of abstinence. Deep brain stimulation (DBS) of the ventral striatum/nucleus accumbens (VS/NAc) has emerged as a potential neuromodulatory strategy to reduce drug relapse by targeting circuits involved in reward and extinction learning. Using conditioned place preference and extinction training, we have shown that low-frequency DBS (LF-DBS, 20 Hz) aimed to the ventral striatum/nucleus accumbens (VS/NAc) enhances extinction memory, reduces the number of extinction trials and increases brain-derived neurotrophic factor (BDNF) expression in the dorsal hippocampus (dHPC). Despite these effects, stimulation confined to extinction did not prevent morphine-reinstatement, and prior designs lacked a drug-free period to assess spontaneous recovery, a relapse-like phenomenon where drug preference returns after abstinence, despite extinction. To address these gaps, we 1) incorporated a 7-day drug- and DBS-free interval followed by a spontaneous recovery test, and 2) applied LF-DBS during both extinction and reinstatement phases to determine DBS-dependent effects in drug-reinstatement. Across conditions, LF-DBS did not significantly protect against spontaneous recovery. For reinstatement, preliminary results showed that stimulation was also insufficient to block relapse, even when delivered during both extinction and reinstatement phases. These findings suggest that while LF-DBS facilitates extinction and engages hippocampal BDNF plasticity, its protective effects are not durable across abstinence or relapse. Future studies will test 1) a prime dose during reinstatement, 2) chemogenetic experiments to determine whether dHPC→NAc projections are necessary and sufficient for extinction enhancement, and 3) whether DBS alone, independent of extinction training, is sufficient to induce BDNF-driven neuroplasticity. Together, our study shed light into the behavioral and molecular mechanisms by which LF-DBS

facilitates extinction of opioid maladaptive behaviors and suggest new strategies to discover long-term effects of DBS during abstinence and relapse.

Disclosures: F.I. Ricardo: None. **I. Berrios Rivera:** None. **M.E. Lloret:** None. **F. Rosado:** None. **J.L. Barreto Estrada:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.15/LBP174

Topic: H.08. Drugs of Abuse and Addiction

Support: K08 DA055157
BBRF Young Investigator Award
William and Katharine Duhamel Addiction Medicine Fund

Title: Noncanonical Nucleus Accumbens Neurons Modulate Dopamine Signaling and Influence Opioid Seeking and Withdrawal

Authors: S. SUTLEY-KOURY[1], M. ASIM[1], J. SOARES[1], M. B. POMRENZE[1], *J. TUCCIARONE[2];
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Abstract: The opioid crisis has escalated over the past decade, creating an urgent need for effective treatments for opioid use disorder (OUD). Negative emotional states during withdrawal and environmental cues linked to prior opioid use are major drivers of relapse and significantly increase the risk of overdose. While it is well-established that dopamine (DA) signaling in the nucleus accumbens (NAc) rises during opioid use and falls during withdrawal, the specific neural circuits underlying these changes remain unclear and debated. Recent transcriptomic analyses have revealed increased cellular diversity within motivation-related brain circuits, suggesting that distinct cell types may play specialized roles across different stages of addiction. Previously we identified Teashirt-1 (Tshz1)-expressing medium spiny neurons (MSNs) as an evolutionarily conserved, MOR-positive, and D1-expressing subpopulation within the striatal patch compartment. These Tshz1 MSNs exhibit noncanonical local circuit properties, and we have shown they: (1) are aversive when stimulated and Inhibit local dopamine release in the NAc during naloxone-precipitated withdrawal; (2) Are required for aversive learning associated with opioid withdrawal; (3) Selectively mediate withdrawal-associated behavioral states without affecting somatic symptoms; (4) Require MOR expression to mediate hypodopaminergic responses during withdrawal. These findings establish Tshz1 MSNs as a critical neural substrate linking MOR signaling to withdrawal-induced aversive learning. However, the precise cellular, circuit, and molecular mechanisms by which MOR activity in these neurons contributes to withdrawal, relapse vulnerability, and maladaptive associative learning remain unknown.

Chemogenetic inhibition or selective deletion of Oprm1 in Tshz1 neurons prevented withdrawal-induced aversion and DA suppression. Finally, chemogenetic activation of Tshz1 neurons enhanced extinction learning and reduced reinstatement of drug-seeking, with ongoing studies investigating the effects of their inhibition in addition to real time calcium imaging of Tshz1 MSNs during opioid IV self-administration.

Disclosures: S. Sutley-Koury: None. **M. Asim:** None. **J. Soares:** None. **M.B. Pomrenze:** None. **J. Tucciarone:** None.

Late-Breaking Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH K99 DA059613
NIH F32 DA055480
NIH T32 DA00727828

Title: A Peri-Ceorulear Neuropeptidergic Pathway for Modulating OFC-Mediated Opioid-Seeking Behavior

Authors: *K. S. GIRVEN[1], B. A. WELLS[2], A. SUKO[3], R. D. PALMITER[2], L. DE LECEA[4], L. S. ZWEIFEL[5], M. R. BRUCHAS[6];
[1]Anesthesiology and Pain Medicine, University of Washington, Seattle, WA; [2]University of Washington, Seattle, WA; [3]University of Washington, Kirkland, WA; [4]Psychiatry, Stanford, Stanford, CA; [5]Pharmacology, University of Washington, Seattle, WA; [6]Department of Anesthesiology and Pain Medicine, University of Washington, Seattle, WA

Abstract: Substance-use disorder (SUD) impairs goal-directed decision making and, when compounded by stress and anxiety, drives persistent cycles of drug misuse. Identifying neuromodulatory circuits that integrate stress and reward processing is therefore essential for developing effective treatments. Neuropeptide S (NPS) is a relatively unknown neuromodulator implicated in arousal, stress, and reward-seeking through activation of its cognate Gq-coupled receptor, NPSR1. Despite pharmacological evidence linking this system to drug-seeking and anxiety-related behaviors, circuit-level mechanisms have remained unexplored due to a lack of tools. To address this gap, we generated NPS-Cre and NPSR1-Cre driver mouse lines and identified a population of NPS-expressing neurons in the peri-locus coeruleus (periLC) that send excitatory projections to orbitofrontal cortex (OFC) neurons expressing NPSR1. We hypothesized that periLC^{NPS} input modulates OFC^{NPSR1} activity post reward consumption and reinforces drug-seeking.
To test this, NPSR1-Cre and NPS-Cre mice received AAV-DIO-GCaMP6s infusions and fiber photometry implants targeting the OFC or periLC. Mice were trained in Pavlovian and operant

sucrose conditioning, as well as a novel oral fentanyl self-administration paradigm (10 μg/mL, 120-min sessions). We observed that OFC^{NPSR1} neurons showed increased activity to reward-predictive cues, suppressed activity during consumption, and a rebound post-reward signal. Importantly, this rebound aligned with $periLC^{NPS}$ neuron activity, suggesting coordinated engagement of this circuit during reinforcement. Two-photon calcium imaging of OFC^{NPSR1} neurons confirmed these dynamics at single-cell resolution during both natural and fentanyl rewards.
Critically, CRISPR/Cas9-mediated knockout of either $periLC^{NPS}$ or OFC^{NPSR1} significantly reduced fentanyl consumption and seeking behavior, demonstrating a causal role for this pathway in opioid reinforcement. These results reveal a previously uncharacterized hindbrain-cortical peptidergic circuit that encodes post-reward processing and drives maladaptive drug-seeking. Together, these findings position the NPS/NPSR1 system as a novel target for intervention in substance use disorders and provide a foundation for investigating how stress and genetic vulnerability engage this circuit.

Disclosures: K.S. Girven: None. **B.A. Wells:** None. **A. Suko:** None. **R.D. Palmiter:** None. **L. de Lecea:** None. **L.S. Zweifel:** None. **M.R. Bruchas:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.17/LBP176

Topic: H.08. Drugs of Abuse and Addiction

Support: Shirley and Stefan Hatos Foundation

Title: Absence of noradrenergic mu-opioid receptors exacerbates anhedonia during opioid withdrawal

Authors: *A. HOFFMAN[1], M. WAN[1], C. CAHILL[2];
[1]University of California, Los Angeles, Los Angeles, CA; [2]Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, Los Angeles, CA

Abstract: The opioid epidemic poses a major threat to public health, and continued opioid use and abuse is driven in part by the desire to avoid withdrawal. Previous studies have established that enhanced activity of noradrenergic (NA) neurons contributes to physical withdrawal following cessation of opioid use. Activation of mu-opioid receptors (MORs) suppresses NA neuronal activity that induces allostatic changes in these neurons; however, it is unknown if this effect is due to direct engagement of MORs on NA neurons. Further, opioid withdrawal contributes to anhedonia, however it remains unclear what role MORs on NA neurons have in this negative affective state. In this study, we aimed to determine the role of NA MORs in opioid withdrawal by measuring motivation for palatable food reward. We hypothesized that mice undergoing opioid withdrawal will show reduced motivation for food reward and this will be

attenuated in mice where MOR was ablated from NA neurons. Methods: We conducted operant box food self-administration tests on adult dopamine beta-hydroxylase (DBH)-cre $MOR^{fl/fl}$ and control cre- littermate mice. Mice were trained to self-administer chocolate food pellets with active and inactive nose pokes, where a light cue indicated reward availability above the active port, imposing a 20 second time out between reinforcers. Motivation for palatable food was determined before and after escalating doses of morphine, where animals were made dependent by a five-day increased dosing morphine injection (10-50 mg/kg, i.p.) followed by 24h natural withdrawal. Mice did not undergo operant behavior testing during the opioid dependency days. Results: Ablation of MOR from NA neurons had no effect on number of active nose pokes or number of reinforcers earned on either fixed ratio 1, fixed ratio 3 or during a progressive ratio test. Mice were re-tested on the progressive ratio task 24h after the last morphine injection. Our results reveal a sex difference and genotype effect in motivation during withdrawal. DBH-cre+/$MOR^{fl/fl}$ male mice exhibited a significant decrease in reinforcers earned, indicating a lower motivation to obtain food reward during withdrawal versus pre-opioid data, compared to DBH-cre-/$MOR^{fl/fl}$ male littermates. In contrast, DBH-cre+/$MOR^{fl/fl}$ female mice showed no change in motivation compared to effort prior to morphine. Interestingly, wildtype female mice showed an increase in motivation during withdrawal. These preliminary data suggest the absence of MOR in NA neurons appears to exacerbate anhedonia associated with withdrawal in male but not female mice. It is unclear why female control mice showed an increase in motivation during withdrawal.

Disclosures: A. Hoffman: None. **M. Wan:** None. **C. Cahill:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

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Program #/Poster #: LBP051.18/LBP177

Topic: H.08. Drugs of Abuse and Addiction

Support: T32DA007278
R00DA052571
Puget Sound VA Pilot Grant

Title: Lateral Habenula Dynamics Encode the Shift in Internal Attitude for Fentanyl Seeking Behavior as Adverse Consequences Rise

Authors: A. PEDEN-ASARCH[1], S. SIEVERTSEN[2], E. ASARCH[3], K. COFFEY[4], ***J. F. NEUMAIER**[1];
[1]Psychiatry, University of Washington, Seattle, WA; [2]Oregon Health and Science University, Portland, OR; [3]Lehigh University, Bethleham, PA; [4]Psychiatry, University of Washington School of Medicine, Seattle, WA

Abstract: Opioid Use Disorder remains a critical public health concern, particularly in understanding the neural mechanisms underlying the decision to stop drug use despite increasing

negative consequences. While it is well-established that aversive stimuli modulate drug-taking behavior, the neural dynamics driving this shift remain poorly understood. Here, we investigated how the lateral habenula (LHb), a key decision-making center known for processing aversive stimuli, responds during this critical transition using miniscopes to capture neuronal activity over multiple sessions. Our study presents the first large-scale in vivo cellular resolution calcium imaging investigation of LHb activity during drug-seeking behavior using a novel drug cessation paradigm involving delayed punishment for fentanyl responding. Male and female rats were trained to self-administer oral fentanyl using a trial-based modification of our established procedures. We then shifted the session structure by introducing shocks that were delivered several seconds after active lever responses, generally after drug consumption. The punished trials occurred following an initial punishment-free drug-loading phase and the shock intensity was gradually increased each day. Rats continued to consume fentanyl avidly during the signaled punishment-free phase but modified their consumption during the punished phase. Interestingly, we observed that rats self-administering fentanyl exhibit increased drug intake when presented with low-intensity shocks (0.1 mA) compared to no shock, suggesting a paradoxical escalation in drug-seeking behavior under mild aversion. However, at higher shock intensities (0.2 - 0.8 mA), fentanyl self-administration gradually decreased across sessions, indicating a point where the negative consequences outweigh the drug's rewarding effects. Additionally, we found distinct patterns of behavior during initial phases of shock exposure that involved shifts in USV production and body movement patterns. Using Leiden Community Detection, we detected sets of LHb neurons that had distinct synchronized activity patterns during fentanyl seeking that shifted as a consequence of punished drug seeking and taking. Thus, we show that LHb neuronal communities integrate negative value signals and reconfigure as rats decide to abstain from fentanyl taking due to escalating adverse consequences**.** These findings provide insights into the neural and behavioral dynamics of fentanyl seeking and the decision to abstain, guiding new ways to stabilize abstinence even when drugs or cravings remain in the system.

Disclosures: A. Peden-Asarch: None. **S. Sievertsen:** None. **E. Asarch:** None. **K. Coffey:** None. **J.F. Neumaier:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.19/LBP178

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA/NIH Grant OD026407
NIDA Grant DA056660
NIDA Grant DA056365

Title: Opioid-induced changes in subthalamic projections to ventral pallidal neurons

Authors: *S. M. WAY[1,2], A. MESCO[2], J. A. HEINSBROEK[2];
[1]UAB, Birmingham, AL; [2]Neurobiology, University of Alabama at Birmingham, Birmingham, AL

Abstract: Substance use disorder (SUD) remains a debilitating condition faced by many in our society and a substantial socioeconomic burden on our health care system. The ventral pallidum (VP) is a central node in a circuit that regulates drug motivation and drug-seeking behaviors. The VP receives strong inhibitory inputs from the nucleus accumbens, but its source of excitatory glutamatergic inputs is less clear. Importantly, glutamatergic neurotransmission in the VP is required for drug seeking and the experience of drug reward. The subthalamic nucleus (STN) has been proposed as the main source of glutamate, but the STN-VP circuit and its role in drug seeking have not been explored. In addition, the types of neurons in the VP that are contacted by STN axons are unknown. In order to study the role of VP glutamate in motivated behavior and drug seeking, and the specific function of the STN-VP circuit, we conducted in vitro whole-cell patch clamp electrophysiology and in vivo heroin self-administration and optogenetic real-time place preference (RTPP) studies. In vitro, optogenetic induction of glutamate release from STN axons in the VP of Vglut2-tdTomato transgenic mice showed strong excitatory currents onto both glutamatergic and GABAergic VP neurons. Preliminary data also suggest that the release of glutamate from the STN-VP pathway is reinforcing, as mice showed a preference for the chamber paired with laser stimulation in the RTPP test. To further examine STN-VP connectivity, immunohistochemistry was conducted to ensure optimal virus expression in the STN and to verify optic fiber placements above the VP. Intravenous heroin self-administration studies in rats showed that pharmacologically blocking AMPA/NMDA receptors in the VP reduces motivation for heroin without altering food drive. Surprisingly, the same manipulation enhanced heroin choice when animals were presented with a limited number of trials to choose between food and heroin. Knocking out the obligatory Grin1 subunit of the NMDA receptor using a CRISPR based approach also reduced heroin intake and seeking in mice. Combined, our experiments demonstrate a critical role for VP glutamate in regulating drug seeking and drug motivation. Excitingly, our data shows that the STN-VP circuit provides a likely source of this glutamate, making this circuit a promising target for future SUD interventions. The STN is already an area of interest for the treatment of movement disorders and is often targeted for deep brain stimulation interventions. Our data show that its axonal projections to the VP also regulate motivation and reward, and that dysfunction of this circuit may contribute to drug addiction.

Disclosures: S.M. Way: A. Employment/Salary (full or part-time); UAB. **A. Mesco:** None. **J.A. Heinsbroek:** A. Employment/Salary (full or part-time); UAB. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH, NIDA.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.20/LBP179

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant DA051551
NIDA Grant DA044308
NIDA Grant DA049568

Title: Vascular endothelial growth factor as a peripheral modulator of opioid reward

Authors: *C. R. DEAN[1,2], J. P. SENS[1], R. S. HOFFORD[1,2], D. D. KIRALY[1,2,3];
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Abstract: Opioids reshape mesolimbic reward circuitry, but their effects extend beyond neurons: by altering immune signaling, they can initiate reciprocal brain-immune feedback loops that drive synaptic and circuit-level plasticity, reinforcing the behavioral cycles underlying opioid use disorder (OUD). While opioid-induced neural adaptations have been extensively characterized, the specific contributions of peripheral immune factors remain poorly understood. To identify peripheral mediators of opioid-induced plasticity, we performed an unbiased serum multiplex assay following 10 days of fentanyl exposure (200 μg/kg/day, i.p.) in male and female C57BL/6J mice. Of 111 cytokines, chemokines, and growth factors quantified, vascular endothelial growth factor (VEGF) emerged as the most robustly regulated analyte, highlighting it as a candidate mediator linking peripheral signaling to central reward circuits. VEGF, classically characterized for vascular remodeling, has been studied in the CNS primarily within the hippocampus where it is known to modulate synaptic plasticity and neuronal function. Its potential effects on reward circuits, however, remain largely unexplored. To establish brain access of peripheral VEGF, biotinylated VEGF was administered intravenously and detected in the nucleus accumbens (NAc) of fentanyl-treated mice, demonstrating that peripheral VEGF crosses the blood-brain barrier and engages central targets relevant to addiction-related plasticity. To assess the effects of peripheral VEGF on opioid reward, mice received daily injections of VEGF (10 μg/kg) or vehicle one hour prior to conditioned place preference (CPP) training with two fentanyl doses. VEGF enhanced CPP at the moderate dose (100 μg/kg), indicating that peripheral VEGF can increase sensitivity to opioid reward. In a separate cohort, NAc tissue was collected 24 hours after repeated fentanyl exposure to quantify VEGF receptor mRNA via qPCR. Analyses revealed selective reductions in *Flt-1* (VEGFR1) and *Kdr* (VEGFR2) transcripts in the NAc, but not in other brain regions. Additionally, intra-NAc administration of recombinant VEGF (1 μg) recapitulated the behavioral effects of peripheral administration, supporting a direct role for NAc VEGF signaling in mediating reward related behaviors. Together, these findings highlight VEGF

as a bridge between peripheral immune signaling and central reward plasticity, with the nucleus accumbens emerging as locus of effect for its mechanistic role in models of OUD.

Disclosures: C.R. Dean: None. **J.P. Sens:** None. **R.S. Hofford:** None. **D.D. Kiraly:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.21/LBP180

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH 1R01DA050589
Open Philanthropy Foundation
HHMI

Title: A Shared Neural Ensemble in Nuclei Accumben Core Underlying Aversion to both Pain and Opioid Withdrawal

Authors: *X. QI[1], Y. ZHANG[2,3];
[1]PCMM, Boston Children's Hospital, Bosotn, MA; [2]Program in Cellular and Molecular Medicine, Boston Children's Hospital, Boston, MA; [3]Howard Hughes Medical Institute,, Boston Children's Hospital, MA

Abstract: The nucleus accumbens (NAc) plays an important role in regulating multiple behaviors, and its dysfunction has been linked to many neural disorders, including addiction and chronic pain. Here we decipher a distinct population of D2-type medium spiny neurons (D2-MSNs) localized in the NAc core, characterized by the selective expression of Calcitonin receptor (Calcr), encode aversion to both pain and opioid withdrawal. We found acute nociceptive stimulus and acute opioid withdrawal increase $Calcr^+$ neuronal activity, and chemogenetic manipulation of $Calcr^+$ neurons bidirectionally regulate pain and opioid withdrawal behaviors. In addition, circuit tracing and stimulation show that projection from calcitonin gene-related peptide (CGRP) neurons in later parabrachial nuclei (LPB) to $Calcr^+$ neurons in NAc core encodes negative valence associated with pain and opioid withdrawal experiences. Our work suggests the presence of a shared neural ensemble in nuclei accumben core underlies aversion to both pain and opioid withdrawal, providing a potential shared neural encoding mechanism that links the experiences of addiction and pain.

Disclosures: X. Qi: None. **Y. Zhang:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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Program #/Poster #: LBP051.22/LBP181

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant K01DA056854

Title: Sex-specific effects of chronic pain and nicotine exposure on social behavior in rats

Authors: *D. BAGDAS[1], B. GRAHAM[2], T. NELSON[1], S. TAVAKOLI[1], N. A. ADDY[3]; [1]Yale University, New Haven, CT; [2]Yale University, New Haven, NC; [3]Psychiatry, Yale University, New Haven, CT

Abstract: Background & Aims: Chronic pain is a major public health problem worldwide. It is often associated with negative affect and with reduced sociability. Pain-related negative affect is a risk factor for nicotine use, and nicotine may serve as a coping strategy for pain-related distress. In this study, we examined social interaction during nicotine withdrawal and the impact of chronic nicotine exposure on sociability. Because women are more likely than men to experience chronic pain and related negative affect, we also compared male and female rats.
Methods: Neuropathic pain was induced in adult male and female Sprague Dawley rats using the chronic constriction injury (CCI) model. Pain status was confirmed with Von Frey testing. Two weeks after surgery, rats received twice-daily subcutaneous injections of nicotine (0.3 or 0.7 mg/kg) or saline for 14 days. Social interaction was assessed during spontaneous nicotine withdrawal, 24 hours after the final injection. Time spent in each chamber, distance traveled, and time spent in the investigation zones surrounding each container were determined with ANY-maze software.
Results: CCI induced persistent neuropathic pain, as reflected by lower paw withdrawal thresholds in the Von Frey test that remained reduced throughout the study. In males, CCI slightly but significantly reduced sociability compared with sham controls. Both 0.3 and 0.7 mg/kg nicotine administration to CCI male rats, restored social preference to sham levels. In females, CCI produced a marked reduction in sociability compared with sham controls, with social preference dropping below 50%. Nicotine at 0.3 mg/kg had no effect in CCI females, whereas 0.7 mg/kg nicotine significantly restored sociability to sham levels. Nicotine had no effect on social behavior in sham rats of either sex. These results show that CCI produces persistent pain and social deficits, and nicotine exposure restores social behavior.
Conclusion: Chronic pain reduces social interaction in a sex-specific manner, with females more affected than males. Chronic nicotine exposure restores sociability in a concentration-specific manner. These findings suggest that pain-induced social deficits may increase nicotine's abuse liability through its effects on social behavior.

Disclosures: D. Bagdas: None. **B. Graham:** None. **T. Nelson:** None. **S. Tavakoli:** None. **N.A. Addy:** D. Fees for Non-CME Services Received Directly from Commercial Interest or their

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Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.23/LBP182

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01MH121848
NIH Grant R01MH128217
NIH Grant R01MH137047
One Mind–COMPASS Rising Star Award
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NIH Grant 1F32DA062467

Title: Psilocybin activates neuron-derived neurotrophic factor-expressing interneurons (NDNF INs) in the mouse medial frontal cortex

Authors: *O. M. BILASH, A. C. KWAN;
Cornell University, Ithaca, NY

Abstract: Psilocybin is a serotonergic psychedelic that alters perception, cognition, and mood. It holds promise for treating neuropsychiatric disorders, yet its mechanism of action in the brain remains poorly understood, especially at the microcircuit level. Psychedelic action has been primarily investigated in the dendrites of frontal cortex pyramidal neurons. However, GABAergic interneurons in the area also express serotonin receptors, making them likely targets of psilocybin. Interneurons can powerfully influence single-neuron computations and network activity and may be critical mediators of psilocybin-driven changes in cortical information processing. Neuron-derived neurotrophic factor-expressing interneurons (NDNF INs) preferentially express the serotonin 5-HT2a receptor subtype, the most-widely studied molecular target of psychedelic compounds. These interneurons, also called neurogliaform cells, are perhaps best known for releasing GABA through volume transmission, allowing them to provide strong dendritic inhibition. Using in vivo two-photon calcium imaging, we measured how psilocybin affects the activity of NDNF INs in the mouse medial frontal cortex. We demonstrate that systemic psilocybin administration drives a significant increase in NDNF IN activity in a state-dependent manner. Our findings hold interesting implications, as cellular and microcircuit-level changes in the medial frontal cortex may be linked to psilocybin's influence over cortical information processing, as well as psilocybin's therapeutic effects.

Disclosures: O.M. Bilash: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Psilocybin was provided by Usona Institute's Investigational Drug &

Material Supply Program. **A.C. Kwan:** F. Consulting Fees (e.g., advisory boards); Boehringer Ingelheim, Eli Lilly, Empyrean Neuroscience, Freedom Biosciences, Xylo Bio, Intra-Cellular Therapies. Other; Psilocybin was provided by Usona Institute's Investigational Drug & Material Supply Program.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.24/LBP183

Topic: H.08. Drugs of Abuse and Addiction

Title: The effects of psilocybin on dendritic spine growth in a chronic stress model

Authors: *C. KNOX, A. GILBERT, A. C. KWAN;
Biomedical Engineering, Cornell University, Ithaca, NY

Abstract: The effects of psilocybin on dendritic spine growth in a chronic stress model.C. Knox, A. Gilbert, A. Kwan
Structural alterations to the brain, including reduced cortical volume, have been associated with major depressive disorder (MDD). Studies have shown that stress-induced frontal cortex atrophy specifically affects pyramidal neurons in the medial region. Psychedelics have shown promising results as a single-dose, long-lasting antidepressant. Previously, we demonstrated that psilocybin induces structural remodeling and increased dendritic spine growth. However, the effects of psilocybin on dendritic spine turnover under chronic stress conditions remain to be explored. The goal of this project is to determine how a single dose of psilocybin affects dendritic spine turnover in the medial prefrontal cortex in the chronic restraint stress mouse model.
Using longitudinal two-photon microscopy, I imaged the dendritic spines of Layer 5 pyramidal neurons in the mouse medial frontal cortex during and after chronic restraint stress. I imaged isolated dendrites and tracked the spine dynamics over a 4-week period. Mice underwent 2 weeks of chronic restraint stress followed by 2 weeks of post-treatment imaging to capture psilocybin's effects on dendritic spine growth. Compared to control mice (stressed and unstressed mice injected with vehicle), a single dose of psilocybin given after chronic restraint stress led to changes in spine density. My results contribute to current research on psilocybin's promising antidepressant effects by demonstrating psilocybin's structural impacts on the brain under stress conditions. These results further support psilocybin's potential as a therapeutic treatment for MDD and other neuropsychiatric disorders.

Disclosures: C. Knox: None. **A. Gilbert:** None. **A.C. Kwan:** None.

Late-Breaking Poster

LBP051: H.08. Drugs of Abuse and Addiction

Location: SDCC Hall B

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

Program #/Poster #: LBP051.25/LBP184

Topic: H.08. Drugs of Abuse and Addiction

Title: Single-nucleus transcriptomics reveals time-dependent and cell-type-specific effects of psilocybin on gene expression

Authors: *A. M. WEINER[1], C. LIAO[2], N. K. SAVALIA[2], M. GIRGENTI[3], K. Y. KWAN[4], A. C. KWAN[5];
[1]Cornell University, Ithaca, NY; [2]Yale University, New Haven, CT; [3]Psychiatry, Yale Medical School, New Haven, CT; [4]Michigan Neuroscience Institute, University of Michigan, Ann Arbor, MI; [5]Biomedical Engineering, Cornell University, Ithaca, NY

Abstract: There is growing interest to investigate classic psychedelics as potential therapeutics for mental illnesses. Previous studies have demonstrated that one dose of psilocybin leads to persisting neural and behavioral changes. The durability of psilocybin's effects suggests that there are likely alterations of gene expression at the transcriptional level. In this study, we performed single-nucleus RNA sequencing of the dorsal medial frontal cortex of male and female mice. Samples were collected at 1, 2, 4, 24, or 72 hours after psilocybin or ketamine administration and from control animals. At baseline, major excitatory and GABAergic cell types selectively express particular serotonin receptor transcripts. The psilocybin-evoked differentially expressed genes in excitatory neurons were involved in synaptic plasticity, which were distinct from genes enriched in GABAergic neurons that contribute to mitochondrial function and cellular metabolism. The effect of psilocybin on gene expression was time-dependent, including an early phase at 1-2 hours followed by a late phase at 72 hours of transcriptional response after administration. Ketamine administration produced transcriptional changes that show a high degree of correlation to those induced by psilocybin. Collectively, the results reveal that psilocybin produces time-dependent and cell-type specific changes in gene expression in the medial frontal cortex, which may underpin the drug's long-term effects on neural circuits and behavior.

Disclosures: A.M. Weiner: None. **C. Liao:** None. **N.K. Savalia:** None. **M. Girgenti:** None. **K.Y. Kwan:** None. **A.C. Kwan:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Usona Institute. F. Consulting Fees (e.g., advisory boards); Boehringer Ingelheim, Empyrean Neuroscience, Freedom Biosciences.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.01/LBP001

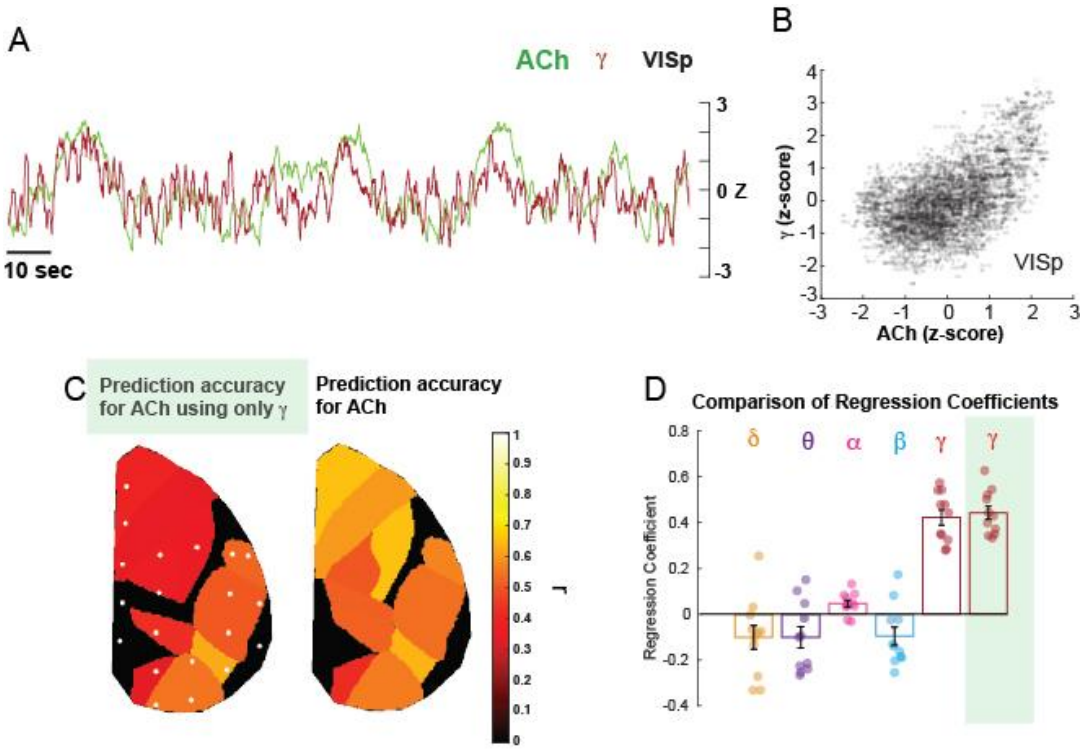
Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Support: NIH Grant U19NS123717
NIH Grant R01DA050159

Title: Cholinergic neuromodulation and gamma rhythms in the cerebral cortex

Authors: *N. X. CHAI[1], B. C. RAUSCHER[2], N. FOMIN-THUNEMANN[3], M. WILSON[4], K. KILIÇ[5], P. BLONIASZ[6], J. JIANG[7], D. KUZUM[8], E. P. STEPHEN[9], D. A. BOAS[3], M. THUNEMANN[3], A. DEVOR[3];
[1]Undergraduate Program of Neuroscience, Boston University, Boston, MA; [2]Graduate Program of Biomedical Engineering, Boston University, Boston, MA; [3]Biomedical Engineering, Boston University, BOSTON, MA; [4]Electrical and Computer Engineering, University of California San Diego, La Jolla, CA; [5]BME, Boston University, Boston, MA; [6]Neuroscience, Boston University, Boston, MA; [7]Boston University, Boston, MA; [8]UC San Diego, La Jolla, CA; [9]Mathematics and Statistics, Boston University, Boston, MA

Abstract: Although a body of prior studies in animals have implicated acetylcholine (ACh) in modulating gamma oscillations, direct experimental measurements of ACh with simultaneous electrophysiological recordings of gamma oscillations across cortical areas are missing. We hypothesized that acetylcholine release dynamics directly correlate with cortical gamma oscillations during spontaneous and sensory-evoked brain states. To directly test this hypothesis, we combined wide-field, mesoscale imaging of two fluorescence channels: ACh sensor $GRAB_{ACH3.0}$ and calcium sensor JRGECO1a, with simultaneous electrophysiological recordings through transparent graphene electrodes in mice implanted with optical "windows." Recordings were obtained during spontaneous activity as well as under visual and somatosensory (whisker) stimulation. ACh activity exhibited a low-dimensional spatiotemporal pattern that was strongly correlated with gamma power across cortical regions both during spontaneous activity (Fig A, B) and under stimulation. We predicted ACh signals from electrophysiological spectra using a linear regression model, first with gamma as a single regressor, and then with multiple spectral bands (theta, beta, etc.). We evaluated model accuracy using correlation between predicted and experimentally obtained ACh. Including addition regressors increased the model accuracy ($r \approx 0.5$ using gamma alone; $r \approx 0.7$ for multiple regressors), particularly in the anterior cortical areas (Fig C).



Disclosures: N.X. Chai: None. **B.C. Rauscher:** None. **N. Fomin-Thunemann:** None. **M. Wilson:** None. **K. Kiliç:** None. **P. Bloniasz:** None. **J. Jiang:** None. **D. Kuzum:** None. **E.P. Stephen:** None. **D.A. Boas:** None. **M. Thunemann:** None. **A. Devor:** None.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.02/LBP002

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

Title: Prenatal Metabolic Programming by the endocrine disruptors, Bisphenol-A and Diethyl hexyl phthalate: Sex-Specific Alterations in Pancreatic function and its sympathetic innervation in the offspring.

Authors: *A. PALANIYAPPAN[1], A. MURUGAN[2], Y.-J. CHUANG[2], P. S. MOHANKUMAR[3], S. M. MOHANKUMAR[4];
[1]Dept. of Biomedical Sciences, University of Georgia, Athens, GA; [2]UNIVERSITY OF GEORGIA, Athens, GA; [3]Dept Pathobiol & Diagnostic Invest, University of Georgia, Athens, GA; [4]Veterinary Biosciences and Diagnostic Imaging, University of Georgia, Athens, GA

Abstract: We have previously reported that prenatal exposure to plasticizers such as Bisphenol A (BPA) di-(2-ethylhexyl) phthalate (DEHP), and their combination predisposed the offspring to

long term metabolic disorders by promoting obesity and impairing glucose tolerance. In the current study, we examined their impact on pancreatic innervation and function with a focus on sex- and diet- specific outcomes. Pregnant SD rats were exposed to 5µg/kg BW of BPA, 7.5mg/kg BW of DEHP or a combination of the two (BD) from day 6-21 of gestation. The offspring were maintained on a chow diet after weaning and a subset of rats were challenged with a High fat diet (HFD) for 2 weeks at 3 mo of age. At the end of observation period, the offspring were sacrificed, the serum and pancreas were harvested for further analysis. Insulin and C-peptide levels in the serum were measured using commercial ELISAs. Frozen tissue punches of the pancreas were used for measuring monoamines using HPLC-EC. Tissues were homogenized in PBS and after removing an aliquot for protein measurement, the homogenate was mixed with an equal volume of 40% ice-cold trichloroacetic acid. After a 10-minute incubation, the homogenate was centrifuged, and the supernatant was injected into the HPLC system. Prenatal exposure to EDCs had no significant impact on the levels of insulin and C-peptide. However, the ratio of insulin to C-peptide deviates from the normal ratio of 1:1 suggesting possible beta cell stress. Analysis of monoamine neurotransmitter levels in the pancreas revealed significantly reduced norepinephrine (NE), epinephrine (EPI), and 5-Hydroxy Indole Acetic Acid (5-HIAA) in males after prenatal exposure to EDCs suggesting altered neural regulation of islet function. In contrast, female offspring remained unchanged. These findings suggest that prenatal EDC exposure could lead to persistent, sex dependent alteration in pancreatic function possibly by affecting sympathetic innervation to the pancreas.

Disclosures: A. Palaniyappan: None. **A. Murugan:** None. **Y. Chuang:** None. **P.S. Mohankumar:** None. **S.M. Mohankumar:** None.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.03/Web Only

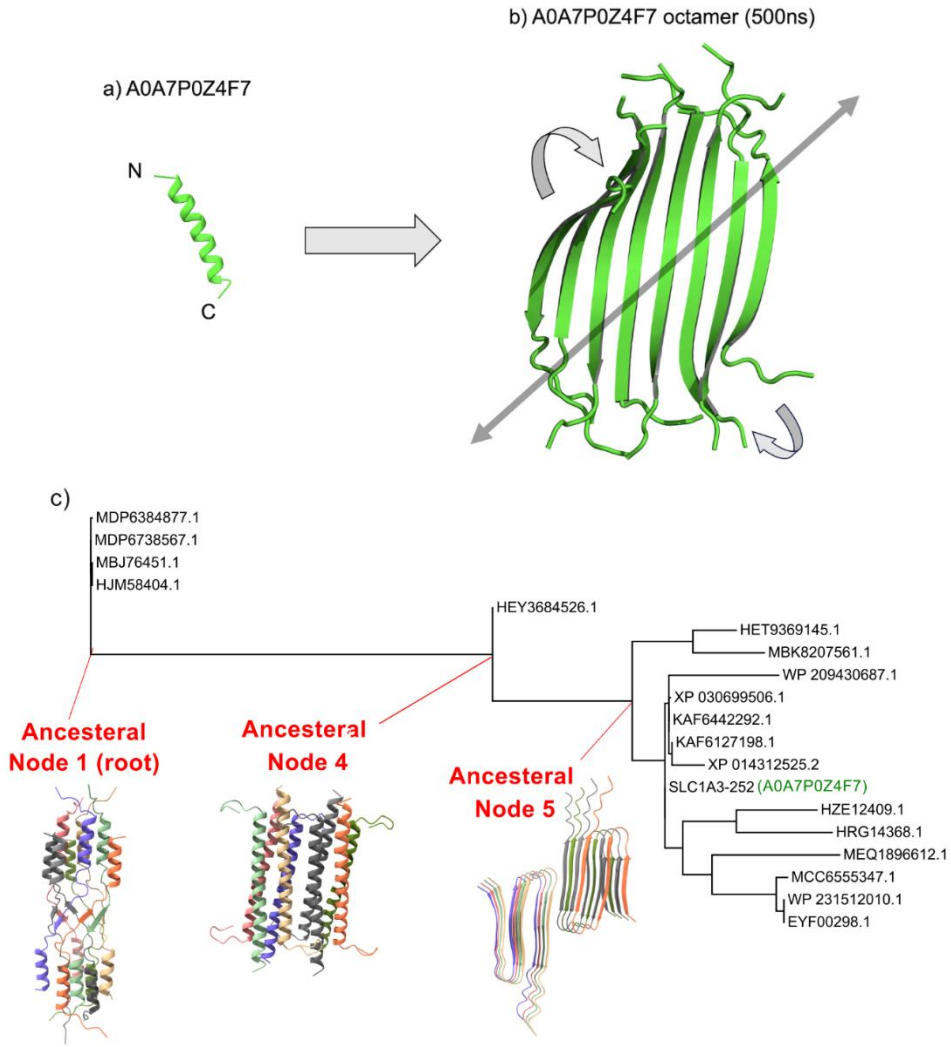
Topic: B.01. Transmitters, Transporters, and Other Signaling Molecules

Title: Helix-to-Sheet Transitions in Glutamate Transporter EAA1 Splice Isoforms Drive Oligomeric Self-Assemblies and Reveal Conserved Evolutionary Motifs

Authors: *A. KARAGÖL, T. KARAGÖL;
Istanbul University Istanbul Medical Faculty, Istanbul, Turkey

Abstract: Excitatory amino acid transporters (EAATs) are essential regulators of glutamatergic signaling, yet their structural diversity extends far beyond canonical full-length assemblies. Alternative splicing of SLC1A3 (EAA1) produces truncated isoforms with previously unrecognized structural and evolutionary properties. Here, we integrate structural characterization, 500ns molecular dynamics simulations, and phylogenetic analyses to analyze these variants. We show that select helical splice isoforms, including the human EAA1 peptides A0A7P0Z4F7 and A0A7P0TAF5, undergo helix-to-β-sheet transitions, self-assembling into

oligomers with stable β-enriched architectures (Figure 1a, 1b). Remarkably, one isoform (A0A7P0TAF5) is strongly hydrophilic and water-soluble, revealing that oligomerization is not confined to membranous fragments. Atomistic simulations demonstrate that β-sheet octamers of A0A7P0Z4F7 remodel lipid bilayers, inducing localized pitting, while reorganizeing into twisted β-barrel-like conformations. Such assemblies parallel amyloidogenic peptides, suggesting a mechanistic link between EAA1 isoform misfolding and neurodegeneration. Evolutionary analyses reveal that β-sheet oligomerization motifs are deeply conserved: A0A7P0Z4F7 homologs persist across mammals, including bats (Rousettus aegyptiacus) and whales (*Globicephala melas*), with E-values of 2e-12 and 3e-10. A universally conserved 10-residue motif (WLDSLLAIDA) underlies this fold-switching propensity, acting as a transferable structural microdomain embedded across unrelated proteins. Phylogenetic reconstruction and structural calculations pinpoint the evolutionary breakpoint where helix-derived isoforms first acquired β-sheet oligomerization capacity (Figure 1c). The data are consistent with constructive neutral evolution (CNE). Together, these findings identify helix-to-sheet transforming isoforms as novel candidates for mechanistic studies of transporter-associated neuropathology and potential therapeutic targeting.



Disclosures: A. Karagöl: None. **T. Karagöl:** None.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.04/LBP003

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

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The Ono Pharmaceutical Foundation for Oncology
Memorial Foundation For Medical And Pharmaceutical Research
Research Grant from JGC Saneyoshi Scholarship Foundation
The Takeda Science Foundation

Title: Compartmentalized cAMP signaling underlies serotonergic actions in the nucleus accumbens

Authors: *T. YAGA[1], J. MATSUBAYASHI[2,3], A. INOUE[1], Y. ITO[2,3], W. ZHONG[1], H. ETANI[1], M. TAJIRI[1], Y. IINO[1], T. YOKOYAMA[4], M. SAKAMOTO[4], T. TAKANO[2,3], S. YAGISHITA[1];
[1]The University of Tokyo, Bunkyo-ku/Tokyo, Japan; [2]Institute for Advanced Study, Kyushu University, Fukuoka, Japan; [3]Medical Institute of Bioregulation, Kyushu University, Fukuoka, Japan; [4]Graduate School of Biostudies, Kyoto University, Kyoto, Japan

Abstract: Cyclic AMP (cAMP) is a key second messenger that mediates the effects of neuromodulators through G-protein-coupled receptors. Although many neurons co-express both Gs- and Gi/o-coupled receptors, how their opposing actions contribute to subcellular cAMP dynamics remains poorly understood. In the nucleus accumbens (NAc), D1- and D2-expressing spiny projection neurons (D1-/D2-SPNs) selectively express Gs- and Gi/o-coupled dopamine receptors, respectively, but co-express both Gs- and Gi/o-coupled 5-HT_4 and 5-HT_1B receptors. Here, we used cAMPinG1, a bright and high-sensitivity genetically encoded cAMP sensor, to visualize neuromodulator-evoked cAMP signaling in the dendrites, soma, and axon terminals of D1- and D2-SPNs in acute brain slices of the NAc and ventral pallidum. We found that serotonin (5-HT) evoked compartmentalized cAMP responses: 5-HT increased cAMP in dendrites and soma via 5-HT_4 receptors (5-HT_4Rs), while strongly suppressing cAMP in axon terminals via 5-

HT_1B receptors (5-HT_1BRs) in both cell types. In contrast, dopamine (DA) produced spatially uniform cAMP responses within each neuron in a cell-type-specific manner: in D1-SPNs, DA elevated cAMP in dendrites, soma, and axons; in D2-SPNs, DA suppressed cAMP in both dendrites and axons. These bidirectional, compartment-specific cAMP signals had distinct functional consequences: 5-HT promoted dendritic spine enlargement via 5-HT_4Rs, while suppressing synaptic transmission at axon terminals via 5-HT_1BRs. To investigate the molecular basis of this spatial specificity, we are conducting proximity-labeling proteomics to identify molecular determinants of receptor localization that underlie this subcellular functional dichotomy. Our findings reveal a mechanism by which 5-HT differentially regulates neuronal function through compartmentalized cAMP signaling. Such spatially specific modulation may be critical for the neuromodulatory control of synaptic input and output in striatal circuits.

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Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.05/LBP004

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

Support: NIH R01 DA056675

Title: Selective inhibition of the N-terminal catalytic domain of angiotensin-converting enzyme prevents endogenous opioid peptide degradation in brain tissue

Authors: *U. GIRDWOOD, F. HANAK, J. SWANSON, P. E. ROTHWELL;
Neuroscience, University of Minnesota, Minneapolis, MN

Abstract: Angiotensin-converting enzyme (ACE) plays a key role in cleaving bioactive peptides in both the body and the brain. ACE is predominantly known for its role in the renin-angiotensin system, cleaving Angiotensin I into the vasoconstrictor Angiotensin II which regulates blood pressure in mammals. However, ACE has also been found in the dorsal striatum and nucleus accumbens of both murine and human brains. Centrally, ACE has been found to cleave and degrade endogenous opioid peptides such as MERF (Met-enkephalin-Arg-Phe), modulating opioid signaling in the brain. ACE is composed of two catalytic domains: the N-terminal domain, and the C-terminal domain. Angiotensin I is thought to be primarily cleaved by the C-domain of ACE, but much less is known about ACE's cleavage of endogenous opioid peptides. To address this, we tested MERF enzymatic activity under 4 different inhibitory conditions. We first collected live brain tissue from mutant mouse lines with C-domain or N-domain functional inactivation and analyzed ACE enzymatic activity using liquid chromatography-tandem mass spectrometry. We found that functional inactivation of the N-domain alone altered MERF

degradation. To confirm our findings, we recreated this domain specific inhibition using two pharmacological inhibitors: the N-domain selective inhibitor RXP 407 and the C-domain selective inhibitor RXPA 380. Again, we found that N-domain inhibition via RXP 407 dose-dependently prevented MERF degradation, whereas RXPA 380 did not. To further analyze the effects of RXP 407, we utilized whole-cell patch-clamp electrophysiology. These results showed that RXP 407 caused long term depression of excitatory synaptic transmission onto medium spiny neurons, as indicated by a decrease in excitatory postsynaptic current amplitude and increase in paired pulse ratio. These findings lead us to believe that the N-domain is the primary site of MERF degradation, and therefore a potential target for modulating the endogenous opioid system without unwanted effects caused by C-domain inhibition. This information could assist in the development of pharmacotherapies which harness the endogenous opioid system to manage pain as well as treat psychiatric and neurological disorders such as depression.

Disclosures: U. Girdwood: None. **F. Hanak:** None. **J. Swanson:** None. **P.E. Rothwell:** None.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.06/LBP005

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

Support: NSF #1942822
NIH T32 1T32GM142623
ARCS Scholarship

Title: Neuropeptide processing enzymes contributions in planarian regeneration and stem cell differentiation

Authors: *C. E. ENDARA-ARNOLD[1], J. E. JENKINS[2], A. E. VILLALOBOS[3], R. H. ROBERTS-GALBRAITH[4];
[1]University of Georgia, Athens, GA; [2]Duke University, Durham, NC; [3]Northwestern University, Chicago, IL; [4]Department of Cellular Biology, University of Georgia, Athens, GA

Abstract: Neuropeptides play numerous roles in metazoans, including aiding neurodevelopment and regulation of neurotransmitter release. Roles for neuropeptides in regulation of regeneration are emerging, but much is still unknown. Planarian flatworms, *Schmidtea mediterranea*, are among the only organisms that can fully regenerate all body organs de novo, making them an ideal model with which to explore neuropeptide function in regeneration and to uncover roles in stem cell regulation. Because neuropeptides have the ability to act as long-range signaling molecules, they could promote regeneration across the entire body (Mendel et al., 2020). Prohormone convertase 2 (PC2) is an essential enzyme in neuropeptide synthesis which has been shown to impact behavior and regeneration when knocked down by RNA interference (RNAi) in planarians (Reddien, Bermange, et al., 2005; Collins et al., 2010). We determined that

PC2(RNAi) animals (n=8-12) have reduced stem cell markers and a dramatic decrease in multiple progenitor markers. Next, we investigated genes that encode other enzymes that cleave neuropeptides to analyze whether their perturbation causes similar phenotypes. Knockdown of genes encoding neuropeptide processing enzymes (carboxypeptidase and peptidylglycine-α-amidation-1) leads to smaller brain size, diminished stem cell differentiation, and perturbed stem cell maintenance. We thus hypothesize planarian neuropeptide processors—likely through their production of neuropeptides— influence regeneration by impacting stem cell function. Additionally, the knockdown of twenty-three individual neuropeptide-encoding genes prevents robust brain regeneration in planarians; these likely function cooperatively to drive repair. Our work demonstrates a central role for nervous system regulation of pluripotent stem cells necessary to drive regeneration. This work indicates that neuropeptides have potential as a therapeutic approach to influence endogenous stem cells and to guide exogenous stem cells in regenerative treatments.

Disclosures: C.E. Endara-Arnold: None. **J.E. Jenkins:** None. **A.E. Villalobos:** None. **R.H. Roberts-Galbraith:** None.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.07/LBP006

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

Support: Ministry of Education, Science, Sports, Culture and Technology(MEXT)
NIG-JOINT
Micron Technology Foundation(MH)

Title: Visualization of seven transmembrane receptors by ligand derivative staining

Authors: *H. MIDORI[1], K. HASEGAWA[2], K. TAKANAMI[3];
[1]Department of Human Health Science, Nara women university, Nara City, Nara Prefecture, Japan; [2]Fukushima Medical University, Fukushima city, Fukushima, Japan; [3]Nara women university, Nara, Japan

Abstract: Gastrin-releasing peptide (GRP) is a 27-amino acid peptide, and its receptor (GRPR) is a bombesin receptor family. In addition to circadian rhythm, feeding, fear memory, and male sexual function, GRP was also reported to be responsible for the itch transmission in the spinal sensory system. We showed that GRP/GRPR in the spinal trigeminal nucleus of the medulla of mice and rats also involved in the facial itch transmission in the trigeminal sensory system (Takanami Hashino et al., Front Mol Neurosci. 2023). We have also found that these neural circuits are common to both rodents and primates (Takanami et al., J Comp Neurol. 2022). Immunohistochemistry is the first option to visualize the receptors localization in histological analysis and requires specific antibodies. GRPR is seven transmembrane receptors, and there are

no available antibodies for use in histology. Using genetically modified animals is another option to visualize GRPR, however they are not readily available and suffer from ectopic expression. Thus, there are many disadvantages to the current labeling method of GRPR. Therefore, new labeling methods are required to visualize endogenous receptors. In this study, we verified "ligand derivative staining", which visualizes receptors by labeling tags to ligand molecules. In this study, we prepared two types of ligands: an endogenous sequence of GRP and a mimic ligand that specifically binds to GRPR among receptor subtypes. First, to confirm the specificity of ligand derivative staining, we analyzed the localization of GRPR in the central nervous system of using GRPR transgenic mice. GRPR was observed in many regions already reported. Especially, GRPR expression was intense in the suprachiasmatic nucleus of hypothalamus and spinal dorsal horn. To examine the ligand binding ability to GRPR, "Western Ligand blot" was performed using hypothalamus and spinal cord. Binding of the endogenous ligand and mimic ligand to receptor was observed at similar molecular weight where GRPR reaction was observed by Western blot, which confirmed the specificity of ligand binding. In addition, since GRP/GRPR has been reported to be overexpressed in multiple cancers, WLB was performed on organs such as the lungs, heart, and stomach, and GRPR expression was observed as in WB. Finally, to perform the histological analysis of GRPR by ligand derivative staining, we are currently investigating ligand types, tag types, concentrations, and reaction times. In the future, ligand derivative staining
methods, unlike antibody-based staining, would be possible to visualize endogenous receptors in all organisms once the sequence of the ligand is known.

Disclosures: H. Midori: None. **K. Hasegawa:** None. **K. Takanami:** None.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.08/LBP007

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

Support: NSF GRFP DGE2139757

Title: Novel class of signaling peptides derived from the proteasome induce NMDA receptor-dependent downstream signaling

Authors: *A. BRENNAN[1], S. S. MARGOLIS[2];
[1]Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Johns Hopkins University School of Medicine, Baltimore, MD

Abstract: The proteasome is a large macromolecular complex that is responsible for the regulated degradation of proteins in all mammalian cells. The specialized Neuronal Membrane Proteasome (NMP) degrades intracellular proteins into extracellular peptides that act as signaling molecules. These signaling molecules (NMP peptides) induce intracellular calcium transients,

downstream activation of the MAPK pathway, and gene expression of c-Fos and Npas4. In this study, we aim to understand the role of distinct receptor types in downstream NMP peptide mediated neuronal signaling. Through GCaMP3 calcium imaging *in vitro*, we have observed reduced calcium transients in the presence of the potent NMDA receptor antagonist, APV. Similarly, NMP peptides increased c-Fos and Npas4 expression by western blot analysis, which was lost in the presence of APV. Interestingly, NMP peptides increased c-Fos and Npas4 expression in the presence of inhibitors of voltage gated sodium channels and AMPA receptors (TTX and CNQX). This NMDA receptor dependent, and AMPA/VGSC independent downstream signaling suggests that NMP peptides could be directly regulating the NMDA receptor. In this study, we aim to understand the role that NMP peptides play in NMDA receptor dependent neuronal signaling. We examined the role of NMP peptides in modulating channel activity by isolating NMDA receptor currents using *in vitro* whole-cell voltage clamp electrophysiology in mouse primary cortical neuronal cultures. NMP peptides alone induced inward current in comparison with control conditions. Surprisingly, whole-cell currents induced by NMP peptides decreased when recorded in the presence of TTX and gabazine compared to NMP peptides alone. This suggests that NMP peptide induced ion flux is at least partially dependent on voltage gated sodium channels or GABA activity. Currently, we aim to isolate current from NMDA receptors to understand the role of NMP peptides on NMDA current specifically. This study is the first to test the electrophysiological effects of NMP peptides in neurons. The temporal and single cell resolution achievable with patch-clamp electrophysiology will be foundational for our understanding of the role of NMP peptides in neuronal modulation in the central nervous system. In conclusion, this study seeks to explore the signaling mechanisms of a novel class of neuronal peptides derived from the Neuronal Membrane Proteasome, as part of a broader effort to understand their function.

Disclosures: A. Brennan: None. **S.S. Margolis:** None.

Late-Breaking Poster

LBP052: B.01. Transmitters, Transporters, and Other Signaling Molecules

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP052.09/LBP008

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

Support: R01AG084473

Title: IGF-1 Diminishes Calcium Flux via AMPA Receptors in Cortical Neurons: Implications for Neuropathology

Authors: *U. FATIMA[1], S. W. BARGER[1,2,3];
[1]Dept Geriatrics, University of Arkansas for Medical Sciences, Little Rock, AR; [2]Dept Neuroscience, University of Arkansas for Medical Sciences, Little Rock, AR; [3]Geriatric Research, Educ. & Clin. Ctr., Central Arkansas Veterans Healthcare Syst., Little Rock, AR

Abstract: Insulin-like growth factor-1 (IGF-1) plays a critical role in neuronal signaling. Disrupted insulin/IGF-1 signaling is implicated in Alzheimer's disease, among other conditions, yet its specific influence on glutamate receptor-mediated calcium responses remains unclear. We aimed to determine the impact of IGF-1 on glutamate receptor function in neurons from rat cerebral cortex. Primary cortical neurons were used to assess calcium responses following stimulation with glutamate, AMPA, or NMDA/glycine, with and without insulin or IGF-1. Pharmacological blockers (CNQX for AMPA, APV for NMDA, and L-type calcium channel inhibitors) were applied to define receptor-specific contributions. In cortical neurons, IGF-1 consistently reduced glutamate- and AMPA-evoked calcium peaks, suggesting an inhibitory effect on AMPA receptors. To rule out effects on voltage-gated calcium channels downstream of AMPA receptors, we tested effects of IGF-1 on depolarization with KCl; calcium elevation in this case was unaffected by IGF-1. Likewise, IGF-1 did not inhibit responses to NMDA/glycine; and IGF-1 did not affect glutamate responses in the presence of CNQX, a selective AMPA receptor blocker. These findings, combined with the observation that IGF-1 effects persisted in the presence of APV (an NMDA receptor antagonist), indicate that the inhibition of glutamate responses by IGF-1 is mediated by modulation of AMPA receptor activity. Excessive calcium entry can trigger circuit disruption, excitotoxicity, mitochondrial stress, and oxidative damage; these are features of several neurological disorders or injuries, including traumatic brain injury, stroke, infection, and neurodegenerative disease. By limiting AMPA receptor-mediated calcium influx, IGF-1 may help maintain neuronal calcium balance and support neuroprotection. Disruption of IGF-1 signaling, as seen in states resembling insulin resistance, may therefore worsen glutamate-driven excitotoxicity and contribute to adverse outcomes. Our findings suggest that IGF-1 selectively suppresses AMPA receptor-mediated calcium entry in cortical neurons, thereby maintaining calcium homeostasis and potentially protecting against excitotoxicity. This mechanism highlights IGF-1 as a critical modulator of neuronal signaling with therapeutic relevance for calcium-dependent neurodegeneration.

Disclosures: U. Fatima: None. **S.W. Barger:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.01/LBP009

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NINDS F31 NS134239

Title: A neuromodulatory feedback loop mediated by the neuronal membrane proteasome, NMDA receptors, and CaMKII

Authors: *T. R. CHURCH, S. S. MARGOLIS;
Neuroscience, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract: The proteasome is a large macromolecular protease complex responsible for most protein degradation in all cell types, but in neurons, synaptic proteasomes have additional roles in neuronal communication not fully explained through canonical proteasome pathways. A unique, neuron-specific proteasome complex, called the neuronal membrane proteasome (NMP), is embedded in the cell membrane and may facilitate these specialized functions. The NMP degrades intracellular proteins into peptides released into the extracellular space as cell-type specific signaling molecules unique from other neuropeptides. These peptides are sufficient to trigger rapid, selective N-methyl-D-aspartate receptor (NMDAR)-dependent calcium influx and downstream neuroregulatory gene expression. Using a series of biochemical assays, we uncovered a feedback loop through which NMDARs reciprocally regulate NMPs, wherein NMDAR inhibition suppresses NMP activity and NMDAR activation both stimulates NMP activity and increases proteasome localization to the membrane. Based on decades of literature establishing a regulatory relationship between NMDARs, proteasomes, and Ca2+/calmodulin-dependent kinase-II (CaMKII), we hypothesized that CaMKII is the molecule responsible for driving NMDAR-associated changes in NMP activity. Using immunogold electron microscopy, we show NMPs can colocalize with NMDARs and that upon NMDAR activation, there is a shift in proteasome localization from the cytosol toward the membrane. Using cell-impermeable and cell-permeable activity-based probes to assess NMP and total proteasome activity, respectively, we determined CaMKII inhibition reduces rapid NMDAR-dependent NMP stimulation but has minimal effect on total proteasome activity. An inhibitor panel targeting different CaMKII mechanisms further ascertained that this relationship is facilitated through a kinase-independent, structural CaMKII regulatory interaction rather than direct, calmodulin-stimulated CaMKII kinase activity. These results provide the first evidence that rapid NMDAR-associated regulation of synaptic proteasomes may primarily reflect activity changes in NMPs rather than cytosolic proteasomes and propose CaMKII as the mediator of this interaction.

Disclosures: T.R. Church: A. Employment/Salary (full or part-time); Johns Hopkins University School of Medicine. **S.S. Margolis:** A. Employment/Salary (full or part-time); Johns Hopkins University School of Medicine.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.02/LBP010

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant R01NS097536
NIH Grant P30GM140963
NIH Grant P20GM103474

Title: Novel binding mode for negative allosteric NMDA receptor modulators

Authors: *A. J. BENTON[1], J. S. LOTTI[1], J. T. SYRENNE[1], A. AL-MOUSAWI[2], L. E. CORNELISON[1], C. J. TROLINDER[1], F. YI[1], Z. ZHANG[2], A. R. RAU[1], R. P. CLAUSEN[2], K. B. HANSEN[1];
[1]University of Montana, Missoula, MT; [2]University of Copenhagen, Copenhagen, Denmark

Abstract: NMDA-type ionotropic glutamate receptors mediate excitatory neurotransmission and synaptic plasticity, but aberrant signaling by these receptors is also implicated in brain disorders and subunit-selective allosteric modulators have therefore garnered considerable interest in the development of novel therapeutic agents. Here, we present the binding site and the mechanism of action for UCM-101, a novel GluN2A-preferring negative allosteric modulator (NAM) that is 7.5-fold more potent compared to its parent compound TCN-213, with a distinct chemical scaffold from existing GluN2A-selective compounds such as TCN-201, MPX-004, and MPX-007. Using two-electrode voltage-clamp recordings, we determined UCM-101 has 59-fold higher binding affinity at GluN1/2A compared to GluN1/2B receptors and inhibits diheteromeric GluN1/2A and triheteromeric GluN1/2A/2B receptors with IC_{50} values of 110 nM (95% CI, 90-130; n = 7) and 240 nM (95% CI, 220-280; n = 14), respectively. UCM-101 and its analog TCN-213 inhibit NMDA receptors by negatively modulating co-agonist binding to the GluN1 subunit via an allosteric mechanism that is conserved with previously described GluN2A-selective antagonists, TCN-201 and MPX-004. In brain slice recordings, UCM-101 (3 μM) inhibited NMDA receptor-mediated EPSCs to 11 ± 3% (n = 6) of baseline versus 84 ± 3% (n = 8) for TCN-213, its structural precursor, demonstrating the increased potency of UCM-101. The novel binding mode for UCM-101 is revealed in a crystal structure of the GluN1/2A agonist binding domain heterodimer. UCM-101 adopts an extended conformation in the binding site, distinct from the U-shaped conformation of TCN-201 and MPX-004, engaging a previously unexplored subsite. Site-directed mutagenesis revealed that GluN2A residues V529, V783, M788, and T797 contribute to UCM-101 selectivity, while TCN-201 selectivity primarily depends on GluN2A V783. Thus, despite the shared mechanism of action, the structural determinants that mediate subunit-selectivity for UCM-101 are distinct from those of TCN-201 and MPX-004. These findings provide detailed insights into the binding site and mechanism of action of a novel NMDA receptor modulator and open new avenues for the development of NMDA receptor ligands with therapeutic potential.

Disclosures: A.J. Benton: None. **J.S. lotti:** None. **J.T. Syrenne:** None. **A. Al-Mousawi:** None. **L.E. Cornelison:** None. **C.J. Trolinder:** None. **F. Yi:** None. **Z. zhang:** None. **A.R. Rau:** None. **R.P. Clausen:** None. **K.B. Hansen:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.03/LBP011

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: National Institute of Neurological Disorders and Stroke (R01NS097536)
National Institute of General Medical Sciences (P30GM140963)

Title: Functional characterization of disease-associated GluN1-M706V variation in NMDA receptors

Authors: *L. E. CORNELISON, A. J. BENTON, J. T. SYRENNE, K. B. HANSEN; University of Montana, Missoula, MT

Abstract: NMDA receptors (NMDARs) are tetrameric ligand-gated ion channels, most commonly composed of two glycine-binding GluN1 subunits and two glutamate-binding GluN2 subunits (GluN2A-D). *De novo* missense variants in NMDAR subunits are known to contribute to the etiology of diverse encephalopathies, which are frequently associated with significant sensory, motor, and cognitive dysfunction. One such variation, GluN1-M706V, located in the interior of the GluN1 agonist binding domain (ABD) but outside the orthosteric binding site, was identified in a patient presenting a severe neurological phenotype. Determination of overall effects of variations on NMDAR function is often complex, as such variants may influence multiple aspects of receptor biology including surface expression, channel open probability, ion permeability, and agonist potency. We demonstrate that the GluN1-M706V variation affects the concentration-response relationship of glycine in a GluN2 subunit-dependent manner. That is, in GluN1-M706V/2A, but not GluN1-M706V/2B, the glycine dose-response data is remarkably slow to reach equilibrium. However, when the GluN1-M706V/2A NMDARs were pre-exposed to a saturating concentration of glycine, this phenotype was ameliorated and the dose-response closely resembled that of wild-type GluN1/2A receptors. Further experiments demonstrated that this effect of glycine pre-treatment is not attributed to an increase in channel open probability or an increase in cell-surface expression of NMDARs. The effect of the mutation on receptor kinetics, as well as the impact of sustained glycine exposure on receptor function, were assessed using fast-application whole-cell patch-clamp electrophysiology in HEK293 cells. In response to prolonged glycine application, current amplitudes of GluN1-M706V/2A receptors increased with repeated exposures, suggesting that glycine binding may recruit GluN1-M706V/2A receptors from a non-responsive state to a conformation capable of responding to agonist binding with functional properties similar to wild-type. This effect was not observed for GluN1-M706V/2B receptors, while triheteromeric GluN1-M706V/2A/2B receptors showed an intermediate phenotype Taken together, these findings suggest that binding of glycine site agonists to GluN1-M706V/2A may mitigate negative effects on receptor function via a mechanism similar to pharmacological chaperones. Further characterization of the GluN1-M706V mutation may therefore provide insights that facilitate the development of therapeutic strategies for patients with similar pathogenic variations that may be rescued by pharmacological chaperones.

Disclosures: L.E. Cornelison: None. **A.J. Benton:** None. **J.T. Syrenne:** None. **K.B. Hansen:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.04/LBP012

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH R01AG0987641
NIH R01-MH120132

Title: NMDA receptors regulate DNA topology by modulating Topoisomerase 2B activity

Authors: *I. DELINT-RAMÍREZ[1], R. MADABHUSHI[2];
[1]Southwestern Medical Center, Dallas, TX; [2]Psychiatry, University of Texas Southwestern Medical Center, Dallas, TX

Abstract: Topoisomerases are enzymes that resolve DNA supercoiling and chromosome entanglements generated during transcription, thereby relaxing DNA. Topoisomerase 2B (Top2B), unlike other Top2 isoforms, is expressed in neurons and contributes to the transcriptional regulation of developmentally and activity-dependent genes. We previously demonstrated that NMDA receptor (NMDAR) activity induces an atypical function of Top2B: abortive catalysis leading to the formation of DNA double-strand breaks (DSBs) at the promoters of specific genes, thereby regulating their expression. Recently, we found that, in neuronal culture, in addition to generating DSBs, synaptic NMDAR activity triggers an intranuclear calcium-dependent mechanism that inhibits the relaxation activity of Top2B, thereby increasing DNA supercoiling. This effect persists for ~30 minutes after stimulation and results in a rapid, genome-wide loss of cohesin from chromatin. Cohesin, a protein complex essential for higher-order chromosome structure, plays a key role in organizing topologically associated domains (TADs) that influence gene expression. Our findings reveal that NMDARs regulate Top2B activity to mediate chromatin reorganization in response to neuronal stimulation.

Disclosures: I. Delint-Ramírez: None. **R. Madabhushi:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.05/LBP013

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: F31NS139574

Title: Human iPSC-derived cortical neurons reveal neurodevelopmental defects caused by R519Q GluN2B variants of NMDA receptors

Authors: *T. M. BENSKE, B. DE FREITAS BRENHA, M. WILLIAMS, T. MU;
Case Western Reserve University, CLEVELAND, OH

Abstract: NMDA receptor (NMDAR) subunits are encoded by *GRIN* genes that are highly intolerant to genetic variation. Mutations in these genes are linked to neurological disorders including epilepsies, intellectual disabilities, and developmental delays. NMDARs mediate excitatory neurotransmission and are essential for synaptic development, plasticity, and memory. Our recent study showed that the R519Q variant of the GluN2B subunit reduces global and surface expression, impairs receptor function and stability, and accumulates in the endoplasmic reticulum with preferential autophagic degradation. However, the proteostasis of NMDARs and the pathogenic influence of this variant in an endogenous neuronal model remain unexplored. We hypothesized that the loss-of-function R519Q variant reduces excitatory calcium signaling, impairing neuronal differentiation, synapse formation, and neuronal maturation. In this study, we employed hiPSCs harboring a homozygous CRISPR-mediated R519Q *GRIN2B* knock-in mutation. hIPSCs were induced into neuronal progenitor cells (NPCs) via embryoid body formation and small-molecule neuronal induction (n=3). R519Q NPCs showed decreased proliferation (Ki67) and lower expression of progenitor markers SOX1 and PAX6, indicating an insufficient capacity for self-renewal and a smaller progenitor pool versus isogenic controls (n=9). Further, upon differentiation into cortical neurons, the R519Q variant altered the precise timing of neuronal differentiation leading to the early emergence of immature neurons as observed by proliferation rates, aberrant neurite extension, and early expression of the post-mitotic neuronal markers DCX and NGN1 relative to the isogenic control, measured by qPCR and immunocytochemistry (n=5). Interestingly, at later stages in the neuronal differentiation, the R519Q neurons showed reduced expression of PSD-95, NeuN, and synaptophysin, markers of mature neurons and measured by qPCR, immunoblot, and immunocytochemistry (n=3). Future studies will use iPSC-derived neurons to assess functional consequences via electrophysiology and examine pathways modulated by R519Q NMDARs. Additionally, 3-D brain cortical organoids will be employed to study neuronal migration and pathogenic effects in a complex neuronal environment. These finding provide novel insights into GluN2B proteostasis and its role in neurodevelopment, identifying potential therapeutic targets for future treatments.

Disclosures: T.M. Benske: None. **B. de Freitas Brenha:** None. **M. Williams:** None. **T. Mu:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.06/LBP014

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant NS031744

Title: Interdependent salt bridges and lipid contacts regulate ionic currents in α7 nicotinic receptor channels

Authors: *L. ALHALHOOLY, S. M. SINE;
Mayo Clinic, Rochester, MN

Abstract: Ion channels transport small inorganic ions rapidly along their electrochemical gradients. In most channels, charged residues within the ion translocation pathway determine the rate and selectivity of ion flow. Here, we identify a different mechanism in the homomeric α7 nicotinic receptor: a conserved intramembrane salt bridge and a nearby lipid-interacting residue together set the unitary current amplitude. Using single-channel electrophysiology and mutagenesis, we find that disrupting either structure alone has little effect but disrupting both markedly reduces the current amplitude. This pore-peripheral structure of each pentameric subunit contributes an equal increment to the unitary current amplitude. Furthermore, permeability studies with monovalent cations of varying size reveal that double-mutant subunits substantially alter the rank order of ionic permeability, indicating changes in pore structure. These findings reveal an interdependent network of salt bridges and lipid contacts that maintains a pore structure suited for physiologically relevant cations.

Disclosures: L. Alhalhooly: None. **S.M. Sine:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.07/LBP015

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Korea MFDS Grant 25212MFDS003
Korea MSIT Grant RS-2024-00405102
Korea NRF Grant RS-2023-00212567
Korea NRF Grant RS-2023-00219399

Title: Synthetic nicotine analogs in e-cigarettes differentially modulate α4β2 nicotinic acetylcholine receptor activity

Authors: D. VARIAS[1], G. SISON[1,2], Y. PARK[1,2], ***B. LEE**[1];
[1]Department of Physiology, College of Medicine, Gyeongsang National University, Jinju, Korea, Republic of; [2]Department of Convergence Medical Science, Gyeongsang National University, Jinju, Korea, Republic of

Abstract: Disposable e-cigarettes are rapidly gaining popularity among global youth, coinciding with the emergence of synthetic nicotine analogs and non-nicotine additives. These substances

are often marketed as alternatives to conventional tobacco smoking, claiming to replicate its sensory experience while circumventing regulatory restrictions on nicotine. However, their safety remains largely untested, particularly regarding how synthetic nicotine analogs, alone or in combination with additives, may differentially activate nicotinic acetylcholine receptors (nAChRs) that play a critical role in nicotine dependence. To address this, we conducted receptor-based screening using Fura-2, AM calcium imaging in α4β2 nAChR-expressing HEK293 cells. We assessed the dependence liability of nicotine, the synthetic analogs 6-methylnicotine and nicotinamide, the flavor additive menthol, carcinogenic metabolites, and nicotine-related impurities. Furthermore, we report differential activation of α4β2 nAChRs by nicotine and 6-methylnicotine when co-applied with nicotinamide, menthol, or the antagonist dihydro-β-erythroidine (DHβE). This in vitro platform provides a critical first step in categorizing substances that mimic or potentiate nicotine's addictive effects, offering key evidence to inform regulatory strategies in response to the rapidly evolving e-cigarette market.

Disclosures: D. Varias: None. **G. Sison:** None. **Y. Park:** None. **B. Lee:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.08/LBP016

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Title: CO2 is an endogenous analog of inhaled anesthetics

Authors: *J. ZHANG[1], S. B. HANSEN[2];
[1]Chinese Institutes For Medical Research, Beijing, Beijing, China; [2]Chinese Institutes for Medical Research, Beijing, China

Abstract: Inhaled anesthetics are hydrophobic small molecules that cause reversible loss of consciousness. Several inhaled anesthetics are naturally occurring, including carbon dioxide. Carbon dioxide is an abundant hydrophobic gas previously used by psychiatrists to cause rapid loss of consciousness in humans. But CO2's molecular mechanism is not well studied. Here we show that CO2 acts as an endogenous anesthetic to disrupt ordered lipid domains and cause anesthesia in a fruit fly. Fruit flies exposed dose dependently to CO2 with 20% oxygen showed a half maximal anesthesia at 29% CO2 and rapid complete loss of consciousness when exposed to 80% CO2. These results agree with the loss of consciousness seen in CO2 therapy by psychiatrists in the 1940s. Genetic depletion of phospholipase D, a gene regulating anesthetic sensitivity in flies, reduced CO2 sensitively and application of media equilibrated with 20 to 40% CO2 to cultured mammalian cells shows a dose dependent decrease in membrane cholesterol. We conclude CO2 is an endogenous analog of inhaled anesthetics with Overton-Meyer like properties. The reduced cholesterol suggests CO2 likely contributes to a membrane-mediated mechanism of general anesthesia.

Disclosures: J. Zhang: None. **S.B. Hansen:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.09/LBP017

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant R01 NS131557

Title: Elevating serotonin receptor 2A signaling restores learning and memory in a Fragile X Syndrome model

Authors: *Y. DU, V. MILLER, K. S. BROADIE;
Vanderbilt University, Nashville, TN

Abstract: Serotonin (5-hydroxytryptamine, 5-HT) has central roles enabling learning and memory, particularly via serotonin receptor 2A (5-HT_{2A}R) signaling. *Drosophila* Fragile X syndrome model (*dfmr1* null mutant) studies reveal impaired learning and memory, which may reflect serotonergic signaling deficits. Here, we use classical olfactory conditioning to assess learning and memory, combined with imaging to assess 5-HT and 5-HT_{2A}R levels in the underlying Mushroom Body (MB) brain circuitry. Data show individual trails (n=16 each), mean ± SEM, and one-way ANOVA with Tukey's multiple comparisons tests. Null *dfmr1* mutants of both sexes of adult flies (7-9 days post-eclosion) exhibit learning acquisition deficits (p=1.924×10^{-6}) and memory consolidation deficits (p=3.0×10^{-11}) that are corrected by elevating MB serotonin signaling through either 1) overexpression of serotonin biosynthetic enzyme tryptophan hydroxylase (Trhn) (learning: p=3.367×10^{-9}; memory: p=2.645×10^{-6}) or 2) knockdown of serotonin reuptake transporter (SERT) (learning: p=4.388×10^{-7}; memory: p=6.644×10^{-7}). Both transgenic approaches elevate serotonin levels in the MB circuit, with contributions from both neurons and glia. Comparisons of these methods show both Trhn and SERT manipulations equally restore learning and memory in *dfmr1* null mutants, although Trhn overexpression more effectively elevates MB serotonin levels (p=1.477×10^{-8}). 5-HT_{2A}R levels in the MB circuit are strongly reduced in *dfmr1* mutants (p=7.858×10^{-3}), and 5-HT_{2A}R knockdown phenocopies the *dfmr1* null learning impairment. 5-HT_{2A}R knockdown only slightly exacerbates the *dfmr1* null learning and memory deficits, suggesting that these impairments are primarily caused by the loss of 5-HT_{2A}R signaling. Consistently, 5-HT_{2A}R overexpression in *dfmr1* mutants restores normal learning and memory, with no persistent deficits compared to controls (learning: p=2.404×10^{-5}; memory: p=2.762×10^{-4}). These findings suggest loss of 5-HT_{2A}R signaling causes learning and memory deficits in this Fragile X syndrome model, and that rectifying this signaling impairment can restore learning and memory, providing a framework for serotonergic intervention strategies.

Disclosures: Y. Du: None. **V. Miller:** None. **K.S. Broadie:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.10/LBP018

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: NIH Grant MH002946-13

Title: Amphetamines induce cholesterol synthesis pathway genes through a trace amine-associated receptor 1 (TAAR1)-dependent mechanism

Authors: *G. J. GRUMBAR[1,2], W. SUN[1,3], S. G. AMARA[1];
[1]Laboratory of Molecular and Cellular Neurobiology, National Institute of Mental Health, Bethesda, MD; [2]Department of Pharmacology and Physiology, Georgetown University School of Medicine, Washington, DC; [3]Department of Pathology, University of Virginia Health System, Charlottesville, VA

Abstract: Stimulants such as amphetamines are commonly used therapeutic agents as well as drugs of abuse. Given that we have shown that amphetamines can activate multiple signaling pathways within dopamine neuron, we wanted to explore potential gene expression changes that occur following administration of amphetamines. A recent preprint from our group examining the gene expression changes resulting from acute and sub-chronic methamphetamine administration revealed that dopamine neurons have a robust enhancement of nuclear transcripts for cholesterol synthesis pathway genes. These findings were recapitulated in actively translated RNAs where both acute amphetamine and methamphetamine induced these genes. However, another commonly prescribed stimulant, methylphenidate, which blocks the dopamine transporter (DAT) but does not enter the cell as amphetamine and methamphetamine do, did not activate these pathways. This suggests that these gene expression changes are not due to blockade of DAT and elevation of extracellular dopamine. Because amphetamines are potent agonists of an intracellular G-protein coupled receptor, the trace amine-associated receptor 1 (TAAR1), we hypothesized that these gene expression changes were downstream of TAAR1. We replicated the *in vivo* amphetamine- and methamphetamine-induced changes in cholesterol synthesis pathway gene expression using qPCR in the N27-A dopamine neuron-like immortalized cell line and examined the potential signaling pathways that might be involved. In the N27-A cell line, both amphetamine and methamphetamine incubation resulted in the induction of the cholesterol synthesis pathway genes, *Hmgcr* and *Ldlr.* Furthermore, we found that this change is dependent on the activation of the trace amine-associated receptor 1 (TAAR1) since these gene expression changes are blocked by the co-application of the TAAR1 antagonist EPPTB. These results highlight the diverse actions of amphetamines and indicate that TAAR1 agonists such as amphetamines can modulate the expression of key cholesterol synthesis genes in dopamine neurons.

Disclosures: G.J. Grumbar: None. **W. Sun:** None. **S.G. Amara:** None.

Late-Breaking Poster

LBP053: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP053.12/LBP020

Topic: B.02. Transmitter Receptors and Ligand-Gated Ion Channels

Support: Else Kröner Fresenius Stiftung (2019_A68)
Interdisciplinary Center for Clinical Research Jena (AMSP 03)
EMBO Short-Term Fellowship (n° 8439)
DAAD short-term research grant (57507442)
PhD scholarship from Boehringer Ingelheim

Title: Opioid-Specific Brain Connectivity Dynamics Distinguish Analgesia from Secondary Effects

Authors: J.-C. MARIANI[1], S. DIEBOLT[2], R. SANTOS[3], T. DEFFIEUX[4], M. TANTER[5], A. KLIEWER[6], ***Z. LENKEI**[7];
[1]CNCS, IIT, Rovereto, Italy; [2]Iconeus, Paris, France; [3]Institute of Psychiatry and Neuroscience of Paris, Paris, France; [4]Physmed Inserm U1273, Paris, France; [5]INSERM, Paris, France; [6]Institute of Pharmacology and Toxicology, Universi, Jena, Germany; [7]Institute of Psychiatry and Neurosciences of Paris, INSERM, Paris, France

Abstract: The μ-opioid receptor (MOP) is a critical pharmaceutical target that mediates both the therapeutic benefits and adverse effects of opioid drugs. However, the large-scale neural circuit dynamics underlying key opioid effects, such as analgesia and respiratory depression, remain poorly understood, hindering the development of safer analgesics. Here, we present a multimodal experimental framework that integrates functional ultrasound imaging (fUSI) through the intact skull with behavioral and molecular analyses to investigate opioid-induced large-scale functional responses and their physiological relevance in awake, behaving mice. Administration of major opioids—morphine, fentanyl, methadone, and buprenorphine—elicited robust, dose- and time-dependent reorganization of functional brain connectivity (FC) patterns, with magnitude scaling according to MOP agonist efficacy. This opioid-specific functional fingerprint is marked by decreased FC between the somatosensory cortex and hippocampal/thalamic regions and increased bilateral subcortical FC within the somatosensory cortex. Notably, this fingerprint was attenuated following tolerance induction and abolished by pharmacological or genetic MOP inactivation. Through power Doppler spectral analysis and lagged correlation measurements, we show that morphine perturbs temporal FC dynamics and the propagation of brain-wide oscillatory activity, disrupting critical-state dynamics. Importantly, we identify a dissociation between fast, transient processes—such as cerebral blood volume (CBV) changes, locomotion, and respiratory depression—and slower processes driving FC reorganization, analgesia, and sustained MOP activation. This study provides mechanistic insights into opioid-induced network reorganization, establishes FC alterations as a reliable biomarker of opioid efficacy, and offers a

framework for advancing the development of analgesic compounds with improved therapeutic windows and reduced side effects.

Disclosures: **J. Mariani:** A. Employment/Salary (full or part-time); Boehringer Ingelheim. **S. Diebolt:** A. Employment/Salary (full or part-time); Iconeus. **R. Santos:** None. **T. Deffieux:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. F. Consulting Fees (e.g., advisory boards); Iconeus. **M. Tanter:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. **A. Kliewer:** None. **Z. Lenkei:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Iconeus. F. Consulting Fees (e.g., advisory boards); Iconeus.

Late-Breaking Poster

LBP054: B.03. Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP054.01/LBP021

Topic: B.03. Ion Channels

Support: NIH Grant R00NS116123
College of Veterinary Medicine NCSU intramural award

Title: Cell-specific isoform of the Calcium-dependent Activator Protein for Secretion 1 regulates $Ca_V2.2$ channels in nociceptors and is required for neurogenic inflammation.

Authors: M. DAESCHNER[1], E. R. MUSTAFA[2], Q. MOSLEY[1], A. MORGAN[1], ***E. LOPEZ SOTO**[1];
[1]College of Veterinary Medicine, North Carolina State University, Raleigh, NC;
[2]Multidisciplinary Institute of Cell Biology, La Plata, Argentina

Abstract: Voltage-gated $Ca_V2.2$ channels are essential for pain signaling by controlling transmitter release at central nociceptor terminals. $Ca_V2.2$ interactions with synaptic proteins ensure efficient release of neurotransmitters and neuropeptides that drive neuronal sensitization during inflammation and post-injury. Here, we identify a cell-specific splice isoform of the vesicle-priming factor Calcium-Dependent Secretion Activator (CAPS1) that couples to- and regulates $Ca_V2.2$ channels and is required for pain hypersensitivity associated with neurogenic inflammation. Transcriptomic analyses confirm broad CAPS1 expression across dorsal root ganglia (DRG) neurons and reveal enrichment of Cadps, CAPS1 gene, isoform transcripts containing exon 16a in Trpv1-lineage/ peptidergic, and non-peptidergic nociceptors. In newly generated conditional *Cadps* knockout mice lacking CAPS1 in Trpv1-lineage neurons (cKO-CAPS1), whole-cell recordings from DRG neurons show 40.25 % reduced total Ca_V currents with a selective loss of ω-conotoxin-sensitive ($Ca_V2.2$) currents compared with wild-type littermates, consistent with impaired $Ca_V2.2$ activity. In tsA201 cells expressing $Ca_V2.2$ (α_1B)

and auxiliary subunits +β_3+$\alpha_2\delta_1$, CAPS1 isoform containing—but not lacking—exon 16a increases 50.46% $Ca_V2.2$ current density and shift activation ~5 mV hyperpolarized. Interestingly, cKO-CAPS1 mice show attenuated mechanical and heat hypersensitivity following intraplantar 0.1% capsaicin compared with controls. To test the requirement of exon 16a for CAPS1-$Ca_V2.2$ coupling, we designed a cell-permeable exon 16a-derived peptide and a scrambled control. *In vitro*, the 16a peptide occludes CAPS1+e16a-dependent increase of $Ca_V2.2$ currents, and *in vivo*, it reduces capsaicin-induced heat hypersensitivity. Together, these findings identify exon 16a as a key CAPS1 determinant for enhancing $Ca_V2.2$ channel activity in nociceptors and highlight the CAPS1-$Ca_V2.2$ interaction as a potential therapeutic target to attenuate pain.

Disclosures: M. Daeschner: None. **E.R. Mustafa:** None. **Q. Mosley:** None. **A. Morgan:** None. **E. Lopez Soto:** None.

Late-Breaking Poster

LBP054: B.03. Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP054.02/LBP022

Topic: B.03. Ion Channels

Support: NIH 1R01NS145389-01
NIH 4R33NS101182-03
NIH 1R15NS130420
AHA 23AIREA1039423

Title: Structural basis for the subtype-selective activation of $K_{Ca}2.2$ channels by rimtuzalcap

Authors: *M. ZHANG, **Y. NAM**;
Chapman Univ., Irvine, CA

Abstract: Small-conductance ($K_{Ca}2.2$) and intermediate-conductance ($K_{Ca}3.1$) Ca^{2+}-activated K^+ channels are gated by a Ca^{2+}-calmodulin dependent mechanism. NS309 potentiates the activity of both $K_{Ca}2.2$ and $K_{Ca}3.1$, while rimtuzalcapselectively activates $K_{Ca}2.2$. Rimtuzalcap has been used in clinical trials for the treatment of spinocerebellar ataxia and essential tremor. We report cryo-electron microscopy structures of $K_{Ca}2.2$ channels bound with NS309 and rimtuzalcap, in addition to $K_{Ca}3.1$ channels with NS309 and $K_{Ca}3.1$_R355K mutant channels with rimtuzalcap. The different conformations of calmodulin and the cytoplasmic HC helices in the two channels underlie the subtype-selectivity of rimtuzalcap for $K_{Ca}2.2$. Calmodulin's N-lobes in the $K_{Ca}2.2$ structure are far apart and undergo conformational changes to accommodate either NS309 or rimtuzalcap. Calmodulin's N-lobes in the $K_{Ca}3.1$ structure are closer to each other and are constrained by the HC helices of $K_{Ca}3.1$, which allows binding of NS309 but not of the bulkier rimtuzalcap. Mutation of one arginine residue in the HB helix of $K_{Ca}3.1$ ($K_{Ca}3.1$_R355K) allows

the binding of rimtuzalcap and renders the mutant channel sensitive to rimtuzalcap. These structures provide a framework for structure-based drug design targeting $K_{Ca}2.2$ channels.

Disclosures: M. Zhang: None. **Y. Nam:** None.

Late-Breaking Poster

LBP054: B.03. Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP054.03/LBP023

Topic: B.03. Ion Channels

Support: NIGMS R01 GM145869

Title: A shared cavity site for lipid and small molecule block of the two-pore domain K+ channel TASK-2

Authors: *T. DOCTER[1], B. SORUM[2], R. RIETMEIJER[3], S. G. BROHAWN[4];
[1]Molecular and Cell Biology, University of California, Berkeley, San Francisco, CA; [2]Biomedical Sciences, Cooper Medical School of Rowan University, Camden, NJ; [3]NeuraBio, South San Francisco, CA; [4]University of California, Berkeley, Berkeley, CA

Abstract: TASK-2 is a pH-sensitive two-pore domain K^+ channel that has been shown to play physiological roles in ionic homeostasis, volume regulation, and regulation of respiratory rate. We report that at acidic pH, TASK-2 retains an extremely low open probability mediated by a previously unresolved intracellular gate and inner leaflet acyl chains that can enter an intracellular vestibule to occlude conduction. We demonstrate that mutation of an internal proton sensor K245 results in a surprising loss-of-function due to a unique function of this residue in both stabilizing a closed internal gate at low pH and disfavoring lipid occlusion at alkaline pH. Loss of lipid-inhibition of TASK-2 results in a pronounced gain-of-function phenotype characterized by a dramatic increase in open probability. Additionally, we show that the anesthetic bupivacaine binds within the inner channel vestibule below the selectivity filter to block ion conduction. These results highlight the importance of the internal channel vestibule to normal channel function and demonstrate how this region may be utilized for the development of potential channel modulators.

Disclosures: T. Docter: None. **B. Sorum:** None. **R. Rietmeijer:** None. **S.G. Brohawn:** None.

Late-Breaking Poster

LBP054: B.03. Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP054.04/LBP024

Topic: B.03. Ion Channels

Support: BHI 2023-08

Title: Synergistic effects of HIV and fentanyl differentially remodel the synapto-proteome and disrupts synaptic excitatory and inhibitory receptors across brain regions

Authors: *L. SÁNCHEZ SÁNCHEZ[1,2], E. GOMEZ[3,2], M. ORTIZ[4,5,6], K. JIRAKANWISAL[4,5,6], B. SALAMEH[3,2], S. BROWNING[7,6], C. KEITH[7,6], M. ENDSLEY[6,7], B. B. GELMAN[8,6,9], I. E. CISNEROS[4,5,6], A. LIMON[3,2];
[1]Neurology, University of Texas Medical Branch at Galveston, Houston, TX; [2]Mitchell Center for neurodegenerative diseases, Galveston, TX; [3]Neurology, University of Texas Medical Branch, Galveston, TX; [4]Pathology, University of Texas Medical Branch, Galveston, TX; [5]Center for Addiction Research, Galveston, TX; [6]Institute for Human Infections and Immunity, Galveston, TX; [7]Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX; [8]Pathology and Neurobiology, University of Texas Medical Branch, Galveston, TX; [9]Texas NeuroAIDS Research Center, Galveston, TX

Abstract: HIV-1 infection of the central nervous system is associated with reduction of neuronal density, abnormal connectivity and strong synaptic dysfunction, which are key features of HIV-associated neurocognitive impairment (NCI). Furthermore, co-occurring factors in people living with HIV (PLH), such as drug misuse can worsen these alterations. Synthetic opioids, particularly fentanyl - the most common drug used by PLH - disrupts the normal functioning of brain inhibitory networks impacting cognition. However, the combined effects of HIV and fentanyl on synapses are not fully understood. In this study, we explored the individual and combined effects of HIV-1 infection and fentanyl daily administration (0.3 mg/kg) and overdose (160 mg/kg) using a mouse model with humanized immune system (NSG mice with peripheral immune reconstitution) (3 Female 22 weeks old mice per group; 1. Control, 2. HIV-1(+), 3. fentanyl only exposure, 4. Fentanyl and HIV-1(+)). To determine potential synaptic changes, synaptosomes from the middle pre-frontal cortex (mPFC), striatum (ST) and hippocampus (HP), were isolated, and analyzed by label-free LC (LC-MSM) proteomic analysis. We also performed electrophysiological recordings from microtransplanted native mice synapses to determine functional changes of excitatory glutamate AMPA-type receptors and inhibitory $GABA_A$ receptors' functionality. Our findings indicate that HIV-1 and fentanyl each alter overlapping synaptic pathways at the protein level, but their combination produces a distinct proteomic signature. Principal component analysis using the 50 most significantly differentially expressed genes across groups (ANOVA p-value <0.0001), showed a clear separation between control and HIV-Fentanyl combination along the PC2 component while PC1 separates the control and the individual HIV and Fentanyl treated groups. Gene-ontology enrichment revealed mitochondrial-

related genes as the most affected. Furthermore, in synaptic function there is a synergistic effect of HIV-1 infection and fentanyl exposure, with a drastic reduction of GABAergic and glutamatergic activity across all brain regions. In conclusion, HIV and Fentanyl-chronic exposure showed a synergistic effect exhibiting mitochondrial pathway dysregulation and synaptic dysfunction of $GABA_AR$ and AMPA receptors. Understanding these synaptic alterations caused by the combination of HIV-1 and Fentanyl in mice is a necessary step for translating these findings to human research in PLH with polydrug misuse.

Disclosures: L. Sánchez Sánchez: None. **E. Gomez:** None. **M. Ortiz:** None. **K. Jirakanwisal:** None. **B. Salameh:** None. **S. Browning:** None. **C. Keith:** None. **M. Endsley:** None. **B.B. Gelman:** None. **I.E. Cisneros:** None. **A. Limon:** None.

Late-Breaking Poster

LBP054: B.03. Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP054.05/LBP025

Topic: B.03. Ion Channels

Support: NIH Grant EY012857
DFG Grant TE 1459/1-1

Title: Uncovering the electrical synapse proteome in retinal neurons via *in vivo* proximity labeling

Authors: *S. TETENBORG, J. O'BRIEN;
Univ. of Houston, Houston, TX

Abstract: Electrical synapses containing Connexin 36 (Cx36) represent the main means for direct electrical communication among neurons in the mammalian nervous system. In comparison to chemical synapses, little is known about the protein complexes that constitute these synapses. In the present study, we applied different BioID strategies to screen the interactomes of Connexin 36 and its zebrafish orthologue Cx35b in retinal neurons. For *in vivo* proximity labeling in mice, we took advantage of the Cx36-EGFP strain and expressed a GFP-nanobody-TurboID fusion construct selectively in AII amacrine cells. For *in vivo* BioID in zebrafish, we generated a transgenic line expressing a Cx35b-TurboID fusion under control of the Cx35b promoter. Both strategies allowed us to capture a plethora of molecules that were associated with electrical synapses and showed a high degree of evolutionary conservation in the proteomes of both species. Besides known interactors of Cx36 such as ZO-1 and ZO-2 we have identified more than 50 new proteins, such as scaffold proteins, adhesion molecules and regulators of the cytoskeleton. Moreover, we determined the subcellular localization of these proteins in mouse retina and tested potential binding interactions with Cx36. Amongst these new interactors, we identified signal induced proliferation associated 1 like 3 (Sipa1l3), a protein that has been implicated in cell junction formation and cell polarity, as a new scaffold of electrical

synapses. Interestingly, Sipa1l3 was able to interact with ZO-1, ZO-2 and Cx36, suggesting a pivotal role in electrical synapse function. In addition to AII amacrine cells, we also expressed the GFP-nanobody-TurboID fusion in On bipolar cells, which allowed us to explore the electrical synapse proteome of AII-On Cone bipolar cell gap junctions from each side: the pre and the postsynaptic compartment. Surprisingly, we identified a similar set of proteins in bipolar and AII amacrine cells, suggesting that each site of these synapses contains a similar core machinery. In summary, our study provides the first detailed view of the electrical synapse proteome in retinal neurons, which is likely to apply to electrical synapses elsewhere.

Disclosures: S. Tetenborg: None. **J. O'Brien:** None.

Late-Breaking Poster

LBP054: B.03. Ion Channels

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP054.06/LBP026

Topic: B.03. Ion Channels

Support: NIH Grant R21NS127229

Title: Characterizing The Role of G Protein-Coupled Inwardly Rectifying Potassium channel in Glioblastoma

Authors: *S. JETTI;
Houston Methodist, Houston, TX

Abstract: Characterizing The Role of G Protein-Coupled Inwardly Rectifying Potassium channel in Glioblastoma

Suresh Kumar Jetti[*], Matthew J. Shorey, Julia Pollak[3], Karan G. Rai[3], Monika Vishnoi[1], Mikhail Y. Kochukov[2], Benjamin R. Arenkiel[2], Katie Cuthill[3], Pooja Ghandi[9], Jan-Marino Ramirez[3,8], and Aguan D. Wei[3], Matthew K. Hogan, Philip J. Horner, Robert C Rostomily[1*]

Glioblastomas (GBM) are aggressive brain tumors marked by profound alterations in their bioelectrical landscape, including a depolarized resting membrane potential (V_m) and disrupted intrinsic excitability. The biophysical mechanisms underlying these changes remain poorly defined. Among channels implicated in tumor biology, G protein-coupled inwardly-rectifying potassium (GIRK) channels are largely uncharacterized in glioblastoma progression. GIRKs regulate V_m, modulate neuronal excitability, and mediate neuron-glia communication, suggesting they may influence GBM proliferation and growth. To investigate their role in GBM, we employed a multidisciplinary approach combining whole-cell patch-clamp electrophysiology, optogenetics, pharmacology, cell viability assays, and Ca^{2+} imaging. Pharmacological modulation revealed differences in proliferation, survival, and cell-cycle dynamics across glioma stem cell (GSC) lines treated with the GIRK agonist ML297 and antagonist TPNQ. Patch-clamp analysis showed that chronic, but not acute, ML297 exposure induced depolarization accompanied by increased proliferation, whereas TPNQ reduced proliferation without altering

V_m. These findings suggest that GIRK activity may modulate tumor cell excitability and growth through mechanisms that extend beyond canonical K^+ conductance. Ongoing studies are probing the relationship between GIRK-dependent V_m changes, Ca^{2+} oscillations, and neuron-tumor network physiology and how these electrophysiological correlates regulate GBM proliferation. This work will provide mechanistic insight into GIRK channel function in glioma biology and evaluate their potential as therapeutic targets to disrupt tumor-neuron crosstalk.

Disclosures: S. Jetti: None.

Late-Breaking Poster

LBP055: B.04. Synaptic Transmission

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP055.01/Web Only

Topic: B.04. Synaptic Transmission

Support: CIHR-221258

Title: Role of Elfn1 in mossy fiber to stratum lucidum information transfer.

Authors: *N. MERLAK[1], K. TOTH[2];
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Abstract: In the hippocampus, GABAergic interneurons constitute only 10-15% of the cell population, yet their diversity and extensive connectivity give them a unique capacity to sculpt network activity. By controlling pyramidal cell excitability and coordinating inhibition, interneurons regulate oscillatory dynamics, synaptic plasticity and the precision of information transfer. Within this population, stratum lucidum interneurons (SLINs) are of particular interest because they receive specialized mossy fiber input from dentate granule cells. Although mossy fibers innervate both pyramidal neurons and SLINs, their synaptic properties and the sheer number of synapses differs substantially by postsynaptic target, suggesting that granule cell output may be filtered primarily through inhibition rather than direct excitation. Here we identify two functionally distinct subpopulations of SLINs that transform mossy fiber input in strikingly different ways. One subgroup exhibits strong frequency-dependent facilitation, dynamically scaling inhibition during repetitive activity, while the other shows stable, frequency-independent responses that maintain consistent inhibitory control. We demonstrate that this divergence is attributable to the expression of Elfn1, a transmembrane protein that recruits presynaptic mGluR7 and enhances facilitation. Interneurons expressing Elfn1 display facilitation, whereas those lacking Elfn1 respond uniformly across frequencies. Thus, identical presynaptic activity produces distinct inhibitory outputs depending on the molecular identity of the postsynaptic cell. This synapse-specific tuning diversifies inhibitory control in the dentate gyrus-CA3 pathway, balancing reliability and flexibility of inhibition. By combining whole-cell in-vitro recordings with detailed morphological reconstruction in wild type and Elfn1 KO animals, our work

delineates the cellular mechanisms that diversify interneuron responses and uncovers a novel coding strategy within the CA3 circuitry. These findings highlight how molecular heterogeneity within interneurons expands the computational capacity of hippocampal networks and shapes the transformation of dentate output during memory processing.

Disclosures: N. merlak: None. **K. Toth:** None.

Late-Breaking Poster

LBP055: B.04. Synaptic Transmission

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Program #/Poster #: LBP055.02/LBP027

Topic: B.04. Synaptic Transmission

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Title: Long Non-coding RNA MIAT Mediates Sex-specific Response to Interleukin-6 in Human iPSC-derived Dopaminergic Neurons

Authors: *Y. HUANG[1], C. MICHALSKI[2], Y. ZHOU[2], J. WANG[2], Y. FENG[3], A. MILLER[2], Z. WEN[2];
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Abstract: Introduction: Elevated inflammation is one of the mechanisms underlying motivational deficits in depression. Our previous work showed that inflammatory cytokine interleukin (IL)-6 led to sex-specific synaptic responses in human induced pluripotent stem cells (iPSC)-derived dopaminergic (DAergic) neurons as females mainly showed DA deficits while males demonstrated a compensatory phenotype. However, the molecular underpinnings underlying this sex difference is unclear. Long non-coding (lnc) RNAs, although lack the ability to produce protein, play crucial roles in many physiological processes including pathogenesis of neuropsychiatric disorders in a sexually dimorphic manner. Our data suggest that IL-6-induced differentially expressed genes (DEGs) in human DA neurons significantly overlap with target genes of the lncRNA *MIAT.* Moreover, healthy control male DA neurons had significantly higher expression of MIAT compared to females. Therefore, this study continues to investigate the effect of *MIAT* in mediating sex-specific responses to IL-6 in DA neurons via gene editing. **Materials & Methods**: Healthy (parental) male iPSC and its isogenic *MIAT* knock-out (KO) iPSC were differentiated into 8-week-old mature midbrain DA neurons. These DA neurons were then treated with vehicle or 5 ng/mL IL-6 for 24 hrs. To identify functional and transcriptomic changes in *MIAT* KO DA neurons, we first measured extracellular DA concentration, network

firing, velocity of synaptic vesicles (SVs), density, size, and docking of SVs at synaptic terminals as well as density of presynaptic terminals. We also performed RNAseq analyses including DEG, Gene Ontology, and sample level gene set enrichment in parental and isogenic DA neurons. **Results:** IL-6 treatment significantly reduced DA release, neuronal firing, and density of docked SVs in *MIAT* KO DA neurons, which were insignificant in parental DA neurons. In addition, many compensatory phenotypes observed in parental male DA neurons were blunted in *MIAT* KO neurons. Moreover, RNAseq analyses suggest significantly altered pathways related to inflammatory response and synaptic function in *MIAT* KO male DA neurons, compared to parental control. The *MIAT* KO DA neurons also had distinct transcriptomic changes in response to IL-6. **Conclusion:** Synaptic deficits that were insignificant in healthy males emerged after knocking out *MIAT* in male DA neurons, mimicking phenotypes in healthy female DA neurons. These together suggest that *MIAT* mediates sex-dependent responses to inflammation potentially via regulating inflammatory and synaptic pathways in human DA neurons.

Disclosures: Y. Huang: None. **C. Michalski:** None. **Y. Zhou:** None. **J. Wang:** None. **Y. Feng:** None. **A. Miller:** None. **Z. Wen:** None.

Late-Breaking Poster

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Topic: B.04. Synaptic Transmission

Support: German Research Foundation (DFG) – EXC-2049 – 390688087
European Commission - ERC Advanced Grant "SynapseBuild"
DFG-ANR collaborative grant (HA2686/20-1)

Title: Mechanical control of neurotransmission via a disordered endocytic protein domain

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Abstract: Sensing the physical state of cell membranes is of central importance for biological processes ranging from multicellular development, cell motility, and mechanosensation to cytokinetic abscission. Whether and how small synapses of central nervous system neurons can sense local alterations in the physical state of cell membranes triggered by the exocytic fusion of synaptic vesicles (SVs) during neurotransmission is unclear. We show that neurotransmission is controlled by sensing vesicle fusion-triggered changes in membrane properties via the phase-separating intrinsically disordered region (IDR) of the endocytic protein FBP17. Exocytosis-induced alterations in membrane packing are translated into changes in FBP17 conformation and oligomerization-dependent endocytic membrane remodelling, revealing a mechanism of mechanotransduction wherein the IDR of FBP17 directly senses the physical properties of the membrane. Loss of FBP17 or its ability to sense membrane mechanics leads to endocytic defects,

increased spontaneous vesicle fusion, and failed network synchronization in engineered human neurons. Our results unravel a molecular mechanism for the mechanical control of neurotransmission that enables synapses to maintain plasma membrane homeostasis and to plastically adapt network properties. We predict similar mechanisms to operate at other subcellular sites and in other types of exo-endocytosis in diverse cells and tissue and, possibly, in membrane traffic in general.

Disclosures: V. Haucke: None.

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Title: GluN2D-containing NMDARs on hippocampal GABAergic terminals modulate inhibitory tone

Authors: *I. WITTEVEEN[1,2], T. G. BANKE[2], V. OLAH[3], R. E. PERSZYK[2], T. T. NGUYEN[2], E. ULLMAN[2], M. J. ROWAN[3], S. F. TRAYNELIS[2];
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Abstract: NMDA receptors (NMDARs) mediate a slow Ca2+ permeable component of excitatory synaptic transmission in the central nervous system and serve multiple roles such as neuronal migration, synapse maturation, learning and memory, and information processing. NMDAR dysfunction has been hypothesized to contribute to neuropathological aspects of Alzheimer's, epilepsy, schizophrenia, and depression. NMDARs are tetrameric assemblies of 2 GluN1 and 2 GluN2 subunits, which has four subtypes (GluN2A-D). While many studies have explored the roles of GluN2A and GluN2B, GluN2D has not been as extensively studied, and its role in circuit function is poorly understood. Here we focus on localization and function of this subunit in hippocampal circuits. Hippocampal pyramidal neurons in the CA1 region receive both excitatory inputs from CA3 pyramidal neurons and inhibitory inputs from CA1 PV basket interneurons, thus making them useful for studying the contribution of GluN2D-containing NMDARs to circuit function. We performed patch clamp recordings of miniature inhibitory post-synaptic currents (mIPSCs) from CA1 pyramidal cells, mIPSC frequency could be

modulated by novel pharmacological tools (+)EU1180-453 and NAB14, which are highly selective for GluN2D-containing NMDARs. CA1 pyramidal cells in slices from PV-specific GluN2D knockout mice were insensitive to GluN2D selective modulators, suggesting a presynaptic regulatory role of GluN2D-containing NMDARs on vesicular release from pre-synaptic PV interneuron boutons. Blocking glutamate reuptake by astrocytes increased the frequency of mIPSCs onto CA1 pyramidal cells but not in CA1 pyramidal cells recorded in the presence of an NMDAR antagonist, indicating presynaptic GluN2D-containing NMDARs modify GABAergic release in response to changes in extracellular glutamate. Ketamine, an NMDAR pore blocking anesthetic, provides a fast-acting and durable anti-depressant effect when administered to patients at low-doses. Ketamine application during patch clamp recordings of CA1 pyramidal cells altered mIPSC frequency, which may underlie some actions by which ketamine exerts its anti-depressant effect. This effect was abolished in slices from mice that lack GluN2D in PV interneurons. Administration of systemic ketamine or the GluN2D selective inhibitor NAB-14 24 hours prior to slice preparation enhanced theta-burst induced LTP in CA1 compared to vehicle, which was lost in recordings from slices from mice that lack GluN2D in PV interneurons. Given that the GluN2D-selective modulators are able to alter circuit inhibition in a manner similar to ketamine, they may be able to provide similar therapeutic effects.

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Topic: B.04. Synaptic Transmission

Support: NIH R01 AG057052

Title: TrkB signaling modulates neuromuscular transmission in mice in a frequency dependent manner

Authors: *B. CRUM[1], R. MARTINEZ[1], H. M. GRANSEE[2], G. C. SIECK[2], C. B. MANTILLA[3];

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Abstract: Neurotrophin signaling plays an important role in modulating cholinergic transmission at neuromuscular junctions. Signaling via the tropomyosin-related kinase receptor subtype B (TrkB) enhances acetylcholine release during repetitive activation. Multiple conditions show selective effects on the most forceful and fatigable motor units that require high frequency activation and are necessary for maximal force generation. TrkB signaling can be disrupted possibly in a motor unit type specific manner. The goal of the present study is to investigate the effects of inhibiting TrkB kinase activity on neuromuscular transmission during repeated stimulation at frequencies that reflect the recruitment of different diaphragm motor units (10 vs. 75 Hz) in mouse diaphragm muscle. $TrkB^{F616A}$ mice, which possess a mutation that renders TrkB kinase activity susceptible to rapid inhibition by 1NMPP1, were used at 6-8 months old (n = 12; 6 females). Diaphragm muscle preparations with intact phrenic nerve were dissected and contractile properties, including maximum twitch and tetanic forces, were collected. Following 1 hour treatment with vehicle or 1NMPP1, the contribution of neuromuscular transmission failure (NMTF) to muscle fatigue was estimated. In the muscle/nerve preparations, the phrenic nerve was repeatably stimulated at either 10 or 75 Hz for 2 minutes with interposed direct diaphragm muscle stimulation every 15 s, with the difference in forces evoked by nerve and muscle stimulation being used to estimate NMTF. There was no effect of 1NMPP1 treatment on muscle contractile properties, but there was a frequency-dependent effect of 1NMPP1 treatment on NMTF. With repeated stimulation at 10 Hz, NMTF did not change following 1NMPP1 treatment compared to vehicle (~25%). At 75 Hz, 1NMPP1 increased NMTF compared to vehicle (~60% % ~50%, respectively), reflecting a frequency-dependent impairment in neuromuscular transmission following TrkB kinase inhibition with 1NMPP1. The role of TrkB signaling in modulating neuromuscular transmission reflects frequency-dependent properties. The greater negative effect of TrkB kinase inhibition during higher frequency stimulation suggests reliance on BDNF/TrkB signaling for sustained activation predominantly at higher force, more fatigable motor units which are responsible for the high forces necessary for airway clearance (i.e., coughing and sneezing). Disruption of TrkB signaling may thus underlie the motor unit type selective effects evident in conditions such as aging or spinal cord injury where neuromuscular dysfunction is present and responsible for the increased susceptibility to respiratory compromise.

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Support: NIH Grant NS091546
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Title: Resolving synaptic events using subsynaptically targeted GCaMP8 variants

Authors: ***J. CHEN**[1], J. LIN[2], K. HE[3], L. WANG[7], Y. HAN[4], C. QIU[5], D. K. DICKMAN[6];
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Abstract: Genetically encoded calcium indicators (GECIs) are powerful tools for monitoring neural activity, but their speed and sensitivity have traditionally lagged behind chemical dyes and electrophysiology. To overcome these limitations, we developed a new suite of GCaMP8-based sensors, specifically localized to presynaptic boutons, active zones, and postsynaptic compartments at the *Drosophila* neuromuscular junction. We first confirmed that these sensors outperform previous versions in sensitivity and kinetics. We then created **CaFire**, a Python-based analysis tool for automated detection and quantification of both evoked and spontaneous Ca^{2+} signals. Using CaFire, we demonstrate that a ratiometric presynaptic GCaMP8m sensor detects physiological Ca^{2+} transients with higher sensitivity and kinetics comparable to synthetic dyes. Additionally, we test the ability of an active zone-targeted GCaMP8f sensor to reveal differences in Ca^{2+} dynamics across release sites. Finally, a novel postsynaptic GCaMP8m, positioned near glutamate receptors, resolves quantal events with precision matching electrophysiological recordings. Together, these next-generation GCaMP8 sensors and analytical tools bridge the gap between genetic indicators and traditional methods, enabling high-resolution synaptic Ca^{2+} imaging with unprecedented sensitivity and speed.

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Topic: B.04. Synaptic Transmission

Support: NSFC 82188101
NSFC 32494762

Title: Percolation of the postsynaptic molecular network: discroveries from in vitro reconstituted PSD condensates and applications on in vivo native PSD assemblage

Authors: *S. ZHU[1], **Y. CHEN**[2];
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Abstract: The postsynaptic densities (PSDs) are electron-dense molecular compartments beneath the postsynaptic membrane, enriching synaptic receptors, signaling enzymes, and are required for synaptic transmission and plasticity. The PSD compartments are assembled via multivalent specific protein-protein interactions among scaffolds. Biochemically purified PSDs from mouse brains behave as detergent-resistant, amorphous gel-like aggregates, but could be reversibly regulated. Our previous studies have demonstrated the phase separation of PSD molecules forming condensed droplets similar to purified PSDs *in vitro*. Using single-molecule tracking (SMT) technique, we observe the unique diffusion behavior of PSD molecules within condensates distinct from Brownian motion in dilute solution. Such diffusion behavior indicates the formation of a mesoscale system-spanning molecular network (percolated network) within the PSD condensate. According to the percolation theory from physics, we design molecular strategies targeting specific interaction nodes to modulate the overall network stability, material properties, and molecular dynamics of reconstituted PSD condensates. We further applied the designed strategies to native PSDs in cultured living neurons. SMT analysis of PSD molecules (e.g. GluA1, PSD-95) also demonstrates the unique diffusion behavior similar to the observations within *in vitro* percolated condensates. Via disrupting or enhancing the interaction nodes between PSD scaffolds, the dynamics of synaptic receptors and scaffolds are significantly changed, indicating the formation of the percolated molecular network within native PSDs. Furthermore, weakening or disrupting the percolated molecular network in native PSDs would perturb the synaptic transmission and plasticity. In summary, our observations from i*n vitro* reconstituted PSD condensates demonstrate the percolation of PSD molecular network in native PSD assemblage.

Disclosures: S. Zhu: None. **Y. Chen:** None.

Late-Breaking Poster

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Program #/Poster #: LBP055.08/LBP033

Topic: B.04. Synaptic Transmission

Title: Cognitive and Emotional Consequences of Neonatal Exposure to Elevated Phenylalanine in Adult Mice

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Abstract: Cognitive and Emotional Consequences of Neonatal Exposure to Elevated Phenylalanine in Adult Mice
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Phenylketonuria (PKU) is a genetic metabolic disorder caused by elevated phenylalanine (Phe) levels in the blood and brain. If untreated during early infancy, Phe accumulation leads to irreversible cognitive deficits, highlighting the heightened vulnerability of the neonatal brain. However, the direct effects of neonatal Phe exposure on brain development remain unclear. Here, we demonstrate that repeated administration of Phe to neonatal wild-type mice, twice daily for two weeks beginning at postnatal day 5, impairs cognitive and emotional behaviors in adulthood. Phe-exposed mice exhibited deficits in object location memory and reduced open field activity at 12 weeks of age. Notably, female, but not male, mice displayed increased immobility in the tail-suspension test. Electrophysiological recordings revealed that perfusion of L-Phe at concentrations observed in the cerebrospinal fluid of PKU patients modified NMDAR-mediated signaling at hippocampal Schaffer collateral-CA1 synapses in neonatal mice. These findings indicate that elevated Phe perturbs excitatory neurotransmission, disrupts normal brain development, and results in persistent behavioral and cognitive deficits.

Disclosures: J. Lim: None. **W. Song:** None. **L. Kim:** None. **M. Kim:** None.

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Topic: B.04. Synaptic Transmission

Support: 1ZIANS003140-11

Title: The intracellular domain of neuroligin-3 translocates to the nucleus and regulates gene expression

Authors: *K. F. MCDANIEL, T. H. DO, K. W. ROCHE;
National Institutes of Health, Bethesda, MD

Abstract: Neuroligin-3 (NLGN3) is an X-linked transmembrane protein that was first identified as a synaptic adhesion molecule critical for the formation, function, and maintenance of synapses. While the vast majority of NLGN3 research has been performed in the context of synaptic adhesion, NLGN3 also undergoes activity-driven ectodomain cleavage. This cleavage results in at least two fragments - a soluble extracellular domain (ECD) present in the extracellular space, and an intracellular domain (ICD), which remains in the cell. The ECD of NLGN3 has been well characterized as a potent mitogen for glioblastoma, an incurable brain cancer. In contrast, not much research been done to investigate the role of the ICD. To characterize the ICD of NLGN3 post-ECD cleavage, we sought to investigate the cleavage pathway in both heterologous cells and primary cortical neuron cultures using immunoblots. Upon inducing cleavage of NLGN3, we discovered a significant increase in an approximately 20

kDa doublet band, the NLGN3 C-terminal fragments (CTFs). To investigate further intracellular cleavage events, we pre-treated with DAPT, a gamma-secretase inhibitor, and detected an increased amount of the CTFs. Here, we established that NLGN3 undergoes a sequential cleavage process, first mediated by metalloproteases cleaving in the extracellular domain, then by gamma-secretase cleaving in the membrane to release the ICD. To determine the localization of these fragments, we induced cleavage in heterologous cells and performed immunocytochemistry. We found a significant increase in NLGN3 ICD localization in the nucleus following cleavage as compared to vehicle treated controls. Additionally, we used truncations of NLGN3 to overexpress the ICD alone and found a significant increase in ICD localization to the nucleus in both heterologous cells and primary hippocampal neuron cultures. To investigate the role of the NLGN3 ICD in the nucleus, we performed whole cell RNA sequencing from cells overexpressing the NLGN3 ICD, compared to controls, and found multiple interesting genes that are upregulated with NLGN3 ICD expression. Current experiments include characterizing the precise mechanisms of NLGN3 ICD transcriptional regulation in both physiological and pathological conditions. Together, these data reveal a novel and unexpected role for NLGN3 as a critical intracellular regulator of transcription and provide new avenues to investigate NLGN3 related pathologies and therapeutics.

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Topic: B.04. Synaptic Transmission

Support: NIH Grant MH113645
Allen Distinguished Investigator Award

Title: Blood-derived extracellular vesicles rescue mPFC inhibitory synaptic deficits via microRNA-mediated mechanisms

Authors: *M. MIRRAMEZANIALIZAMINI[1], J. FRANCIS-OLIVEIRA[1], P. GARCIA[1], E. DOHI[2], K. MATOBA[1], S. KANO[3];
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Abstract: Extracellular vesicles (EVs) are emerging as critical mediators of intercellular communication, shaping synaptic development, plasticity, and homeostasis. Yet, their role in modulating inhibitory circuits in neurodevelopmental disorders remains poorly defined. Here, we identify blood-derived extracellular vesicles (bEVs) as regulators of inhibitory synaptic transmission in the medial prefrontal cortex (mPFC) across multiple mouse models with social

behavioral deficits. Rag1-/- mice, lacking functional T and B cells, exhibited impaired sociability and reduced spontaneous inhibitory postsynaptic current (sIPSC) amplitude in mPFC pyramidal neurons. Systemic delivery of wild-type (WT) bEVs rescued both behavioral and synaptic deficits. Mechanistically, Rag1-/- bEVs showed reduced levels of miR-23a-3p and miR-103-3p, microRNAs regulating GABA_A receptor signaling. Supplementation of these miRNAs in Rag1-/- mice restored inhibitory transmission, supporting a causal role. Parallel experiments in mPFC pyramidal neurons of Cntnap2-/- and Shank3-/- mice revealed a shared inhibitory synaptic phenotype, with WT bEVs rescuing sIPSC deficits. Strikingly, bEVs lacking miR-23a-3p failed to restore synaptic or behavioral functions, highlighting the miRNA-dependent nature of this rescue effect. Together, these findings uncover a previously unrecognized role for circulating miRNAs in tuning inhibitory synaptic transmission and behavior. By restoring GABAergic balance in mPFC, bEVs miR-23a-3p emerges as a key modulator of circuit dysfunction in neurodevelopmental disorders, with implications for broader therapeutic strategies. Future studies will investigate whether excitatory postsynaptic currents exhibit parallel synaptic phenotypes and respond to bEV modulation.

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Late-Breaking Poster

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Topic: B.04. Synaptic Transmission

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EE250301

Title: SK Channel Dysfunction Underlies Excessive Neurotransmission in Fragile X Syndrome Mouse

Authors: *T. WU, T. XIAO, Y. DARWISH, H. HUANG;
Tulane University, New Orleans, LA

Abstract: Fragile X syndrome (FXS) is the most prevalent inherited cause of intellectual disability and the most common monogenic cause of autism spectrum disorder (ASD), resulting from silence of *FMR1* gene and loss of Fragile X Messenger Ribonucleoprotein (FMRP). Among other deficits, FXS patients and *Fmr1* knockout (KO) animals demonstrate auditory hypersensitivity and impaired sound localization. FMRP is extensively expressed in the auditory brainstem, including the medial nucleus of the trapezoid body (MNTB), a nucleus critical for sound localization. Here, we investigated neurotransmission dysfunction of the MNTB of *Fmr1* KO mice. Under normal conditions, globular bushy cell inputs reliably drive one-to-one spiking of MNTB principal neurons via the calyx of Held synapse. In *Fmr1* KO mice, both ex vivo and

in vivo, this reliability was disrupted, with one presynaptic stimulation often triggering multiple postsynaptic spikes. We observed reduced function of small-conductance calcium-activated potassium (SK) channels in MNTB neurons of *Fmr1* KO mice, due to the decreased calcium sensitivity. Normally, SK channels are activated by Ca^{2+} influx during action potential firing and contribute to the spike afterdepolarization (ADP). Pharmacological blockade of SK channels with apamin reproduced this phenotype without altering presynaptic release, whereas the SK channel opener 1-EBIO rescued reliable transmission. In vivo, *Fmr1* KO mice displayed elevated auditory brainstem response (ABR) wave IV amplitudes, reflecting hyperexcitability of the superior olivary complex. Systemic 1-EBIO administration, which crosses the blood-brain barrier, normalized ABR wave IV amplitudes to wild-type levels. These findings reveal a critical role for SK channel dysregulation in neurotransmission dysfunction in FXS and highlight SK channels as a potential therapeutic target.

Disclosures: T. Wu: None. **T. Xiao:** None. **Y. darwish:** None. **H. Huang:** None.

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Topic: B.04. Synaptic Transmission

Support: R01 MH085974
U19 NS123714 (AGC)

Title: Synaptic organization of anterior midline thalamic circuits

Authors: *N. DAO, A. G. CARTER;
Center for Neural Science, New York University, New York, NY

Abstract: The anterior midline thalamus (aMT) plays a key role in motivated behaviors such as reward seeking and threat conditioning. Previous studies have shown dense connections between the aMT and corticolimbic system, including the medial prefrontal cortex (mPFC), the nucleus accumbens (NAc), and the basolateral amygdala (BLA). While the aMT consists of multiple nuclei, most studies have focused the paraventricular thalamus (PVT). Consequently, the properties of different cell types across aMT, and their ability to receive and send different conditions, remains poorly understood. Here we combine anatomy and physiology to study the synaptic organization of specific nuclei within the aMT. First, we use retrograde and anterograde labeling to identify the distributions of defined cell types. Next, we use *ex vivo* recordings to assess the morphological and physiological properties of projection-specific populations. Lastly, we use optogenetics with *ex vivo* recordings to assess how afferents contact and drive these neurons. Together, our findings reveal unexpected molecular identity and synaptic connectivity of new circuits in the aMT.

Disclosures: N. Dao: None. **A.G. Carter:** None.

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Program #/Poster #: LBP055.13/LBP038

Topic: B.04. Synaptic Transmission

Support: NIH

Title: Integrating feeding and emotional information by GLP-1 signaling on lateral septal neurons

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Abstract: Depression and obesity are prevalent conditions with significant public health consequences that frequently co-occur within individuals. Current therapies of obesity based on glucagon-like peptide-1 (GLP-1), a gut-brain peptide encoded by the *Gcg* gene, effectively suppress appetite, reshape food preference and improve glucose metabolism. However, their clinical applications are associated with adverse effects such as nausea and vomiting, and by weight regain after treatment discontinuation. This is a critical gap in our understanding of how GLP-1 signaling regulates feeding and reward at the neural circuit level in the brain. Interestingly, the lateral septum (LS), which contains a larger population of GLP-1 receptor (GLP-1R) expressing neurons, is proposed to integrate signals related to food intake and affective state. To determine whether and how these neurons regulate food intake and affective state, we first employed single-cell sequencing, spatial sequencing, and immunostaining to cluster the LS neurons and found a novel subtype (co-expressing *Epha3*) of *Glp1r*$^+$ neurons. These neurons are in the caudal LS (LSc), the subregion of LS potentially contributing to anti-depression and food seeking. Secondly, we employed the ChR2-EYFP-based whole-brain mapping of *Glp1r*+ neurons in LSc and found that these neurons preferentially target forebrain cholinergic regions, including anterior substantia innominata (aSI). This region is both related to feeding and emotional behaviors. Next, we employed the whole-cell recording of neurons in aSI and optogenetic activation of fibers in aSI from LSc *Glp1r*$^+$ neurons. It suggests that ~70% neurons receive $GABA_A$ receptor-mediated inhibitory inputs from the LSc *Glp1r*$^+$ neurons. Importantly, the activation of GLP-1 receptors on these fibers by Exendin-4, a GLP-1 analog, amplified the inhibitory input strengths to ~300%. In summary, we found a novel subtype of *Glp1r*$^+$ neurons in LSc, which specifically inhibits forebrain cholinergic regions and its output is regulated by GLP-1 signaling. The findings will inform the design of targeted strategies with fewer side effects and contribute to a deeper understanding of how neuromodulators shape brain function relevant to obesity, ultimately alleviating obesity and mental disorders.

Disclosures: J. Li: None. **M. Yang:** None. **Z.P. Pang:** None.

Late-Breaking Poster

LBP056: B.05. Synaptic Plasticity

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP056.01/LBP039

Topic: B.05. Synaptic Plasticity

Support: HR00112320037

Title: Pharmacological Modulation of iTBS-Induced Cortical Plasticity Probed with TMS-EEG in Depression

Authors: *G. VARONE[1,2], S. RUSSO[3,4], P. GANESH[1], H. KIM[1,2], R. A. OZDEMIR[5,6], M. SHAFI[5,6], J. C. BROWN[1,2];
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Abstract: Major depressive disorder (MDD) affects more than 350 million people worldwide, with up to 30% of patients showing inadequate response to current treatments. Impaired synaptic plasticity is thought to underlie many treatment-resistant cases, underscoring the need for interventions that directly enhance cortical adaptability. **Intermittent theta burst stimulation (iTBS)** of the left dorsolateral prefrontal cortex (dlPFC) is a promising noninvasive intervention that modulates prefrontal-limbic circuitry, but clinical outcomes remain variable, partly because the underlying neurophysiological mechanisms are still poorly understood. **TMS-EEG** offers a direct, temporally precise way to probe these mechanisms. TMS-evoked potentials (TEPs) reflect cortical excitability, a physiological substrate of plasticity, and thus provide a useful readout of stimulation-induced reorganization. **Pharmacological augmentation** with agents such as D-cycloserine (DCS), a partial NMDA receptor agonist, may further enhance or stabilize plasticity by targeting receptor-level mechanisms. In this randomized, double-blind study, thirteen adults with MDD (mean age 39.3 ± 15.2 years) received either 250 mg DCS or placebo the night before a single day of **accelerated iTBS** (10 sessions; 1,800 pulses each; 50-minute inter-session intervals). Cortical excitability was probed using single-pulse TMS-EEG before and after the 1st, 2nd, and 10th iTBS sessions. TEPs were analyzed in terms of both regional voltage amplitudes and canonical peak components (N15, P25, N40, P60, N100, P185, N200) to capture local and network-level dynamics. While the limited sample size precluded statistical significance after correction, exploratory analyses suggested distinct patterns: **(1)** DCS enhanced early TEP components (8-60 ms), consistent with increased postsynaptic excitability; **(2)** placebo+iTBS produced stronger late activity (180-210 ms), reflecting thalamocortical modulation; and **(3)** combined DCS+iTBS amplified both early and late components, compatible with metaplastic

interactions. Peak analysis suggest that early components (N15, N40) may index baseline pharmacological effects, whereas later components (N100, P185) are more sensitive to iTBS-induced plasticity. Taken together, these findings highlight the **potential of TMS-EEG to track cortical plasticity mechanisms** and suggest that pharmacological augmentation with DCS could modulate iTBS-induced excitability in MDD. Although preliminary, this work points toward strategies for refining neuromodulation approaches to improve treatment outcomes in depression and related disorders.

Disclosures: G. Varone: None. **S. Russo:** A. Employment/Salary (full or part-time); S.R. is the Chief Scientific Officer of Manava Plus. **P. Ganesh:** None. **H. Kim:** None. **R.A. Ozdemir:** None. **M. Shafi:** None. **J.C. Brown:** None.

Late-Breaking Poster

LBP056: B.05. Synaptic Plasticity

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Topic: B.05. Synaptic Plasticity

Support: NIH Grant R15AG065927 (TDO & DO)
KCOM Biomedical Graduate Program Grant (GJF & TDO)

Title: Redox-sensitive early long-term potentiation of glutamatergic signaling in a respiratory brainstem nucleus

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Abstract: The nucleus tractus solitarii (nTS) integrates peripheral chemoreceptor information to drive respiratory responses to hypoxia. Although glutamatergic transmission mediates this process at the first central synapse, it is not fully understood how repeated excitation shapes plasticity in the caudal nTS. Furthermore, oxidative stress in disease conditions can modulate glutamatergic signaling, but its impact on respiratory-related plasticity is not well defined. The present study asked whether repeated glutamatergic activation induces plasticity of respiratory responses *in vivo*, and whether this process is sensitive to oxidative modulation.
Respiratory activity was monitored via EMG electrodes implanted in the diaphragm. Nanoinjections of glutamate (20 nL, 40 mM) were delivered into the caudal nTS to assess respiratory responses to repeated stimulation. Oxidative stress was induced with H_2O_2 (40 nL, 37.5 mM) to the same nTS site. Channelrhodopsin was expressed in nTS neurons via AAV for optogenetic activation.
Acute bolus injection of glutamate into the caudal nTS evoked a transient increase in respiratory rate (RR) lasting ~35 sec with a peak increase averaging 13 breaths/min. Tidal volume remained

largely unchanged. The overall respiratory response (RR × duration) was then analyzed across repeated glutamate injections. Glutamate conditioning (3×, 5-min spacing) induced a potentiated respiratory response after a 10-min pause, with ~40% greater responses than to the initial injection ("pre-Max"). Continued glutamate stimulation (10×, 5-min spacing) maintained potentiation for ~20 min before responses gradually declined. Introducing an oxidative environment with a bolus of H_2O_2 after conditioning abolished response potentiation, reducing responses to ~70% of pre-Max. To test whether response potentiation depends on glutamatergic signaling, we used direct optogenetic stimulation of nTS neurons. Our preliminary data show no potentiation following light conditioning (3×, 5-min spacing), with responses ~85% of pre-Max. These data show that repeated glutamate stimulation of the caudal nTS induces a time-dependent and persistent potentiation of respiratory output. The effects are consistent with an early form of long-term potentiation (LTP). Absence of early LTP with optogenetic stimulation may suggest dependence on glutamatergic receptor signaling rather than intrinsic excitability of nTS neurons. Moreover, the absence of potentiation under oxidative conditions demonstrates a strong redox sensitivity, highlighting oxidative stress as a potential modulator of plasticity within the nTS during pathophysiological conditions.

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Late-Breaking Poster

LBP056: B.05. Synaptic Plasticity

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Program #/Poster #: LBP056.03/LBP041

Topic: B.05. Synaptic Plasticity

Support: NIH K99/R00 MH118425
T32NS045540
T32MH119049

Title: The VGCC auxiliary subunit α2δ-1 is an extracellular AMPAR interactor that regulates synaptic transmission and LTP at hippocampal synapses

Authors: *G. SANDOVAL[1], A. KOLLI[2], M. SANDOVAL[3], L. Y. CHEN[2], J. DÍAZ-ALONSO[4];
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Abstract: AMPA receptors (AMPARs) are the main mediators of fast excitatory synaptic transmission in the CNS. Activity-dependent trafficking of AMPARs and subsequent long-term synaptic strengthening underlie different forms of learning and memory. The current state of the literature posits that intracellular interactions regulate AMPAR trafficking and as of recent,

extracellular mechanisms have been proposed as a synergistic role in synaptic targeting of AMPARs. The AMPAR subunit GluA1 amino-terminal domain (ATD) is essential for synaptic AMPAR docking, but the precise mechanisms involved are not fully understood. Using unbiased proteomics, we identified the epilepsy and intellectual disability-associated VGCC auxiliary subunit α2δ-1 as an extracellular AMPAR slot, and confirmed that the GluA1 ATD is sufficient for α2δ-1 interaction. At CA1 synapses, postsynaptic deletion of α2δ-1 enhanced constitutive synaptic AMPAR-mediated currents. Conversely, presynaptic α2δ-1 deletion impaired AMPAR insertion during LTP. α2δ-1 deletion in Grik4-expressing cells resulted in impaired hippocampal-dependent memory, and decreased seizure susceptibility. Altogether, this study identifies α2δ-1 as an extracellular AMPAR interactor with contrasting pre- and postsynaptic roles, exerting dual regulation of synaptic AMPAR insertion: in *cis*, limiting AMPAR access to synapses; in *trans*, facilitating the incorporation of AMPARs recruited during LTP. These findings advance our understanding of how α2δ-1 shapes hippocampal synaptic function and reveal potential mechanistic insights underlying the actions of gabapentinoid drugs.

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Late-Breaking Poster

LBP056: B.05. Synaptic Plasticity

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP056.04/LBP042

Topic: B.05. Synaptic Plasticity

Title: 24 hours at the seat of memory formation: Circadian changes in PKA-dependent forms of long-term potentiation and depression

Authors: *S. ROUGE[1], A. JACOBI[2], Z. ZENG[2], X. XING[3], M. C. HORNE[4], J. W. HELL[5]; [1]University of California Davis, Davis, CA; [2]University of California, Davis, Davis, CA; [3]Department of Pharmacology, University of California, Davis, Davis, CA; [4]Pharmacology, Univerity of California, Davis, Davis, CA; [5]Department of Pharmacology, UC Davis, Davis, CA

Abstract: In mammalians, circadian rhythm regulates independently the memory process in hippocampus (Ruby et al., 2008). Protein phosphorylation fluctuates with Zeitgeber Time (ZT), modulating synaptic strength by promoting receptor trafficking, a key factor in hippocampal synaptic plasticity (Brüning et al., 2019).Our prior research identified a crucial post-synaptic protein super-complex for memory formation. This complex operates via norepinephrine (NE) binding to β2-adrenergic receptors (β2AR), triggering ATP-to-cAMP conversion by Protein Kinase A (PKA), which phosphorylates Cav1.2 at Serine1928 (Patriarchi et al., 2016; Qian et al., 2017). We hypothesize that NE's circadian-dependent release regulates synaptic plasticity through CaV1.2 activity.To assess ZT-dependent synaptic changes, we measured long-term potentiation (LTP) and depression (LTD) in the mouse hippocampus.Our results indicate a synchronized potentiation decrease in both forms of synaptic plasticity along the inactive phase

(ZT3-9, LTP -52%, LTD -26.7%), consistent with the NE decrease. During the inactive to active phase transition (when NE increase), LTP increase (ZT9-15, +22.87%), consistent with PKA expression and activity at the awaking of the mice (Wang et al., 2024). Furthermore, S1928A KI mutant mice, which lack LTD (Ireton et al., 2023), retain LTP, but it remains ZT-independent. These findings support S1928 phosphorylation role in circadian-regulated synaptic plasticity.

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Late-Breaking Poster

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Program #/Poster #: LBP056.05/LBP043

Topic: B.05. Synaptic Plasticity

Support: National Research Foundation of Korea (NRF), MSIT, No. RS-2024-00335928

Title: Realistic Dopamine-Modulated STDP Model of Pavlovian Learning in Spiking Neural Networks

Authors: *W. PARK, K. LEE;
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Abstract: Dopamine plays a central role in regulating synaptic plasticity by modulating both long-term potentiation (LTP) and long-term depression (LTD). Within the framework of the three-factor learning rule, dopamine-modulated spike-timing-dependent plasticity (STDP) has been proposed as a mechanism by which animals reinforce neural activity linked to dopaminergic reward signals [Izhikevich, 2007]. However, experimental findings [Zhang, 2009] show that high dopamine levels can convert LTD-inducing protocols into LTP, a phenomenon not captured by the classical Izhikevich model and motivating the need for a revised framework. Here, we propose a modified rule in which elevated dopamine shifts plasticity toward potentiation by converting LTD into LTP, in contrast to the classical model where both LTP and LTD are uniformly enhanced. We implement this rule in a spiking neural network of Izhikevich neurons trained to discriminate external stimuli delivered to a subpopulation of neurons. The network successfully forms associations, as only dopamine-paired inputs to a particular target subpopulation establish a strong feedforward architecture capable of eliciting reliable, global population bursts. Notably, this organization emerges only within an optimal dopamine range (0.05-0.70 μM). At concentrations exceeding 0.70 μM, dopamine destabilizes network dynamics and disrupts feedforward organization, preventing global burst generation. In sharp contrast, the classical model supports learning even under unrealistically high dopamine levels (e.g., ~30 μM), well beyond biologically plausible conditions.

References

Izhikevich, E. M. (2007). Solving the distal reward problem through linkage of STDP and

dopamine signaling. *Cerebral cortex*, *17*(10), 2443-2452.
Zhang, J. C., Lau, P. M., & Bi, G. Q. (2009). Gain in sensitivity and loss in temporal contrast of STDP by dopaminergic modulation at hippocampal synapses. *Proceedings of the National Academy of Sciences*, *106*(31), 13028-13033.

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Late-Breaking Poster

LBP056: B.05. Synaptic Plasticity

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Topic: B.05. Synaptic Plasticity

Support: National Research Foundation of Korea(NRF) grant funded by the Korea government(MSIT) (No. RS-2024-00335928)

Title: Dopamine and acetylcholine shape memory encoding through triplet STDP in recurrent networks

Authors: *I. JEONG[1], K. LEE[2];
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Abstract: Memory encoding and retrieval are thought to depend on cell assemblies—strongly interconnected groups of neurons. Previous work suggested that the interplay of Hebbian and "fast homeostatic" plasticity could support such assemblies, but the timescale of this mechanism is inconsistent with most experimental findings. By contrast, neuromodulator-dependent modulation of Hebbian plasticity operates on comparable timescales, pointing to a potential role in assembly formation, although its underlying mechanisms remain unclear. Here we introduce a neuromodulator-modulated triplet STDP model informed by in vitro data from hippocampal neurons. In agreement with slice experiments, acetylcholine (ACh) and dopamine (DA) induced LTD and LTP, respectively, for pre-post spike pairs. To assess network-level consequences, we implemented the rules in a recurrent network of leaky integrate-and-fire neurons stimulated with spike-train representations of MNIST images. DA reward was delivered globally with a 1-s delay only for a target image, while ACh concentration was modeled as a sigmoidal function of overall firing activity. We then examined changes in connectivity and firing dynamics across repeated presentations. This mechanism robustly promoted the emergence of cell assemblies. Without DA, only strong inputs formed assemblies; DA lowered the threshold, enabling even weak inputs to do so. Critically, ACh prevented runaway network activity by suppressing the "quadratic LTP component" of triplet STDP. Together, these results suggest that the coordinated action of DA and ACh provides a key mechanism for balancing selectivity and stability in memory circuits.

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Late-Breaking Poster

LBP056: B.05. Synaptic Plasticity

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Program #/Poster #: LBP056.07/LBP045

Topic: B.05. Synaptic Plasticity

Support: DFG Grant SFB1286/A9

Title: Presynaptic protein synthesis - quantitative ultrastructural analysis of presynaptic ribosomes

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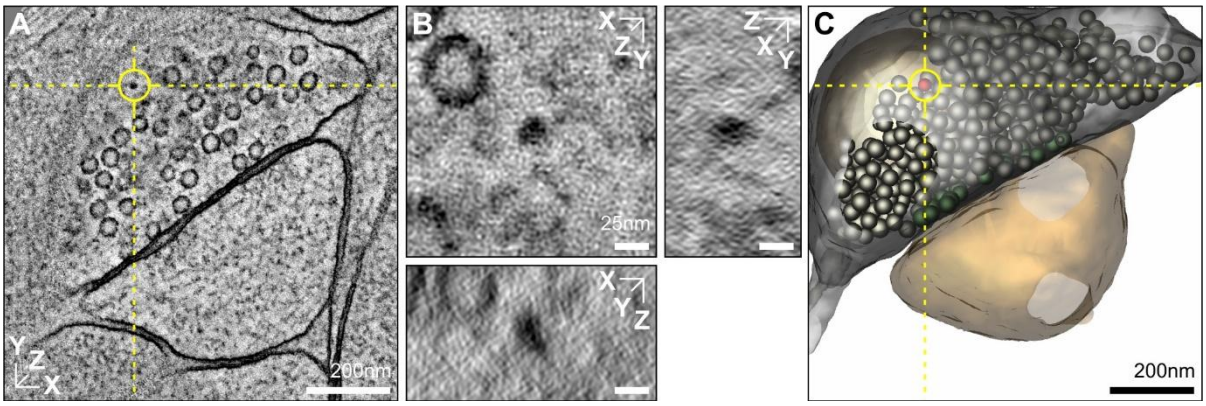
Abstract: Neurons signal via synapses, which consist of a presynaptic neurotransmitter-releasing and a postsynaptic sensing compartment. Long-term changes in synapse strength, which are essential for memory formation, require newly synthesized synaptic proteins to alter synaptic signalling efficacy (PMID 17418795, 30315172, 12165474). While local postsynaptic protein translation modulates synapse strength (PMID 12165474, 7062109, 11283313), the existence of local presynaptic protein translation is still debated. Indeed, there is no convincing ultrastructural evidence that ribosomes - the protein translation machines - are present in presynaptic compartments. We quantified ribosome abundance in hippocampal presynapses using high-resolution 3D ultrastructural imaging, combining near-native preservation of synaptic ultrastructure and the capture of large fractional volumes of presynaptic boutons. Rough ER served as a positive control to define the signal-to-noise and contrast profiles of identified ribosomes. We quantified presynaptic monosomes in three hippocampal synapse types that had previously been linked to presynaptic protein synthesis based on light microscopic studies - Schaffer collateral (PMID 31097639), mossy fiber-CA3 (PMID 35728596),and perisomatic (PMID 27764673) synapses. Our analysis revealed a much lower abundance of presynaptic ribosomes than previously estimated, theoretically compatible only with minor functionally relevant plasticity-linked protein synthesis. Further analyses, supported by a newly developed deep-learning-based tool for semi-automated segmentation of electron micrographs, SynapseNet (PMID 40875337), yielded only partial evidence for a correlation between morphological synapse-strength indicators (e.g. relative occupancy of presynaptic boutons by mitochondria) and presynaptic ribosome abundance. This observation and the general sparsity of presynaptic ribosomes indicate that local presynaptic protein synthesis is very substantially limited by ribosome availability.



Disclosures: F. Moschref: None. **V. Schwarze:** None. **S. Muth:** None. **O. Kovtun:** None. **C. Pape:** None. **N. Brose:** None. **B.H. Cooper:** None.

Late-Breaking Poster

LBP057: B.06. Intrinsic Membrane Properties and Signal integration

Location: SDCC Hall B

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Program #/Poster #: LBP057.01/LBP046

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

Support: NIDA Grant DA057776
NIDA Grant 2T32DA007244-36

Title: Heroin withdrawal induces cfos expression in the lateral habenula

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Abstract: The prevalence of opioid use, particularly heroin, has contributed to a national crisis of opioid abuse and overdose deaths. One key factor driving continued heroin use is the difficulty in managing withdrawal symptoms, which can lead to relapse and sustained substance use. Previous research has demonstrated that heroin exposure and withdrawal directly influence brain function and behavioral phenotypes associated with stress. Specifically, heroin withdrawal enhances fear learning in a rat model of stress-enhanced fear learning (SEFL), a mechanism involving dorsal hippocampus astrocytes (Parekh et al., 2020; 2024). Separately, previous work has indicated that withdrawal from cocaine and ethanol leads to increased cellular activation in the lateral habenula (LHb), as well as changes in synaptic plasticity and glial function (Clerke et al., 2021). However, the effects of opioid withdrawal are unclear. Given this gap in knowledge,

the aim of the present study is to explore the role of heroin administration and withdrawal on lateral habenula activity. Male rats were administered either saline or an increasing concentration of heroin across a 10-day period, similarly as described (Parekh et al., 2020), followed by immunohistochemistry for cfos, dfosB, and GFAP in the lateral habenula, medial habenula, and dorsal hippocampus. A significant increase in cfos activation was observed in the lateral habenula in heroin-withdrawn rats at 24h, but not 0h after the last administered dose. No effect of heroin or time was observed on cfos induction in the medial habenula or dorsal hippocampus. Ongoing studies are in progress to measure GFAP expression, and future studies will be employed to address the functional role of the lateral habenula in SEFL.

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Late-Breaking Poster

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

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Title: Enhanced distal input signaling in human hippocampal neurons despite lower intrinsic excitability

Authors: *T. BUTOLA[1], V. ROBERT[2], O. M. BILASH[3], K. M. O'NEIL[4], A. SEEDAT[5], S. DEVORE[6], R. TOMER[7], I. SEGEV[8], O. DEVINSKY[5], J. BASU[9];
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Medicine, Brooklyn, NY; [7]Columbia University, New York, NY; [8]Safra Center for Brain Sciences, Hebrew University, Jerusalem, Israel; [9]Department of Neuroscience and Physiology, NYU Neuroscience Institute, New York, NY

Abstract: In humans and other mammals, the hippocampus and entorhinal cortex are critical for episodic memory and spatial navigation, and central to the pathophysiology of temporal lobe epilepsy (TLE)—the most common drug-resistant epilepsy. Yet our understanding of cortico-hippocampal circuit signaling and subregion-specific neuronal function is largely based on rodent studies, which may not fully model human features. Here, we combined patch-clamp electrophysiology, fluorescence immunohistochemistry, and high-resolution confocal and light-sheet microscopy to compare freshly resected hippocampal tissue from TLE patients to healthy mouse hippocampus. We found striking species- and region-specific differences in neuronal structure and function. Human hippocampal neurons are intrinsically less excitable than mouse neurons—requiring more current to fire—but paradoxically show higher action potential firing rates. Human neurons more effectively preserve long-range cortico-hippocampal signal propagation along their extensive dendritic arbors to the soma. Neurons in each hippocampal sub-region display distinct activity-dependent synaptic plasticity dynamics. Morphologically, human neurons are larger with more elaborate and diverse dendritic branching patterns, suggesting enhanced synaptic integration and transmission. Our findings reveal fundamental cross-species differences in hippocampal neuronal properties between humans and mice, underscoring the need to directly study single neuron functional dynamics of the human brain to understand disease mechanisms and develop more effective therapies for neurological patients.

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Late-Breaking Poster

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Program #/Poster #: LBP057.03/LBP048

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

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ExCELLS (23S2)
EM Facility of the NIPS

Title: Compartmental modeling of the whole-cell activity of wake-promoting orexin neurons shows robust reduction in firing rate after sleep deprivation-induced astrocytic inhibition of excitatory inputs

Authors: *C. SOZUER[1], V. PANDEY[2], Y. KUBOTA[3], K. SEMBA[1];
[1]Dalhousie University, Halifax, NS, Canada; [2]University of Osaka, Osaka, Japan; [3]Natl Inst Physiol Sci, Okazaki, Japan

Abstract: Sleep/wake states are regulated by multiple groups of neurons, and orexin neurons are recognized as major players in promoting wakefulness. We previously showed that six hours of sleep deprivation induces astrocyte-mediated presynaptic inhibition of excitatory inputs to orexin neurons and withdrawal of perisynaptic astrocytic processes at synapses onto orexin neurons (astrocyte withdrawal) (Briggs et al., 2018, JNeurosci; Semba et al., 2023, SfN). Follow-up computational modeling predicted that astrocyte withdrawal leads to presynaptic inhibition of these excitatory synapses. While these synaptic alterations could serve as a sleep-homeostatic mechanism by attenuating orexin neuron activity, the impact of these synaptic alterations remains unknown. We developed the first detailed conductance-based compartmental model of an orexin neuron to predict how the observed alterations in excitatory synaptic inputs affect the firing activity of orexin neurons. Implemented in the NEURON simulator, the model replicates a wide range of electrophysiological behaviors of orexin neurons. We drove this orexin neuron model with excitatory postsynaptic currents generated by our computational synapse model and representing different degrees of astrocyte withdrawal, and we observed a corresponding reduction in the firing rate of orexin neurons. This reduction was robust to random perturbations to neuronal parameters and to the inclusion of additional sleep-deprivation-induced changes in orexin neurons. To understand how astrocyte withdrawal impacts different input structures, we further drove the model with excitatory synaptic inputs of varying synchrony. By linking astrocyte withdrawal to the firing activity of orexin neurons, we extended our previous synaptic modeling to a multiscale framework that suggests a role for nanoscale synaptic-level changes as a potential cellular mechanism for regulating sleep need and sleep homeostasis.

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Late-Breaking Poster

LBP057: B.06. Intrinsic Membrane Properties and Signal integration

Location: SDCC Hall B

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Program #/Poster #: LBP057.04/LBP049

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

Title: Heterogeneous responses of supraoptic magnocellular neurons to acute hypertonicity

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Abstract: Hypertonicity induces structural, functional, and genetic changes in supraoptic nucleus (SON) neurons. Genetic evidence suggests subpopulations with distinct osmotic sensitivities; however, their electrophysiological profiles remain unclear. Here, we investigated the electrical properties of vasopressinergic magnocellular neurons under basal conditions and following acute hypertonic stimulation to identify potential subpopulations. We performed patch-clamp recordings in hypothalamic slices from 8-week-old genetically modified mice (IRES-AVP/OT-CRE), following institutional animal care approval (#2683090524). In both males and females, a subset of VP neurons displayed increased firing frequency during hypertonic challenge (Female: Control =2.59 ± 0.77; Hypertonic = 4.18 ± 0.81; Wash = 3.11 ± 1.1 n =10, $p< 0.05$; Male 2.05 ± 0.7; Hypertonic = 3.9 Hypertonic = 0.7; Wash = 2.78 ± 0.9; n = 10 $p< 0.05$). In females, this was accompanied by a depolarization of the resting membrane potential (Control = -65.7 ± 2.45; Hypertonic = -60.6 ± 0.1.5; Wash = -66 ± 2.3 n =10; $p<0.05$), whereas males showed no significant changes. Input resistance remained stable across all conditions. Strikingly, a distinct subpopulation of VP neurons exhibited no alterations in firing activity or membrane potential, remaining silent even under hypertonic stimulation, with input resistance also unaffected. These findings reveal functional heterogeneity within SON VP neurons, highlighting subpopulations with differential sensitivity to osmotic stress. Ongoing work aims to increase sample size and incorporate single-cell transcriptomic profiling to directly link molecular identity with electrophysiological phenotype. Together, our results advance the understanding of osmoregulatory mechanisms and may uncover novel molecular markers underlying magnocellular neuron diversity.

Disclosures: M.P. Silva: None. **J. Nogueira lima:** None. **K. Martins dos Santos:** None.

Late-Breaking Poster

LBP057: B.06. Intrinsic Membrane Properties and Signal integration

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP057.05/LBP050

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

Title: Electrophysiological effect of focused ultrasound on hippocampal neurons

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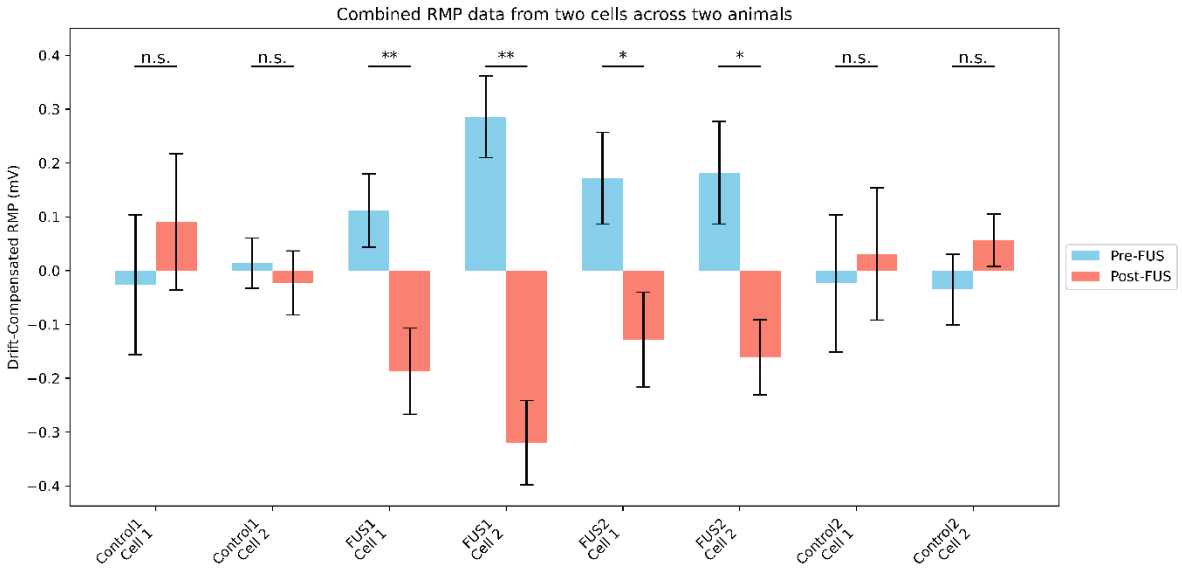
Abstract: Focused ultrasound (FUS) is emerging as a non-invasive method for modulating neuronal activity, but conditions for consistent effects remain unclear. Prior studies suggest

ultrasound can alter action potential properties and membrane dynamics, yet direct evidence from patch clamp recordings in mammalian brain tissue is limited. In this unblinded pilot study, we tested how 10 MHz FUS affects hippocampal CA1 pyramidal neurons using whole-cell patch clamp recordings. Sagittal brain slices (200 um) were prepared from wild-type C57BL/6 mice aged postnatal days 21-35. Both sexes were used, although sex differences were not assessed. All procedures were approved by the University of Melbourne Animal Ethics Committee. Recordings were obtained with borosilicate pipettes (3-5 MOhm) and a Multiclamp 700B patch clamp amplifier. A 10 MHz transducer, driven by a RIGOL function generator and a 38 dB Mini-Circuits amplifier, was positioned to target the CA1 region under defined intensity, duty cycle, and pulse repetition frequency. FUS was applied 0.5 s before and during a 120 pA current step across 10 sweeps per condition. The sequence was: Control1 -> FUS1 -> FUS2 -> Control2, with FUS omitted in control trials. Resting membrane potential (RMP) and action potential firing were measured. Data were collected from two neurons (n = 2, 2 animals), with non-FUS periods confirming stability. Exposure to FUS led to reproducible shifts in neuronal excitability. In both cells, the first exposure caused membrane hyperpolarisation of ~0.3-0.5 mV (paired t-test, $p < 0.01$); the second consecutive exposure resulted in smaller but still significant hyperpolarisation of ~0.2-0.4 mV ($p < 0.05$). No changes were observed during control periods, and the effects reversed once stimulation ceased. These early findings suggest that FUS can reproducibly modulate neuronal excitability in acute hippocampal slices. They highlight the importance of parameter selection, replication, and proper controls, and form a basis for future studies in larger cohorts and additional experimental conditions.



Disclosures: N. Zoka: None. **S. Hosie:** None. **J. Drummond:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of a patent on focused ultrasound. **D.B. Grayden:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of a patent on focused ultrasound. **S. John:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor of a patent on focused ultrasound.

Late-Breaking Poster

LBP057: B.06. Intrinsic Membrane Properties and Signal integration

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP057.06/LBP051

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

Support: 1102522 from CONAHCyT
UNAM-DGAPA-PAPIIT grant IN207423

Title: PACAP induces increased excitability in D1 and D2 expressing nucleus accumbens shell medium spiny neurons

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Abstract: One of the main eating disorders associated with overweight and obesity is binge eating disorder. Binge eating is characterized by excessive consumption of high-calorie foods over a short period of time, approximately 2 hours. The nucleus accumbens (NAc) plays a key role in modulating the hedonic value of high-calorie foods, commonly referred to as palatable foods. Specific subregions of the shell portion of the NAc (NAcSh), known as hedonic hot spots, may play an important role in the motivational aspect of food consumption. Previous work has shown that the pituitary adenylate cyclase-activating polypeptide (PACAP) injected into the NAc reduces palatable food intake, suggesting that this peptide could be a potential tool for treating binge eating. However, the mechanisms of action of PACAP on the NAc are poorly understood. Here, we used whole-cell recording and calcium imaging techniques in NAcSh brain slices from D1-Cre and A2A-Cre mice to investigate PACAP modulation of medium spiny neuron (MSN) activity. We found that PACAP administration increased the firing rate of D1- and D2-expressing MSNs. In addition, in a binge-eating mouse model, nasal PACAP reduced binge-eating behavior.

Disclosures: S. Ortega-Tinoco: None. **J. Garduño:** None.

Late-Breaking Poster

LBP058: B.07. Network Interactions

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP058.01/LBP052

Topic: B.07. Network Interactions

Support: NSF IUCRC BRAIN Award #2137255
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New York Council on the Arts
The National Endowment for the Arts
Vangeline Gand, artistic director, choreographer, and dancer of the Butoh choreography

Title: Ultra-slow rhythms in shared and individualized neural substrates of Butoh meditative dance

Authors: *A. SUNDERLAGE[1], Y. E. LIMA CARMONA[1], D. DAS[1], C. GALE[1], C. THEOFANOPOULOU[2], J. L. CONTRERAS-VIDAL[1];
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Abstract: Dance is a whole brain activity that engages neurobehavioral processes involving sensory, motor, cognitive, social, emotional, rhythmic, creative, and reward processes. The neural network pathways subserving dance production remain obscure. Butoh is a Japanese meditative dance characterized by extended sequences of ultra-slow movement punctuated by sudden, explosive actions. This project investigates the neural basis of Butoh dance using mobile brain-body imaging through hyperscanning of 5 professional Butoh dancers. Data were collected during 2 rehearsals and 1 performance (Theofanopoulou et al., 2024); this analysis uses 3 dancers' data from the second dance rehearsal. Multimodal data included electroencephalography (28 ch., 1000 Hz), electrooculography (4 ch., 1000 Hz), an Inertial Measurement Unit (128 Hz), and synchronized video. Artifacts were identified and mitigated based on adaptive noise canceling and Independent Component Analysis. Dipoles were localized via k-means clustering, and Brodmann areas (BA) were estimated using Talairach coordinates. Spectral analysis of independent components characterized the spectral content of task-related identified networks. Our clustering analysis revealed that all 3 dancers (A, B, & C) showed shared activation in the following areas: a) BA 4—motor control and coordination; b) BA 24—reward and autonomic regulation; c) BA 7—visual-spatial processing and visuo-motor integration; and d) BA 19—visual processing and integration. We also identified clusters shared by pairs of dancers: Dancers A & B also exhibited activity in a) BA 4 and b) left-posterior region of the cerebellum—motor coordination and speech, among other functions. Dancers B & C exhibited activity in BA 6 — movement planning, sequencing, and sensory-motor integration. Lastly, we observed dancer-specific patterns: Dancer A, BA 8 —attention and motor planning; Dancer B, cerebellar vermis— controlling posture, locomotion, and eye movements; and Dancer C, BA 10—high-order executive functions. Spectral decomposition of the clusters showed that both shared and individual neural networks expressed **ultra-slow oscillatory activity (<0.1 Hz**). These rhythms were consistently engaged during Butoh performance, suggesting that the neural

basis of this dance form is rooted in very slow fluctuations that may support a combination of sustained attention, motor control, and sensorimotor integration, among other functions. Identifying such ultra-slow neural dynamics provides a potential framework for understanding how the brain produces meditative movement practices and highlights potential approaches for neurorehabilitation.

Disclosures: A. Sunderlage: None. **Y.E. Lima Carmona:** None. **D. Das:** None. **C. Gale:** None. **C. Theofanopoulou:** None. **J.L. Contreras-Vidal:** None.

Late-Breaking Poster

LBP058: B.07. Network Interactions

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP058.02/LBP053

Topic: B.07. Network Interactions

Support: U54GM133807
R25NS127776

Title: Preliminary Findings on Resting-State QEEG Power Profiles in Patients with Post-Acute Sequelae of SARS-CoV-2 (PASC)

Authors: *N. FUENTES-SANABRIA[1], C. A. CENTENO-ROMÁN[2], G. TIRADO SANTIAGO[1], G. TAPIA NAZARIO[3], Y. ORTIZ ORTIZ[1], I. CASTILLO REYES[1];
[1]University of Puerto Rico-Rio Piedras Campus, San Juan, Puerto Rico; [2]Ponce Health Sciences University, Ponce, Puerto Rico; [3]Ponce Health Science University, Ponce, Puerto Rico

Abstract: Some individuals affected by COVID-19 experience persistent symptoms, a condition widely referred to as post-acute sequelae of COVID-19 (PASC) or long COVID. Studies in the United States estimate that 10-35% of patients develop this syndrome following SARS-CoV-2 infection. While neuroimaging and clinical reports have suggested altered frontal lobe activity in PASC, characteristic electroencephalographic (EEG) patterns remain poorly defined. This preliminary study explored frequency-band alterations through a descriptive evaluation of QEEG topographic maps of absolute and relative power obtained in the resting state with eyes closed. Sixteen individuals (12 women and 4 men, aged 31-50 years) with confirmed PASC and ongoing cognitive complaints were recruited from a specialized clinic. Each participant completed a 19-channel EEG resting-state session of ~10 minutes. Recordings were processed and quantified with reference to the normative Applied Neuroscience, Inc. (ANI) database. Topographic maps were visually inspected considering Z-score deviations. Analyses revealed a generalized increase in slow-wave activity (delta and theta) with frontal and central predominance, accompanied by marked reduction of alpha rhythm, particularly in occipito-parietal regions where alpha is normally dominant during rest. Relative power analysis demonstrated a shift toward greater weighting of slow frequencies, while alpha power was reduced globally but with a paradoxical increase in some frontal regions. These EEG alterations are consistent with reduced attention and

vigilance, as well as cognitive fatigue, aligning with clinical complaints frequently reported by PASC patients. Beta-band changes were inconsistent, showing focal increases more often in frontal regions, but without a systematic pattern. Findings suggest global cortical dysfunction consistent with brain alterations caused by PASC. These results should be considered preliminary given the small sample size and descriptive methodology, but they support the potential of QEEG as a non-invasive functional biomarker of brain involvement in PASC. Future work will expand this dataset with larger cohorts, include matched control groups, and incorporate statistical comparisons as well as cognitive performance measures. Additional analyses are planned to determine specific regions of interest (ROIs) most affected in this population and to evaluate the relationship between EEG alterations and cognitive impairment severity. Such efforts may contribute to a better neurophysiological characterization of PASC and inform targeted therapeutic or rehabilitative interventions.

Disclosures: N. Fuentes-Sanabria: None. **C.A. Centeno-Román:** None. **G. Tirado Santiago:** None. **G. Tapia Nazario:** None. **Y. Ortiz Ortiz:** None. **I. Castillo Reyes:** None.

Late-Breaking Poster

LBP058: B.07. Network Interactions

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP058.03/LBP054

Topic: B.07. Network Interactions

Support: NIH R34NS127101
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Title: Circadian effects on REM sleep oscillations of the retrosplenial cortex

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Abstract: Spatial memory depends on good sleep hygiene, yet the temporal architecture supporting memory related activity during REM sleep remains poorly understood. Within the retrosplenial cortex (RSC), a brain region implicated in spatial cognition and memory, a unique 110-160 Hz oscillation that occurs during REM sleep has been identified, referred to as spline rhythms (Ghosh, et al., 2022). These oscillations are distinct from gamma (30-80 Hz) and are expressed in superficial layers of the RSC. The circadian cycle contributes to changes in memory formation within the RSC (Urban, et al., 2021), which raises the question of how these oscillations are modulated by circadian rhythm. Understanding this change across the circadian cycle may reveal whether these oscillations are computationally specialized at certain times of day. To test this, we recorded local field potentials (LFP) bilaterally from L2/3 of the RSC in

male C57BL/6J mice across ten 24-hour sessions, capturing 763 discrete REM bouts on a 12:12 light cycle. Spectral power and interhemispheric coherence were calculated to assess variation in spectral features across the circadian cycle, using circular-linear regression. Spline power and coherence varied significantly with circadian time of day, (power: ($F(2, 760) = 6.93$, $p = 0.001$, partial $\eta^2 = 0.018$); coherence: ($F(2, 760) = 19.13$, $p < 0.001$, $\eta^2 = 0.048$), with splines peaking at the end of the dark phase. In contrast, gamma power and coherence peaked near the end of the light phase and were also significantly modulated by circadian time (power: $F(2, 760) = 18.48$, $p < .001$, $\eta^2 = 0.046$; coherence: $F(2, 760) = 11.14$, $p < 0.001$, $\eta^2 = 0.028$). These findings indicate that REM associated oscillations in the RSC are not uniform across the 24-hour cycle. They are selectively and differentially modulated by circadian time. This rhythmic modulation suggests that REM sleep may serve temporally specialized roles in cortical processing associated with internal circadian states.

Disclosures: A.D. Lekander: None. **O.J. Ahmed:** None.

Late-Breaking Poster

LBP058: B.07. Network Interactions

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP058.04/LBP055

Topic: B.07. Network Interactions

Support: NIAAA grant P60AA007611
NIAAA grant AA029409
NIAAA grant AA029970
UROP Internship

Title: Mechanisms of Excitability: Simulating Up States in Computational Model of Monkey Cortex

Authors: *A. T. TASHPULATOVA[1], A. S. KUZNETSOV[2], C. C. LAPISH[3], W. H. BARNETT[4];
[1]IU Indianapolis, Indianapolis, IN; [2]Mathematical Sciences, Indiana University Indianapolis, Indianapolis, IN; [3]Indiana University School of Medicine, Indianapolis, IN; [4]Anatomy, Cell Biology, and Physiology, Indiana University School of Medicine, Indianapolis, IN

Abstract: Cognitive flexibility is a higher cognitive function that is critical for decision making, and disorders of cognitive flexibility are associated with impairments to executive control. Mechanisms of cognitive flexibility have been extensively studied at the cellular and network levels, but the mechanisms responsible are not well understood. To investigate this issue, cortical slices of macaque monkeys expressing the calcium sensor GcaMP6 were subject to electrical stimulation with either varying amplitude or varying number of pulses. These experiments found differences in neuronal activity to high amplitude single stimulus vs trains of multiple stimuli. Specifically, persistent increases in neuronal activity followed multiple stimuli and flexibility

was observed in the membership of neurons in active ensembles. In the present study, this data was used as the basis for a computational model capable of simulating the activity of cortical neuron ensembles. We extended the Izhikevich model to incorporate calcium dynamics and NMDA glutamate receptors. Phase portraits computed from the model neuron's activity showed how increasing intracellular concentration activated NMDA receptors and the neuron became less selective in responding to excitatory input. These insights were used to tune the calcium dynamics of the network model, where a train of stimuli induced persistent calcium-dependent increases in neuronal activity. These findings demonstrate the role of calcium dynamics in regulating excitability in neural networks. Future work will focus on the neural network properties of flexible group membership responsible for eliciting the observed activity. Our results are critical for understanding the network mechanisms that support cognitive flexibility.

Disclosures: A.T. Tashpulatova: None. **A.S. Kuznetsov:** None. **C.C. Lapish:** None. **W.H. Barnett:** None.

Late-Breaking Poster

LBP058: B.07. Network Interactions

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP058.05/LBP056

Topic: B.07. Network Interactions

Support: AHA 24SCEFIA1260811

Title: Corticoreticular projections to the pontomedullary reticular formation: Insights from a spiking neuronal network model

Authors: *G. J. YU[1], A. V. PETERCHEV[2], W. M. GRILL[1], C. C. CHARALAMBOUS[3]; [1]Duke University, Durham, NC; [2]Psychiatry & Behavioral Sciences, Duke University, Durham, NC; [3]Neurology, Duke University, Durham, NC

Abstract: Corticoreticular tract (CRT) forms the upper component of the corticoreticulospinal tract, a major motor descending tract. CRT originates mainly from three motor cortical areas, primary motor cortex (M1), supplementary motor area (SMA), and premotor cortex (PM), and it projects bilaterally to pontomedullary reticular formation (PMRF), which includes the pontine (PRF) and medullary (MRF) regions. Despite its importance in motor control, the relative contributions of CRT projections to PRF and MRF activation remain poorly understood, partly due to the lack of computational models incorporating detailed anatomical data. To address this gap, we developed a spiking neuronal network (SNN) model of the PMRF with bilateral CRT inputs from M1, SMA, and PM to determine how each cortical region differentially influences PRF- and MRF-evoked responses.
The SNN model included three neuron types: the reticulospinal projection neurons, GABAergic inhibitory interneurons, and Chx10 excitatory non-projection interneurons. Neuronal spiking dynamics were implemented using a type 4 Generalized Leaky-Integrate-and-Fire (GLIF) model,

which captures the effect of afterhyperpolarization on membrane potential and threshold. Particle swarm optimization was employed to fit model parameters to match both passive properties and frequency-current (F-I) response curves. Neurons were arranged along the rostrocaudal axis and connected based on the anatomical framework of the PMRF described by Humphries et al. (2006).
Bilateral inputs from M1, SMA, and PM were incorporated using cortex-specific data. The relative numbers of fibers and the approximate path length to the PMRF were defined based on human normative streamline maps. Conduction velocity distributions were assigned based on data from cats. The relative contributions for each cortical region were constrained using data from anterograde tracer injections and surface cortical stimulation in macaques.
Activation of a cortical region was simulated by sampling from a post-stimulus time histogram obtained through intracortical microstimulation in the macaque motor cortex. Lateralized activations of cortical areas were performed individually for comparison. Contralateral and ipsilateral CRT projections from both M1 and SMA had a stronger effect on PRF and MRF, respectively. In contrast, CRT projections from PM had the opposite pattern: contralateral and ipsilateral projections had a stronger effect on MRF and PRF, respectively.
The SNN model reveals that CRT projections from three motor cortical areas exhibit distinct termination and activation patterns in the PRF and MRF with hemisphere-lateralized biases.

Disclosures: G.J. Yu: None. **A.V. Peterchev:** None. **W.M. Grill:** None. **C.C. Charalambous:** None.

Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.01/Web Only

Topic: B.08. Epilepsy

Title: Modelling Dup15q Syndrome using multiple iPSC-based platforms (genetic versus ASO induced) by measuring neural network activity

Authors: L. BUTLER[1], A. K. CHOUHAN[2], **R. BURLEY**[3], D. F. FISCHER[4], *D. MAGNANI[1]; [1]Charles River Laboratories, Saffron Walden, United Kingdom; [2]Small Molecule Drug Discovery, Charles River Laboratories, Saffron Walden, United Kingdom; [3]Early Discovery, Charles River Laboratories, Little Chesterford, United Kingdom; [4]Discovery, Charles River, Saffron Walden, United Kingdom

Abstract: Modelling Dup15q Syndrome using multiple iPSC-based platforms (genetic versus ASO induction) by measuring changes in neural network activity Larissa Butler[1], Amit K. Chouhan[1], Russell Burley[1], David F. Fischer[1], Dario Magnani[11] Charles River Laboratories, CRP, United KingdomMaternal 15q duplication syndrome (Dup15q) is a rare neurodevelopmental disorder caused by the presence of at least one extra maternally derived copy of the Prader-Willi/Angelman critical region (PWACR). This region ~5 Mb long is located

within 15q11.2-q13.3 chromosome region. Individuals with maternal Dup15q syndrome exhibit a wide spectrum of clinical symptoms including hypotonia and motor delays, variable intellectual disability, autism spectrum disorder and epilepsy. Although over 40 genes map to the PWACR, accumulating data implicate ubiquitin-protein E3A ligase (*UBE3A*) overexpression as the predominant underlying mechanism.Neuronal Hyperexcitability phenotype in iPSC-derived neurons from patients with 15q11-q13 duplication syndrome has been reported before. However, targeting UBE3A upregulation by ASOs in patient's cells only partially recover the abnormal firing pattern. This suggests a role for other genes in the duplicated region (PWACR) to also contribute to the abnormal firing pattern of patient iPSC-derived neurons.Paternal *UBE3A* is epigenetically silenced by a long non-coding antisense (*UBE3A-ATS*) in neurons and ASO targeting *UBE3A-ATS* have also been developed for the treatment of Angelman Syndrome which display similar clinical features to Dup15q syndrome.In this study, we induce UBE3A upregulation in iPSC derived neuronal cocultures from a healthy donor and induce ~50% UBE3A increase in these cells using *UBE3A-ATS* targeting ASOs. Further electrophysiological characterization of these neurons by MEAs shows that ASO treatment induces significant differences in parameters associated with glutamatergic neuron hyperexcitability. However, we were unable to identify robust seizure-like firing events, which is in contrast with our genetic model using Dup15q patient cells.These results are consistent with previous studies and demonstrate a primary role for *UBE3A* upregulation in eliciting abnormal neuronal firing. Here, we also highlight a potential contribution of additional, potentially genetic, factors contributing to the neuronal phenotype in patient cells. This may need be to be taken into consideration for therapeutic developments targeting Dup15q Syndrome which may require a combinatorial approach including targeting UBE3A upregulation.

Disclosures: L. Butler: None. **A.K. Chouhan:** None. **R. Burley:** None. **D.F. Fischer:** None. **D. Magnani:** None.

Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.02/LBP057

Topic: B.08. Epilepsy

Title: Development of an iPSC-derived KCNQ3 encephalopathy drug screening platform for drug discovery

Authors: A. K. CHOUHAN[1], *P. ZHOU[2], N. BUTELET[2], B. TORROBA[3], D. F. FISCHER[4], **W. W. POON**[2], D. MAGNANI[5];
[1]Small Molecule Drug Discovery, Charles River Laboratories, Saffron Walden, United Kingdom; [2]NeuCyte, Inc., Mountain View, CA; [3]Charles River Laboratories, Leiden, Netherlands; [4]Discovery, Charles River, Saffron Walden, United Kingdom; [5]Discovery UK, Charles River Laboratories, Saffron Walden, United Kingdom

Abstract: Encoding voltage-gated potassium channel subunit Kv7.3, KCNQ3 plays a critical role in the regulation of neuronal excitability by contributing to M-currents, which act to stabilize the membrane potential and suppress repetitive neuronal firing. KCNQ3 mutations contribute to a variety of neurodevelopmental disorders (NDDs) heterogeneous in nature, either simply causing benign familial neonatal seizures or resulting in severe epileptic encephalopathy with cognitive dysfunction. Due to the wide clinical spectrum of KCNQ3 mutations, a mechanistic understanding of each mutation is needed to fully understand the diverse consequences of KCNQ3 mutations on brain development and function. Here, we describe the generation of cryopreserved iPSC-derived glutamatergic and GABAergic neurons from a patient with a R230C KCNQ3 mutation. These iPSC-derived neurons express canonical neuronal markers, form functional excitatory/inhibitory neuronal networks that appropriately respond to GABA blockers (bicuculline, or picrotoxin) and AMPA blocker (CNQX) when co-cultured on multi-electrode arrays (MEA) with human astrocytes. Examination of the spike waveforms of neurons after spike sorting neuronal extracellular electrophysiological readouts identified that this KCNQ3 mutation is likely a gain-of-function variant, mimicking the effects of KCNQ activator retigabine, and opposing the effects of KCNQ blocker XE991, on neuronal spike waveforms that may contribute to identified neuronal network level impairments. These identified KCNQ3 mutation neuronal phenotypes were used to interrogate the efficacy of a therapeutic candidate on restoring normal KCNQ3 function. Taken together, these results describe the use of human iPSC-based models for drug discovery without the need for animal models and in line with the recently announced FDA Modernization Act 3.0.

Disclosures: **A.K. Chouhan:** A. Employment/Salary (full or part-time); Charles River Laboratories. **P. Zhou:** A. Employment/Salary (full or part-time); NeuCyte, Inc. **N. Butelet:** A. Employment/Salary (full or part-time); NeuCyte, Inc. **B. Torroba:** A. Employment/Salary (full or part-time); Charles River Laboratories. **D.F. Fischer:** A. Employment/Salary (full or part-time); Charles River Laboratories. **W.W. Poon:** A. Employment/Salary (full or part-time); NeuCyte, Inc. **D. Magnani:** A. Employment/Salary (full or part-time); Charles River Laboratories.

Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.03/Web Only

Topic: B.08. Epilepsy

Title: Neuronal regeneration for drug-resistant epilepsy: scoping review

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MÉNDEZ GRACIA[16], G. SAYAGO SANTIAGO[18], M. GARCÍA GONZÁLEZ[19], O. NORIEGA ARANDA[20], A. VARGAS PERALTA[20], D. AGUIAR[21], C. RIOS[22], C. PINEDA[2], ***I. PEREZ-NERI**[23];
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Abstract: Epilepsy is characterised by abnormal brain electrical activity. It remains a public health concern due to its impact on disability and premature mortality. About 30% of cases remain uncontrolled despite appropriate use of at least two antiseizure drugs. Neuronal regeneration has emerged as a promising therapeutic alternative. This study aims to address the research question: What is the therapeutic potential of modulating neuronal regeneration in patients with drug-resistant epilepsy according to current literature? A structured approach was adopted using the Right Review tool to identify the most appropriate study design. One researcher developed the search strategy, which was independently reviewed in accordance with PRESS guidelines. Algorithms were created with 2Dsearch, and the final strategy was validated line by line. Searches were conducted across Web of Science, MEDLINE, Scopus, EBSCOhost, Ovid, and Google Scholar. Clinical and preclinical studies on neuronal regeneration in drug-resistant epilepsy or related animal models were eligible for inclusion. Excluded were retracted, non-translatable, or inaccessible full-text studies. Two reviewers independently assessed eligibility using SysRev, with discrepancies resolved by a third reviewer. Feedback was provided by a caregiver whose daughter lives with epilepsy to reflect lived experience. The search identified 19,738 studies; 13,020 duplicates and five retractions were removed. We carried out a Title/Abstract screening pilot test, before final assessments. A guidance document was created to apply eligibility criteria, then refined to clarify neural regeneration definition, relevant outcomes, experimental models, epilepsy types and syndromes, surgical vs non-surgical interventions, and exclusion of status epilepticus or peripheral nervous system studies. As of Sept 5, 2025, 969 studies were screened, 518 excluded and 195 included, yielding 60% reviewer concordance.

Neurostimulation techniques are very prevalent in the literature. Screening remains challenging due to inconsistent reporting of interventions and varied terminology for drug-resistant epilepsy. This review aims to provide a comprehensive synthesis of neuronal regeneration strategies for drug-resistant epilepsy.

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Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.04/LBP058

Topic: B.08. Epilepsy

Title: Combining EEG and BOLD resting state analysis to improve surgical planning in Temporal Lobe Epilepsy

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Abstract: Patients with epilepsy have brain networks defined by resting state analysis in which the irritative zone demonstrates a strong positive correlation with other brain regions in the irritative zone. Some work suggests this network is also inversely correlated with the forebrain outside the irritative zone. To explore these relations, we defined the irritative zone in epilepsy subjects and performed resting state analysis. First, using epilepsy monitoring unit EEG from each subject, epilepsy neurologists marked interictal spike times using standard criteria. The EEG data were corrected for ECG artifacts, and centered on the spikes. Each spike was fit to a dipole using the MNE Python package, and goodness of fit more than 80% were included. These fits were performed after fitting the standard 10-20 array to the subject specific skull as defined in T1 MRI imaging, and the fits were visualized on the T1 MRI. The resting state MRI was registered to the T1 space, and the voxels in the resting state data were seeded with the positions of the dipole locations. Those seeds were used to create a time series that is a convex combination of the time series corresponding to the seeded voxels. The largest positive and negative correlations to the seeded time series were included in the irritative zone network and its negative. We find that the irritative zone was included in a large positively correlated brain

region with positive correlations up to 0.94, and that a smaller negative zone, with correlation coefficients up to 0.9, was also included. The irritative zone and its negative display a more robust correlation than is typically seen in non-epileptic patients. In our first subject, the irritative zone network had a dense concentration in the medial temporal lobe and was opposed by the rest of the forebrain. Through combination of EEG and resting state MRI data, we hope to provide clinicians with better insight into the networks and connectivity of the epileptic brain for surgical planning and/or further treatment.

Disclosures: K.R. Pennington: None. **D.T. Blake:** None.

Late-Breaking Poster

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Program #/Poster #: LBP059.05/LBP059

Topic: B.08. Epilepsy

Support: ERIUK
MRC
Wellcome Trust
Gatsby Charitable Foundation

Title: Seizure mechanisms in focal cortical dysplasia

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Abstract: Focal cortical dysplasia (FCD) is a leading cause of pharmacoresistant epilepsy, and is often associated with cognitive impairments and autistic features. Characterised by cortical dyslamination and the presence of cytomegalic/dysmorphic neurons, FCD is caused in most cases by somatic mutations of genes encoding members of the mTOR signalling cascade. FCD-associated epilepsy is also often a poor candidate for resective surgery because the dysplastic region typically occurs in an eloquent cortical territory. The need for novel treatment strategies to address FCD is clear. The lack of potential pharmaceutical targets arises from our poor understanding of the epileptogenic mechanisms that makes seizures possible, and the acute network mechanisms that give rise to individual seizures. Despite the overt structural abnormality, whether seizures arise from dysplastic neurons and their connections remains unclear. Here, we use a mouse model of FCD generated by *in utero* electroporation of a constitutive activator of mTOR ($Rheb_{S16H}$), which recapitulates many molecular, morphological, electrographic, and behavioural features of FCD type II in patients, including subclinical abnormalities. We utilise electrophysiological and imaging data to dissect the contribution of heterotopic/dysmorphic and morphologically normal appearing neurons in the dysplastic region both *in vitro* and in the behaving mouse. Patch-clamp recordings of dysplastic neurons obtained in acute brain slices from FCD mice show a profound intrinsic hypoexcitabilty, while

neighbouring, morphologically normal cells show reduced rheobase, increased membrane resistance, and higher stable firing rates than control cells. This data appears in conflict with *in vivo* recordings, which show a hyperactive predisposition for burst firing in dysplastic neurons *in situ*. This is supported by morphological analysis and computational modelling, which demonstrate dysplastic neurons aberrantly integrate incoming synaptic drive and tend to fire trains of action potentials. This subset of neurons in the prefrontal cortex disposes the network to unusually high glutamatergic drive, capable of overwhelming inhibitory stabilisation of the network, and providing a substrate for seizure onset.

Disclosures: R.T. Graham: None. **D.M. Kullmann:** None.

Late-Breaking Poster

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Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.06/LBP060

Topic: B.08. Epilepsy

Title: NeuroUI: An Epilepsy-Focused AI Modeling Interface for Reproducible Simulation and Intervention Testing

Authors: A. ANGRISH[1], *M. BEHL[2], A. KAPADIA[3];
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Abstract: Epilepsy modeling is poorly served by general-purpose neural simulators, which often require programming expertise, expose irrelevant parameters, and lack focus on seizure dynamics. In this work we present **NeuroUI**, an AI-based tool designed specifically for epilepsy research and aligned with FDA-endorsed New Approach Methodologies (NAMs). NeuroUI offers a single-surface interface that standardizes workflows, reduces cognitive load and errors, and enables rapid, reproducible simulations by users with little to no programming background.We compared NeuroUI to the Yale NEURON GUI in a within-subjects, counterbalanced test of two tasks (2-neuron demo; 3-population absence seizure model). Metrics included task time, click path length (CPL), window/context switches (WCSR), parameter visibility ratio (PVR), single-surface coverage (SSC), jargon index (JII), and one-click save/load. Across both tasks, NeuroUI consistently showed lower JII, higher SSC and PVR, WCSR fixed at 1, markedly reduced CPL, and successful one-click operations. These results demonstrate significantly faster and more reliable performance.Planned extensions include expanding seizure repertoires (focal, tonic-clonic, myoclonic, atonic) with diverse mechanisms (persistent Na^+, Ih, T-type Ca^{2+}, KCC2, plasticity, gap junctions, tunable GABA) and adding an intervention library for pharmacological (Na^+ block, GABA potentiation, KCNQ openers) and neuromodulatory strategies (DBS-like trains, closed-loop triggers). Batch sweeps, optimization, and closed-loop evaluation will allow systematic study of latency-to-abort and relapse.NeuroUI thus provides an epilepsy-focused interface that enhances usability and reproducibility, while serving as a

platform for modeling multi-effects, testing mitigation strategies, and as a teaching tool across diverse scenarios. By combining accessibility with rigor, NeuroUI represents a step toward advancing seizure research and therapeutic development.

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Late-Breaking Poster

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Program #/Poster #: LBP059.07/LBP061

Topic: B.08. Epilepsy

Support: VA I01BX003195

Title: Preliminary evidence of the protective role of the kynurenine pathway in seizures

Authors: *D. SANTANA COELHO[1], E. PIEDRA[2], F. A. VIGIL[3], J. C. O'CONNOR[4]; [1]Pharmacology, University of Texas Health Science Center, San Antonio, San Antonio, TX; [2]UT Health San Antonio, San Antonio, TX; [3]University of Texas Health San Antonio, San Antonio, TX; [4]Pharmacology, UTHSCSA, San Antonio, TX

Abstract: Changes in the kynurenine pathway (KP) have been associated with epilepsy. Furthermore, deficiency in the rate-limiting enzyme of the KP, indoleamine-2,3- dioxygenase (IDO), affects seizure susceptibility. However, the mechanism by which this protective effect occurs is unknown. Therefore, in the present study, we aimed to better understand how the modulation of the kynurenine pathway can affect seizures. The downstream metabolism of the KP branches into two pathways, each producing different neuroactive metabolites. In one branch, kynurenic acid (KA) is produced by the enzyme kynurenine-3-monooxygenase (KMO), while the alternative branch produces quinolinic acid (QUIN) through the activity of the enzyme 3-hydroxyanthranilic acid dioxygenase (HAAO). KA and QUIN can modulate glutamatergic neurotransmission in opposite ways. Also, KA is deemed to be neuroprotective while QUIN is considered to be neurotoxic. Due to the activity of those metabolites in neurotransmitter systems, we hypothesize that different metabolites will exert different effects on seizure development. To test this hypothesis, we used knockout mice deficient in the enzymes that participate in the metabolism of the different branches of the KP. Adult C57BL6N, HAAO -/-, and KMO-/- mice were used in the study. Male and female mice were treated with 40mg/kg pentylenetetrazol to induce acute seizures. Latency for tonic/clonic seizures was increased in male HAAO-/- mice when compared to Wild-type and KMO-/-. In females, seizure parameters did not differ between genotypes. To further investigate the protective effect of knocking out HAAO, we used the PTZ kindling model of epileptogenesis. Male mice were treated with the sub convulsive dose of 25mg/kg of PTZ three times a week. The total of 14 injections were administered until all WT mice developed tonic-clonic seizures. In this model, the HAAO-/- mice also presented with decreased susceptibility to seizures. Our preliminary data suggest a role for the kynurenine

pathway in the development of seizures in male mice in acute and chronic PTZ models. Further analysis is necessary to characterize the mechanism by which male HAAO-/- mice are potentially less susceptible to seizures.

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Late-Breaking Poster

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Topic: B.08. Epilepsy

Support: NIH R01FG25962
AES Postdoctoral Research Fellowship
NIH 5T32NS045540-20

Title: Hippocampal representation of a new environment in a rodent model of temporal lobe epilepsy

Authors: *B. L. BOUBLIL[1], G. TARCSAY[1], J. D. YI[2], L. A. EWELL[3];
[1]Anatomy and Neurobiology, UC Irvine, Irvine, CA; [2]Anatomy and Neurobiology, University of California, Irvine, Irvine, CA; [3]Anatomy & Neurobiology, UC - Irvine, Irvine, CA

Abstract: Place representation in the hippocampus is disrupted in animal models of TLE. Much of the research on the hippocampus in epilepsy has focused on CA1, and little is known about how the function of upstream regions such as CA3 and DG may be altered in epilepsy. We used the supra-hippocampal kainic acid (KA) model of focal temporal lobe epilepsy. We performed high density single-unit recordings from hippocampal subregions CA1, CA3, and DG in KA and saline control mice. Mice were trained to forage in a familiar environment while tetrodes were slowly advanced towards all subregions. Once tetrodes reached their target, we recorded hippocampal neural activity while mice explored both familiar and novel environments (N = 16, 6 control, 10 KA). Place cells were first distinguished from non-place cells using a shuffling procedure of spatial information. Control CA1 had a larger proportion of place cells compared to KA CA1 ($\chi^2 = 14.97$, $p < 0.001$). There was no significant difference between control and KA animals for CA3 and DG. Next, we analyzed properties of place coding in a familiar environment. Spatial coherence significantly decreased in CA1 ($z = 3.92$, $p < 0.0001$) and CA3 ($z = 3.63$, $p < 0.0001$) of KA animals compared to controls. There was no significant difference in spatial coherence for DG. We did not observe significant differences in the half map correlations between control and KA animals for CA1 ($p = 0.42$), CA3 ($p = 0.31$), or DG ($p = 0.27$). Next, we examined whether place coding was impaired in KA animals in a novel environment. Spatial correlation significantly decreased between Familiar1-Familiar2 and Familiar1-Novel1 for control ($z = 5.63$, $p < 0.0001$) and KA ($z = 3.62$, $p < 0.001$) animals in

CA1, as well as for CA3 in control ($z = 3.74$, $p < 0.001$) and KA ($z = 4.48$, $p < 0.0001$) animals, and for DG in control ($p < 0.01$) and KA ($z = 4.31$, $p < 0.0001$) animals. These data suggest that the hippocampus in both control and KA mice can form distinct place codes in completely novel environments. Next, we compared spatial correlations between Novel1-Novel4 for hippocampal CA1, CA3, and DG from control and KA animals to investigate if place maps stabilized after repeated experience in the novel environment. There was a significant difference between control and KA spatial correlations for CA3 ($z = 2.38$, $p < 0.05$), but no significant difference for CA1 or DG, suggesting that while CA3 in KA animals can form place maps in a novel environment, those representations are not stable. By better understanding hippocampal dynamics and how they change with epilepsy we can gain insight into impaired memory processing in epilepsy.

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Late-Breaking Poster

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Topic: B.08. Epilepsy

Support: NIH R01
2024 Double Hoo Award
2023 Ingrassia Family Echols Scholars Research Grant

Title: Midline thalamus as a synchrony center in absence seizure generation

Authors: *A. M. CARNS[1], E. DULKO[1], A. RAJESH[2], S. KILIANSKI[1], I. LESMANA[2], M. P. BEENHAKKER[1];
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Abstract: Background: Childhood Absence epilepsy (CAE) comprises between 10-17% of pediatric epilepsy cases. Despite the prevalence of this disease, one third of patients do not respond to treatment. Absence seizures appear as spike-wave discharges (SWDs) on an electroencephalogram (EEG) and are associated with aberrant neuronal synchrony. We aim to understand the mechanisms of excessive synchrony generation underlying SWDs in order to inform the development of more targeted, effective treatments. Preliminary data from our laboratory suggests that midline thalamic nuclei (mediodorsal thalamus, MD; central lateral thalamus, CL; posterior nucleus of thalamus, PO) are highly synchronized with multiple nearby structures during absence seizures. We hypothesize that these midline structures serve as hubs that facilitate pathological neuronal synchrony during SWDs. **Methods:** C3H/HeJ mice ("Gria4"), a well-established model of CAE, expressing spontaneous SWDs were used in this study. Mice received bilateral injections of neuron specific (hSyn promoter) inhibitory

DREADDs (hM4D(Gi)-mCherry) or control virus (mCherry only) targeted to the midline thalamic nuclei (AP: -1.40 mm, ML: +/- 0.80 - 0.50 mm, DV: -3.50 - -3.20 mm). Following recovery, mice were implanted with electrocorticography (ECoG) electrodes in the frontal and parietal cortices. Mice received vehicle injections (saline) to establish a baseline seizure count and clozapine N-oxide (CNO 3mg/kg, 6 mg/kg) in a randomized order during ECoG recordings. Following recording, AAV delivery was confirmed via fluorescence microscopy. Data was analyzed using custom MATLAB code to quantify seizure count and duration. **Results:** Preliminary results show an approximately 30% decrease in seizure count when mice received CNO at 3mg/kg compared to vehicle injections. Additionally, higher doses of CNO produced a greater decrease in seizure count. These findings highlight a role for the midline thalamic nuclei (MD, CL, PO) in generating widespread synchrony, suggesting that these structures may serve as a target for new treatments of CAE.

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Program #/Poster #: LBP059.10/LBP064

Topic: B.08. Epilepsy

Support: NIH R01

Title: Wide-field imaging of seizures in a rodent model of absence epilepsy

Authors: *S. LASHKERI, M. P. BEENHAKKER, S. KILIANSKI;
Pharmacology, University of Virginia, Charlottesville, VA

Abstract: Absence epilepsy is a neurological disorder characterized by brief episodes of impaired consciousness, most commonly occurring in children aged 4 to 10. These episodes are associated with abnormal electrical activity in the brain, most commonly manifesting as spike-and-wave discharges (SWDs) on electroencephalogram (EEG) recordings. Understanding the neural mechanisms underlying seizure propagation is crucial for advancing therapeutic strategies. Our research investigates these propagation patterns by analyzing cortical activity using in vivo mesoscopic calcium imaging in Thy1-GCaMP6s x C3H/HeJ mice which have spontaneous SWDs. Fluorescence and EEG are recorded simultaneously in these experiments. This offers a dual modality approach that enables a broad, unbiased spatial survey of activity across the dorsal surface of the cortex while also recording the temporally precise EEG. Preliminary data indicate that GCaMP fluorescence generally decreases during SWDs and abruptly rises after termination. This observed decrease in fluorescence during SWDs is likely due to a real reduction in neural activity across the cortex as other studies have reported. Our current analysis investigates which cortical areas show the biggest changes during SWDs and

whether or not the activity follows a stereotyped path. Altogether, our experiments will help to identify brain regions involved in seizure initiation and spread, providing insight into the network mechanisms of absence epilepsy.

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Late-Breaking Poster

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Topic: B.08. Epilepsy

Support: NIH NINDS K08NS121464
Kenneth Eisenberg Emerging Scholar Award, Taubman Institute, University of Michigan
Neuroscience Summer Research Fellowship, Program in Biology, University of Michigan

Title: Characterization and rescue of hyperthermia-evoked seizures in a focal cortical dysplasia model of epilepsy

Authors: *R. SHEN[1], C. RANA[2], X. ZHANG[1], M. JIANG[1], T. YANG[1], R. QURESHI[1], H. HABERLAND[1], Y. WANG[1], J. MATTIS[1];
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Abstract: Focal cortical dysplasia (FCD) is a common cause of drug-resistant epilepsy. Although rodent FCD models exhibit spontaneous seizures, inducing naturalistic seizures at defined times would enable real time observation and manipulation of ictal dynamics. We tested whether hyperthermia could serve as a repeatable trigger and whether selective inhibition of dysplastic neurons reduces susceptibility to hyperthermia evoked-seizures. FCD mice were generated by in utero electroporation on embryonic day 15 with RHEb.P37L, a gain-of-function mTOR pathway mutation. For chemogenetics experiments, the inhibitory DREADD hM4DGi was introduced via co-electroporation. Controls received a fluorescent plasmid. Mice were gradually heated via a heat lamp until exhibiting a behavioral seizure or until their body temperature reached 42.5 °C. Seizures were identified and scored behaviorally (using modified Racine scale) or with electrocorticography. All procedures and scoring were blinded. Hyperthermia triggered behavioral seizures in 80% (20/25) of adult P35+ FCD mice (mean threshold 40.0 ± 0.4 °C). Seizures could be repeatedly evoked across sequential experimental days, facilitating a within-mouse experimental design. Using this novel experimental platform, we tested whether chemogenetic inhibition of dysplastic (Rheb+) neurons was seizure protective. Indeed, we found a significant increase in seizure threshold following clozapine N-oxide (CNO) versus vehicle injection ($p=0.008$; chi square, n=18-19 mice). In a subset, we tested whether this

finding would also extend to spontaneous seizures by alternating daily injections of CNO versus vehicle while recording with EEG across 6 days. Spontaneous seizures were significantly reduced within 6 hours of CNO injection (total seizure counts: p=0.037, nested t-test; time to first seizure: p=0.0022, chi square; n=6 mice). Overall, hyperthermia reproducibly induces seizures in the Rheb-FCD mouse model, providing a tractable platform for mechanistic interrogation of ictogenesis. Using this platform, we found that selective inhibition of dysplastic neurons is protective against seizure onset. Future directions include using this acute hyperthermic seizure strategy to facilitate in vivo recording from Rheb+ neurons during seizures.

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Late-Breaking Poster

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Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.12/LBP066

Topic: B.08. Epilepsy

Title: Novel animal models implicate hippocampal hyperexcitability and learning deficits in the pathogenesis of CSNK2B-related neurodevelopmental disorder

Authors: *A. U. CARBONELL, C. PERSAD, D. WILLIAMS, G. JIMENEZ, D. LICHTE, Z. ZHU, W. N. FRANKEL, C. D. MAKINSON, T. T. SANDS;
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Abstract: RATIONALE: CSNK2B-related neurodevelopmental disorder is a genetic epilepsy caused by variants in the CSNK2B gene, presenting in childhood with seizures and developmental delay. Seizure control is often not achieved or requires multiple antiseizure medications. Most reported CSNK2B variants are predicted to be protein-truncating, arguing for haploinsufficiency as a genetic mechanism. However, the circuit changes by which these mutations cause disease are unknown, and targeted therapies do not exist. CSNK2B encodes a subunit of protein kinase CK2, which targets a host of proteins regulating neural development, excitability, and plasticity. We hypothesize that CSNK2B participates in the pathogenesis of epilepsy and intellectual disability by regulating hippocampal excitability and synaptic plasticity. METHODS: Using a novel Csnk2b-floxed line, we generated models of constitutive (Sox2-cre) and forebrain (Emx1-cre) deletion of Csnk2b in the C57BL/6J strain and an F1 cross with the FVB strain. Comparing mutants with littermates, we tested growth/survival, developmental milestones, and behavioral assays related to learning/memory. To test susceptibility to generalized and temporal lobe seizures, we measured electroconvulsive thresholds (ECT) using high-frequency and 6-Hz paradigms. To test excitability, we recorded burst activity of CA2/CA3 neurons in acute hippocampal slices from P14-P21 pups. To test synaptic plasticity (a cellular substrate of learning/memory), we induced long-term potentiation (LTP) at the Schaffer CA3-CA1 synapse and monitored fEPSPs. RESULTS: Constitutive Csnk2b deletion reduced survival,

seizure ECT in the 6-Hz paradigm, novel arm preference, and fear conditioning. Targeted deletion from forebrain excitatory neurons/glia also yielded changes in survival (homozygotes), seizure susceptibility, and spatial memory. In the burst assay, Csnk2b haploinsufficiency increased burst frequency and duration. Magnitude of LTP at the Schaffer collateral synapse was reduced, consistent with memory impairment in learning tasks. RT-qPCR confirmed region-specific loss of Csnk2b expression. CONCLUSIONS: This work represents the first investigations of any CSNK2B disease model focused on mechanisms of seizure susceptibility and learning deficits. Our results implicate hippocampal circuitry as a central region of dysfunction in CSNK2B-related disorders. These findings support the role of CSNK2B as a hub gene regulating the excitability and plasticity of brain circuits critical for epileptogenesis and cognition, providing therapeutic targets for related neurodevelopmental disorders.

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Topic: B.08. Epilepsy

Title: Development of a portable automated stereotaxic system with anesthesia delivery and vital signs monitoring for animal research

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Abstract: Stereotaxic surgery remains a cornerstone for experimental neuroscience, yet conventional stereotaxic frames are bulky, non-portable, and restricted to controlled laboratory settings. This limitation motivated the development of an innovative portable automated stereotaxic system, recently documented as a patent application, that integrates anesthesia delivery, real-time vital signs monitoring, and wireless remote control. The invention is centered on a lightweight spherical housing with a retractable platform for animal positioning. Automated actuators secure the skull, while a motorized tool-selector module provides precise movements along Cartesian axes. An external anesthetic reservoir, connected through internal ducts, ensures continuous sedation, and embedded sensors monitor body temperature, respiration, and heart

rate. All operations are executed remotely via Bluetooth or WiFi, minimizing direct handling and maintaining aseptic conditions. This patented system was designed not only as a technological prototype but also as a transferable platform capable of addressing unmet needs in preclinical neuroscience. Proof-of-concept experiments in small animal models demonstrated reliable immobilization, effective anesthesia administration, and stable physiological monitoring throughout procedures. Remote operation reduced contamination risks and allowed interventions beyond conventional laboratory facilities. By combining portability, automation, and integrated anesthesia management under a protected intellectual property framework, this stereotaxic system represents a novel approach to neurosurgical experimentation. The patent underscores its originality and potential for translational impact. Future efforts will focus on refining precision, validating across diverse animal models, and exploring pathways for broader dissemination of this patented technology in neuroscience research.*Schematic representation of the portable automated stereotaxic system. The device consists of a lightweight spherical housing with a retractable tray for animal positioning. Automated actuators immobilize the skull, while a motorized tool selector provides precise movements along Cartesian axes. An external anesthetic reservoir delivers continuous sedation through internal ducts, and embedded sensors monitor temperature, heart rate, and respiration. Wireless control is enabled via Bluetooth/WiFi, allowing remote operation from a computer or mobile device.*

Disclosures: R. Beltran-Ramirez: None. **J.A. Dominguez-Ramirez:** None. **X.M. Becerra-González:** None. **J. Martinez-Mendoza:** None. **C. Román:** None. **I. Rojas:** None. **A. Padilla:** None. **A. Cardenas:** None. **M. Ibarra:** None. **E. Becerra López:** None. **J. Valenzuela López:** None.

Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.14/LBP068

Topic: B.08. Epilepsy

Support: Jazz Pharmaceuticals

Title: Characterization of spike-and-wave discharges modulation by ethosuximide in the GAERS model of absence seizures with extended homecage EEG monitoring

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Abstract: Absence epilepsy is an epileptic syndrome where patients show episodes of unresponsiveness to environmental stimuli and cessation of activity. Typical absence seizures are nonconvulsive and associated with generalized synchronous and regular spike-and-wave

discharges (SWDs). Genetic absence epilepsy rat from Strasbourg (GAERS) is an inbred strain of Wistar rat selected for its spontaneous SWDs. GAERS is a reference model, presenting behavioral, electrophysiological, and pharmacological features of absence seizures. Cortical EEG recordings are characterized by SWDs lasting 17-25/sec, with 45-60 SWDs/h during wake. Compound efficacy in GAERS is commonly evaluated for a limited duration (~2 hours) while animals are maintained in forced quiet wakefulness, disrupting their natural behavior. Evaluating them in undisturbed conditions and for longer durations could provide a superior model of human pathology. We used telemetric EEG recordings over 48 h in 12 male GAERS animals left undisturbed in their homecage to evaluate spontaneous SWDs during full light/dark cycles. We found that SWDs follow a circadian rhythm, with more frequent events during the dark phase (16 SWDs/h), and fewer during the light phase (10 SWDs/h). Compared to the forced wakefulness protocol, the number of SWDs per hour is substantially lower in this more physiologically relevant model. In contrast to the number of SWDs, we observed no circadian rhythm for the average duration of SWDs, which remained stable across the light/dark cycle. To pharmacologically validate this naturalistic model, we evaluated the effect of the classical antiabsence medication ethosuximide. When administered at the beginning of the dark phase, ethosuximide (30-300 mg/kg PO) provoked a dose-dependent inhibition of SWDs. Ethosuximide significantly reduced the number of SWDs (-33%, -76%, and -99% from vehicle values at 30, 100, and 300 mg/kg, respectively, over the first 12 hours, $P<0.0001$), as well as the duration of the remaining SWDs (-1%, -4%, and -68% from vehicle values, $P<0.0001$). We also show that the effect extends much further than the typically documented 2h postdose in forced wakefulness conditions. We could still observe significant inhibition of SWDs for up to 24h after dosing. These measures of SWDs using telemetric EEG highlight the importance of evaluating the GAERS model in naturalistic conditions. The epileptic activity is notably different from evaluations in forced wakefulness, and it can better match the spontaneous SWDs in humans. The assessment of pharmacological effects over 24 hours can allow a better pharmacodynamic characterization of antiabsence compounds in preclinical studies.

Disclosures: **A. Evrard:** A. Employment/Salary (full or part-time); SynapCell SAS. **H. Monchal:** A. Employment/Salary (full or part-time); SynapCell SAS. **N. Vautrelle:** A. Employment/Salary (full or part-time); SynapCell SAS. **N.F. Shanks:** A. Employment/Salary (full or part-time); Jazz Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jazz Pharmaceuticals. **B. Brigham:** A. Employment/Salary (full or part-time); Jazz Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Jazz Pharmaceuticals.

Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.15/LBP069

Topic: B.08. Epilepsy

Support: TKP2021-EGA-28
KKP133871/KKP20
151490/EXCELLENCE_24

Title: Phase-locked transcranial Intersectional Short Pulse (ISP) stimulation in terminating epileptic seizures

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Abstract: Phase-locked transcranial Intersectional Short Pulse (ISP) stimulation in terminatingepileptic seizures
Transcranial Electric Stimulation (TES) has emerged as a promising non- or minimally-invasive therapeutic approach for pharmacoresistant epilepsy treatment. However, the optimal timing of stimulation relative to the ongoing brain oscillations remains to be established for optimizing efficiency.This study investigates the phase specificity of transcranial Intersectional Short-Pulse stimulation (ISP) in terminating epileptic seizures, using both animal models and clinical data. By analyzing deep-brain activity during seizures in rats and post-hoc analysis of clinical data from human patients underwent closed-loop ictal stimulation, we unveil the optimal timing for intervention. In this study, we recorded intracranial EEG (iEEG) signals in electrically kindled rats, and delivered phase targeted ictal transcranial stimulation by ISP stimulation. This allowed us to map and understand the underlying neuronal activities at the seizure onset zone and their responses to the ISP stimulation. Our findings consistently demonstrate that closed-loop stimulation is effective in shortening both the seizure lengths and the proportion of the generalized segments, emphasizing the potential clinical impact of phase-dependent intervention. Additionally, stimulating at, or near the peak of seizure oscillations yielded the most significant reductions in seizure duration. This phase-specific effect is further validated through data from our first-in-patient clinical study performed to demonstrate the feasibility of closed-loop seizure termination in human patients. In conclusion, these insights not only refine therapeutic strategies, but also underscore the translational potential of preclinical models in guiding personalized epilepsy care.Ultimately, understanding the phase dependence of closed-loop neurostimulation represents a critical step towards advancing epilepsy treatment.
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Disclosures: **N. Forgó:** A. Employment/Salary (full or part-time); Neunos Ltd, Szeged, 6725, Hungary,. **L. Barcsai:** A. Employment/Salary (full or part-time); Neunos Ltd, Szeged, 6725, Hungary,. **M. Gorog:** A. Employment/Salary (full or part-time); Neunos Ltd, Szeged, 6725, Hungary,. **Z. Somogyvari:** A. Employment/Salary (full or part-time); Neunos Ltd, Szeged, 6725,

Hungary,. **L. Eross:** None. **O. Devinsky:** 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.; NINDS, NIMH, MURI, CDC, NSF. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); GW Pharmaceuticals. F. Consulting Fees (e.g., advisory boards); Emotiv, Ultragenyx, Praxis Precision Therapeutics. Other; Blackrock Neurotech, Tilray, Tevard Biosciences, Regel Biosciences, Script Biosciences, Actio Biosciences, Empatica, Ajna Biosciences, California Cannabis Enterprises (CCE), PhiFund Ventures. **Z. Chadaide:** A. Employment/Salary (full or part-time); Neunos Ltd, Szeged, 6725, Hungary,. **A. Berenyi:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Amplipex Kft., Szeged, Hungary. Other; Neunos ZRt, Szeged, Hungary, Blackrock Neurotech.

Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.16/LBP070

Topic: B.08. Epilepsy

Title: Electrophysiological measurements of medial meptal mucleus DREADD activation in a preclinical epilepsy model

Authors: *M. BERGOSH[1], N. C. ZEPEDA[2], E. WATKINS[3], C. GARNER[3], S. MEDVIDOVIC[4], D. J. LEE[5];
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Abstract: Recent preclinical findings have demonstrated that electrical stimulation of the medial septal nucleus (MSN) improves seizure threshold and improves working memory. Stimulation of the MSN is thought to rescue its critical role in generating theta waves (5-12 Hz), which may underpin the improvements in seizure threshold and working memory through neural entrainment. We hypothesized that Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) would recapitulate these seizure and electrophysiological benefits. This chemogenetic tool has potential to non-invasively address treatment-refractory epilepsy. In the present study, static epilepticus was induced via pilocarpine injection (1 mg/kg) in male SD rats. DREADD receptor expression in the MSN was induced via intracranial viral injection. 21 days later animals were administered saline (n=6) or clozapine (CNO; n=7) to activate the DREADD receptors. Local field potentials (LFPs) of the medial prefrontal cortex (mPFC) and hippocampus were recorded immediately before CNO injection, and 45 minutes post-injection. Periodic (theta amplitude, frequency, bandwidth), aperiodic (offset and slope), fast ripple (amplitude, frequency,

duration), and complexity (sample entropy) measurements were derived. In a separate cohort, similarly treated groups (saline: 10; CNO: 10) underwent flurothyl testing of seizure threshold 45 minutes after saline/CNO injection. The group treated with CNO had a significantly higher seizure threshold than the saline group ($p<.05$). Post-injection, median fast ripple amplitude in the hippocampus was significantly lower in the CNO group ($m=7.7$, $SD=.36$) compared to saline ($m=7.0$, $SD=.038$; $p=.024$). In the mPFC, theta peaks were detected significantly more often in the CNO group (5/7) compared to saline (0/5; $p=.028$); and sample entropy was significantly higher in the CNO group ($m=.034$, $SD=.038$) compared to saline ($m=.008$, $SD=.003$; $p<.01$). Improved seizure threshold and reduced fast ripple amplitude in the hippocampus after DREADD activation in the MSN supports the hypothesis that chemogenetic stimulation of the septohippocampal network can reduce seizure activity similarly to electrical stimulation. Enhancements in theta oscillations and signal complexity in the cortex after activation support the neural entrainment hypothesis for reduced seizure activity and improved cognitive function. These findings encourage further development of these non-invasive treatment strategies for epilepsy, and promote the therapeutic use of these precision chemogenetic techniques in a broader scope.

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Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

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Program #/Poster #: LBP059.17/LBP071

Topic: B.08. Epilepsy

Support: CNPq Grant 446688/2024-0

Title: Calm Before the Storm: Neuronal Silence Predicts Seizure Onset

Authors: D. L. M. SOUZA[1], L. E. BENTIVOGLIO[1], P. RICARDO PROTACHEVICZ[1], S. DURA-BERNAL[2], ***F. S. BORGES**[1];
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Abstract: We study mean silence time as a physiologically measurable biomarker of the abrupt transition to seizure-like burst-synchronized activity. Using biophysical model simulations that include slow ion channels dynamic, we show that networks reliably enter a prolonged population-wide silent interval immediately prior to transitions into highly synchronized up-states. The mean silence time rises steadily as the networks approach an up-state and cross a critical threshold, providing a consistent early warning (most predicted transitions occur 40-160 ms before the onset of the seizure). A Random Forest machine learning algorithm trained only on lagged mean silence values predicts burst synchronization with high accuracy, demonstrating the

predictive power of the mean silence time. Using this biomarker, a suppression protocol that provides brief depolarizing stimulation to a few neurons within the network upon crossing the silence threshold reduces the duration of the upstate by 93%. Importantly, prolonged preseizure silence analogous to model prediction is observed in intracranial recordings from human epilepsy patients, supporting translational relevance. Mechanically, prolonged silence reduces slow currents and neuronal adaptation, facilitating rapid synchronization, consistent with previous work on the roles of potassium and calcium ionic channels in burst generation and with population-level silence phenomena reported in the neocortex. These results position mean silence time as a mechanistic biomarker for the prediction of seizures and as a target for seizure control through neuronal stimulation.

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Late-Breaking Poster

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Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.18/LBP072

Topic: B.08. Epilepsy

Support: Beiwe Bio, Direct Support
R41AG076327

Title: mTORC1-selective Meclizine as a potential alternative to Everolimus for Tuberous Sclerosis (TSC) seizures

Authors: *C. MONTGOMERY[1], H. ANAND[2], A. TOMILOV[1], G. CORTOPASSI[1];
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Abstract: A human-approved use for the Blood Brain Barrier (BBB)-permeant mTORC1 inhibitor Everolimus is seizures due to Tuberous Sclerosis Complex (TSC). However, in addition to inhibiting mTORC1, Everolimus also inhibits mTORC2, and this produces side-effects in mice and humans like with Rapamycin. We demonstrated the Blood-Brain Barrier permeant compound Meclizine as the first non-rapalog mTORC1 inhibitor in 2018. Unlike rapalogs Everolimus and Rapamycin, Meclizine is completely mTORC1-specific, dose-dependently inhibits mTORC1 and does not inhibit mTORC2 in vitro or in vivo. As rapalogs have been observed to extend lifespan, we submitted Meclizine to NIA's ITP, who has demonstrated mTORC1-inhibitor Meclizine increases lifespan. We investigated whether the inhibition of mTORC1 could have anti-neuroinflammatory effects, which could explain the lifespan effects. In BV2 microglia, LPS induce inflammatory cytokine gene expression and circularity, and Meclizine dose-dependently inhibited these. Dosed to UM-HET3 mice in vivo, Meclizine inhibited only mTORC1 dependent transcript but not mTORC2-dependent transcripts, and

inhibited neuroinflammatory cytokine elicitation in brain. These data are consistent with the hypothesis that Meclizine may extend longevity through reducing neuroinflammation. Since Meclizine is BBB permeant and has been dosed safely in humans for 70 years, and is solely mTORC1-specific unlike approved Everolimus that also inhibits mTORC2, we propose Meclizine for TSC seizure indication rather than Everolimus.

Disclosures: C. Montgomery: 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.; Beiwe Bio STTR/SBIR with UC Davis. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Beiwe Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Beiwe Bio. **H. Anand:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Beiwe Bio. **A. Tomilov:** 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.; Beiwe Bio STTR/SBIR with UC Davis. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Beiwe Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Beiwe Bio. **G. Cortopassi:** 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.; Beiwe Bio STTR/SBIR with UC Davis. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Beiwe Bio. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Beiwe Bio.

Late-Breaking Poster

LBP059: B.08. Epilepsy

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.19/LBP073

Topic: B.08. Epilepsy

Support: National Organization for Rare Disorders Grant 18008

Title: Pathogenic significance of NORSE specific miRNAs and hyperinflammatory monocytes in FIRES

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Abstract: New-onset refractory status epilepticus (NORSE) is a devastating seizure disorder that appears explosively in individuals with no history of epilepsy. In some cases, particularly in

children, the onset of refractory status epilepticus (RSE) is preceded by fever and is referred to as febrile infection-related epilepsy syndrome (FIRES). Many cases present in the absence of metabolic, autoimmune, toxic, structural, or genetic etiology and result in death, vegetative state, severe disability, or the development of drug-resistant epilepsy, resulting in the final diagnosis of cryptogenic NORSE. The inability to stop seizures in patients with cryptogenic NORSE represents a critical unmet human health need. Identification of biomarkers and pathogenic mechanisms in NORSE patients is critical to the understanding and development of therapeutic strategies for drug-resistant epilepsies. PBMCs were isolated from serial blood draws during RSE and following resolution associated with intrathecal dexamethasone therapy in a previously healthy patient. Cells were stimulated with bacterial or viral ligands and levels of inflammatory factors in the blood and CSF were measured and compared to pediatric healthy control ranges. Preliminary data shows that cryptogenic NORSE patients exhibit a hyperinflammatory monocyte response coupled with an exaggerated release of IL6 and CXCL8 in response to pathogenic challenge during RSE. A persistently dysregulated transcriptional response to immune challenges has also been shown even years after the initial acute event, which led us to hypothesize that the disease is related to differential miRNA expression. We have identified a unique repertoire of 16 miRNAs expressed in cryptogenic NORSE patient PBMCs and our preliminary evidence suggests that these regulatory factors influence the response to bacterial pathogenic challenges. These findings highlight the critical roles of inflammation in driving the pathogenesis of seizures and epilepsy. We aim to determine the pathogenic significance of these NORSE-specific miRNAs by measuring the impact of these miRNAs on basal and stimulated cellular responses.

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Late-Breaking Poster

LBP059: B.08. Epilepsy

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Program #/Poster #: LBP059.20/LBP074

Topic: B.08. Epilepsy

Support: NIA R01AG070255

Title: Measuring synaptic plasticity and excitatory-inhibitory ratio in astrocytoma-associated human epileptic brain tissue

Authors: *J. OH[1], B. SALAMEH[1], S. BUDHWANI[1], J. GRANCHI[1], B. KRISHNAN[1], A. LIMON[2], P. KARAS[1];
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Abstract: Astrocytoma-associated epilepsy remains a major clinical challenge, with seizures often arising from functionally abnormal regions affected by the neoplasm. Although rodent models have provided insights into excitatory-inhibitory (E/I) imbalance and aberrant synaptic plasticity in such epileptic tissues, electrophysiological studies that directly measure from human synaptic structures are limited, due to the lack of relevant assays. To test whether these synaptic functions and responses can be measured in human astrocytoma-associated epileptic tissue, we isolated synaptosomes from surgically resected cortical tissue from six participants with drug-resistant epilepsy and/or astrocytoma (Astrocytoma group n=3; No pathology group n=3.) E/I ratio was measured by microtransplanting synaptosome into frog oocytes' cell membrane, followed by two-electrode voltage-clamp recordings. Excitatory or inhibitory currents were evoked by applying kainite or GABA. From each brain surgery specimen, multiple measurements of E/I ratio were obtained. Chemically induced long-term potentiation (cLTP) of synaptosomes was measured as a proxy for physiological long-term potentiation, using the fluorescence-assisted single-synapse long-term potentiation (FASS-LTP) assay, measuring surface AMPA receptor expression after chemical induction of LTP compared to baseline activity (% from baseline). E/I ratio measurements from six brain surgery tissues shows a trend of excessive E/I ratio in astrocytoma-associated tissues compared to tissues with no pathology. Consistently, the kainite-GABA relationship in astrocytoma group shows greater kainite response over GABA response, compared to those of no-pathology group; The slope of the correlation between kainate responses to GABA responses was higher in the astrocytoma group relative to the no-pathology group. Nested ANOVA with repeated measurements nested within surgery showed no significant difference in E/I ratio between astrocytoma and no-pathology group; $F_{(1,4)}=1.42$, $p=0.30$, $\eta^2=0.26$, $\omega^2=0.07$. FASS-LTP measurements also showed a trend of reduced plasticity in the astrocytoma group although the difference did not show statistical significance (No pathology group mean: 207.9%, Astrocytoma group mean: 107.8%, $t=1.51$, $df=2.4$, $p=0.25$.) Our results indicate that synaptic metrics of E/I ratio and plasticity can be obtained from surgically resected human brain tissue. Future studies expanding the cohort with additional participants will elucidate synaptic abnormalities underlying astrocytoma-related epilepsy.

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Late-Breaking Poster

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Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP059.21/LBP075

Topic: B.08. Epilepsy

Title: Continuous deep brain stimulation suppresses entorhinal hyperexcitability and enhances spatial memory in epilepsy patients

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Abstract: Memory acts as the undercurrent for our lived experience - etching and stitching moments together into a longitudinal framework that structures who we are. Yet, millions of patients worldwide suffer from severe memory impairment arising from conditions affecting medial temporal lobe (MTL) structures - i.e., the "seats" of memory in the brain. The entorhinal cortex (EC) is an MTL structure that is particularly affected by aberrant hyperexcitability in severe memory disorders arising from MTL epilepsy and Alzheimer's disease. The EC acts as the central interface with the hippocampus transmitting processed components of experiences into the hippocampus for memory encoding and consolidation — roles that require temporally precise signals that are likely impaired in the presence of EC hyperexcitability. There is significant recent interest in the suppression of EC hyperactivity for the treatment of severe memory impairment in conditions such as MTL epilepsy and Alzheimer's. However, traditional anti-epileptic medications prove ineffective in suppressing hyperactivity or improving cognition in the 20-40% of MTL epilepsy patients that become "drug-resistant" (DRE). Deep brain stimulation (DBS) of the anterior thalamic or EC/hippocampal area - a treatment modality involving the implantation of electrodes for stimulation at low-amplitude, high-frequency settings - is used in some DRE patients when anti-epileptics alone are insufficient, though the mechanisms underlying DBS's efficacy in epilepsy are still being elucidated. Here, we report that continuous, high-frequency, 3-hour stimulation of the EC in epileptic patients implanted with depth leads for seizure monitoring led to a suppression of synchronous neuronal firing in the EC. Analysis of entire spiking activity (ESA) revealed that burst rates decreased significantly following stimulation ($N = 2$; Cohen's $d = -1.13 \pm 0.04$ [mean ± SEM], $p < 1.5 \times 10^{-11}$, paired t-test), indicating reduced synchronous population firing events. We concurrently observed enhanced performance on a spatial memory task when compared to baseline performance. Participants exhibited improved spatial learning, with a mean 38% reduction in excess path length post-stimulation compared to pre-stimulation. Additional studies are warranted to further evaluate the potential efficacy of EC DBS to improve memory in epilepsy patients.

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Program #/Poster #: LBP059.22/LBP076

Topic: B.08. Epilepsy

Support: Wilson Foundation
UTSW Radiology Department seed grant

Title: Python-based Analyzer for Presurgical CCEP Mapping in Drug-resistant Epilepsy

Authors: *S. ZAFARMANDI ARDABILI[1], T. PRUITT[2], C. KNOX[3], C. DAVILA[4], B. C. LEGA[5];
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Abstract: Python-based Analyzer for Presurgical CCEP Mapping inDrug-resistant EpilepsyTyrell Pruitt and Sevda Zafarmandi Ardabili[1,2], Clyde Knox[1],Carlos E. Davila[2], Bradley Lega[11]Department of Neurological Surgery, University of Texas Southwestern Medical Center, Dallas, TX, USA[2]Department of Electrical and Computer Engineering, Southern Methodist University, Dallas, TX, USAAbstractDrug-resistant epilepsy often necessitates invasive brain mapping to guide surgical or neuromodulatory in-terventions. Cortico-cortical evoked potentials (CCEPs) provide a direct measure of causal connectivity bydelivering brief electrical stimuli to one brain region and recording evoked responses in others. Despitetheir clinical potential, there is currently no widely available, streamlined, open-source toolbox designedspecifically for presurgical CCEP analysis and visualization. This gap limits the efficiency and consistencywith which CCEP data are incorporated into surgical decision-making.Here we present a new Python-based CCEP Analyzer created to accelerate data processing, enhancevisualization, and improve localization accuracy for presurgical planning. The open-source graphical inter-face supports raw iEEG import (EDF format) with electrode coordinates, automatic detection and epochingof stimulation events, signal filtering (including notch and high-gamma bandpass), and quantitative analysisof evoked responses. The platform provides both time-domain averaging and spectral (RMS high-gamma)mapping to quantify network strength. A region-of-interest feature enables targeted analysis of cortical ar-eas, and a 3D brain visualization module projects response amplitudes onto a standard *fsaverage* corticalmesh in both pial and white-matter views.In preliminary patient datasets, the Analyzer rapidly identified robust CCEP waveforms across multipleelectrodes, with high-intensity responses pinpointing putative epileptogenic networks. Three-dimensionalconnectivity maps revealed cortical regions strongly coupled to stimulation sites, offering intuitive guidancefor resection or device targeting. By integrating automated preprocessing with advanced visualization, thisplatform reduces analysis time and subjectivity compared to manual methods. Its modular design supportsfuture expansion, including real-time monitoring and automated classification.By directly addressing the lack of dedicated presurgical CCEP toolboxes, the Python CCEP Analyzerhas the potential to improve the efficiency and precision of epilepsy mapping, ultimately contributing tomore reliable and personalized neurosurgical care.

Disclosures: S. Zafarmandi Ardabili: None. **T. Pruitt:** None. **C. Knox:** None. **C. Davila:** None. **B.C. Lega:** None.

Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP060.01/LBP077

Topic: B.09. Glial Mechanisms

Support: McNair Scholars Program
NSF Grant 2011220
NMSU Foundation

Title: Comparative anti-proliferative effects of cannabidiol and capsaicin on astrocyte and glioma cell lines

Authors: A. M. RIVAS, *E. E. SERRANO;
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Abstract: Glioblastoma (GBM) is an aggressive and structurally complex brain tumor that is considered one of the most treatment-resistant human cancers. GBM resistance underscores the need to identify new therapeutic strategies, such as those that can be used in a combinatorial treatment approach. This exploratory study was designed to systematically compare the anti-growth properties of the plant bioactive compounds cannabidiol (CBD; a non-psychoactive constituent from *Cannabis sativa*) and capsaicin (CAP; the pungent compound in chili pepper) on astrocyte and glioma cell lines derived from *Rattus norvegicus*. Prior studies have shown that CBD and CAP can cross the blood brain barrier and suggest that both have the potential to reduce GBM proliferation. By comparing astrocyte and glioma cell lines in parallel, we aimed to systematically evaluate how growth is affected by the treatments, thereby establishing a system for future mechanistic studies. CTX-TNA2 astrocytes (ATCC CRL-2006; RRID:CVCL_3670) and F98 glioma cells (ATCC CRL-2397; RRID:CVCL_3510) were cultured at passage 3-5 in 24-well plates and treated with a range of CBD and CAP concentrations (1, 5, 25, 50, 200 μM). All treatment solutions were labeled by an independent person, and the experimenter added the treatments and analyzed the outcomes without knowledge of their identity. Cell confluence was quantified as proxy for growth over 72 hours using a live-cell imaging and analysis incubator system that measures confluence as the percentage of the image area occupied by cells (Sartorius Incucyte S3; 4 wells/treatment condition; 9 images/per well every 3 hours; 10x magnification). Images and confluence measurements were analyzed with Incucyte software and exported to Microsoft Excel. Analysis showed that CTX-TNA2 growth was more vigorous than F98 in all paired treatment conditions. CBD elicited a strong dose-dependent reduction in confluence in both cell lines while CAP promoted less anti-growth activity as compared with CBD at equivalent concentrations. Our findings suggest that CBD, and to a lesser extent CAP, can suppress growth in glial cells, with greater inhibitory effects observed in glioblastoma cultures than in astrocytes exposed to the same concentration. Taken together outcomes support the premise that CAP and CDB have therapeutic potential. The finding that CBD reduced confluency at lower concentrations than observed with CAP may reflect differences in their

proposed molecular targets and mechanisms of action. Ongoing experiments are extending the exposure regimen to additional concentrations and incorporating a human astrocytoma cell lines into the experimental paradigm.

Disclosures: A.M. Rivas: None. **E.E. Serrano:** None.

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Program #/Poster #: LBP060.02/LBP078

Topic: B.09. Glial Mechanisms

Support: R21NS108508
R01NS121542

Title: Biological and Artificial Neuro-Astro Networks

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Abstract: Reward learning depends on the brain's ability to flexibly integrate external cues with internal states. Here, we show that Bergmann glia—specialized astrocytes in the cerebellar cortex—generate distinct norepinephrine-dependent calcium signals during a reward-guided task in awake mice. These signals fall into two timescales: slow oscillations mediated by α1-adrenergic receptors and fast transients by α2 receptors. α1 activity regulates parallel fiber input, while α2 shapes climbing fiber-driven signals, thereby modulating distinct streams of excitatory drive onto Purkinje cells. This reveals input-specific astrocytic control of Purkinje cell integration during behavior. These findings uncover a neuromodulatory mechanism by which cerebellar astrocytes influence circuit dynamics, highlighting astrocytes as active participants in the neural computations underlying learning and decision-making. To translate these principles into computation, we developed a biology-inspired actor-critic network in which neuronal units serve as the actor and astrocytic units function as the critic. The critic incorporates both fast and slow astrocytic timescales, motivated by our biological findings. This framework provides a testable platform for exploring how astrocytic dynamics could contribute to stability, adaptability, and reward prediction in reinforcement learning, bridging insights from cerebellar astrocyte-Purkinje cell interactions to artificial intelligence.

Disclosures: C. Li: None. **L. Gong:** None. **W. Li:** None.

Late-Breaking Poster

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Title: Dehydration affects supraoptic nucleus astrocytic activity and responsiveness to hyperosmotic stimulation

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Abstract: Hydromineral homeostasis is regulated minute-to-minute by a complex hypothalamic circuit that detects osmotic changes and trigger responses to restore plasma osmolarity to homeostatic levels. One of the nuclei that is activated by osmotic changes is the supraoptic nucleus (SON), which releases vasopressin and oxytocin to circulation and starts a peripheric response to control hydromineral balance. While magnocellular neurons of SON had been much explored, the participation of glial cells, mainly astrocytes, is still unclear. It is known that astrocytes can participate in osmotic balance and affect magnocellular activity, but the role of SON astrocytes in osmosensation and their response to stress conditions, such as dehydration, remains to be understood. This study aimed to assess the basal activity of SON astrocytes following 24 and 48 hours of dehydration and to determine whether these cells still respond to osmotic stimulation. Experiments were conducted in adult C57BL/6 male mice assigned to three groups: euhydrated controls, 24-hour (D24h) and 48-hour dehydrated (D48h) (Ethical committee: 8836280223). Coronal brain slices containing SON were collected and rested in SR101 for astrocytic staining. Whole-cell patch-clamp recordings were performed on labeled astrocytes in normal and under hyperosmotic conditions. In control animals, astrocytes exhibited a resting membrane potential (Vm) of -89.98±1.91 mV (n=14) and depolarized after the hyperosmotic stimulus (Na^+: -87.90±2.36, n=14, $p<0.0001$). After 24 hours of dehydration, astrocytes showed a depolarized resting membrane potential compared to control group (D24h: -78.08±1.5, n=19 *vs* Control: -89.98±1.91 mV, (n=14), p=0.002) and failed to respond to the osmotic challenge (D24h basal: -78.08±1.5 vs D24h + Na^+: -78.08±1.5, n=19, p=0.3294). In contrast, after 48 hours of dehydration, astrocytes remained depolarized relative to controls (D48h: -72.48±3.25, n=13 *vs* Control: -89.98±1.91 mV, (n=14), $p<0.0001$) but regained their ability to respond to hyperosmotic aCSF (D48h basal: -72.48±3.25 vs D48h + Na+: -67.79±4.15,

n=13, p=0.0120). Comparison among all groups Vm confirmed that astrocytes remained depolarized after both 24 and 48 hours of dehydration. These findings suggest that dehydration alters the electrophysiological state of SON astrocytes, impairing their osmotic sensitivity after 24 hours. The recovery of osmotic responsiveness at 48 hours may reflect cellular or network-level plasticity, potentially enabling adaptation to sustained osmotic stress. Further investigations are warranted to elucidate the underlying mechanisms of this functional recovery.

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Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

Support: NSTC113-2320-B-182A-013-
CORPG8P0543
CMRPG8N0281-3

Title: MCT4 suppression mediated maternal high fructose diet impaired astrocytic glycogen metabolism

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Abstract: Maternal high fructose diets (HFD) during the perinatal stage impaired astrocytic lactate metabolism in the hippocampus of the offspring. However, the underlying mechanism remains largely unclear. Given that glycogen serves as a major source of lactate production, and that glycogen synthase (GS) and monocarboxylate transporter 4 (MCT4) are highly responsive to energy demand, we investigated the potential role of glycogen metabolism. Butyrate, a short-chain fatty acid, is known to promote glycogen synthesis, whereas MCT4 facilitates butyrate transport. Thus, the disruption of butyrate and MCT4 expression might contribute to impaired glycogen metabolism. In this study, we demonstrate that maternal HFD suppressed MCT4 expression, accompanied by reductions in hippocampal butyrate, lactate, and glycogen content. Notably, astrocytic glycogen levels and glycolytic activity were significantly decreased, along with downregulation of GS and MCT4 expression. Exogenous butyrate (10 μM) treatment effectively restored GS and MCT4 expression suppressed by maternal HFD. Moreover, MCT4 overexpression rescued GS expression, further linking MCT4 activity to glycogen metabolism. Together, these findings suggest that maternal HFD disrupts butyrate-MCT4 signaling, thereby impairing astrocytic glycogen metabolism in the hippocampus of offspring.

Disclosures: K.L. Wu: None. **C.J. Wu:** None.

Late-Breaking Poster

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Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP060.05/LBP081

Topic: B.09. Glial Mechanisms

Title: Brain area specific heterogeneity of astrocyte functions and effects on spatial working memory after chemogenetic activation of astrocytes

Authors: *J. LIPPMAN[1], A. EARP[2], D. SERRANO[2], J. BONANNO[3], J. LIN[2], J. D'ORAZIO[2], K. U. TANG[4], H. TANAKA[2], E. LI[5], Z. DING[2], J. ROSENBLUM[2], E. SEKER[2], L. A. NEWMAN[6];
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Abstract: Astrocytes modify blood flow, energy production, neurotransmitter levels, and immune responses. Our project employs chemogenetics (Designer Receptors Exclusively Activated by Designer Drugs, or DREADDs) to increase intracellular calcium and activate astrocytes in the prefrontal cortex and hippocampus of Long Evans rats (ns>6 per group). Utilizing DREADDs virus that has a glial fibrillary acidic protein (GFAP) promoter (pAAV-GFAP-hM3D(Gq)-mCherry) or a GFAP promoter with a microRNA targeting cassette ((PHP.eB)-GfaABC1D-DREADD hM3D-mCherry-4x6T-CW3SL), we targeted the prelimbic cortex (PrL) or dorsal hippocampus (HC) of male and female rats and two weeks later tested the rats on a delayed spontaneous alternation task, meant to test spatial working memory (SWM) in the presence of the vehicle, saline, and compound 21 (C21) in a counterbalanced order. NeuN and GFAP immunofluorescence was used to identify cell type expression of DREADDs and Sholl analysis of GFAP expression was done to measure astrocytic activation. Female rats with GFAP only promoting DREADDs were found to have a significant decrease in performance on the SWM task when DREADDs were activated in both the prelimbic cortex and hippocampus ($F_{1,23}=16.61$, $p<0.001$). mCherry tagged DREADDs receptors were also seen in neurons in the DREADDs virus with the GFAP promoter only and but not with the addition of the miRNA targeting cassette. Control groups and miRNA cassette rats exhibited no significant differences with C21 versus saline. An increase of GFAP expression was seen in astrocytes expressing DREADDs regardless of virus type as compared to astrocytes not expressing DREADDs in the PrL ($F_{1,13}=5.29$, $p=0.039$). In contrast, in the molecular layer of the hippocampus, astrocytes expressing the DREADDs virus showed less GFAP expression as compared to those that did not express the virus ($F_{1,15}=8.13$, $p=0.015$). This may suggest an increase of intracellular calcium inside these astrocytes is leading to differential functional activity in these distinct brain areas and support the idea of astrocyte heterogeneity. This functional heterogeneity could help bridge gaps in our understanding of astrocytes, particularly how their function can differ in SWM tasks dependent on location in the brain.

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Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

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Program #/Poster #: LBP060.06/LBP082

Topic: B.09. Glial Mechanisms

Support: The Academy of Finland (decision Nos. 326494, 326495, 345280, and 355256)

Title: Nanoprocess geometry shapes whole-cell astroglial calcium dynamics in the cerebellum

Authors: *L. KETO, T. MANNINEN;
Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland

Abstract: Astroglial cells form hundreds of nanoprocesses that enwrap synapses, extend endfeet to vasculature, and generate a complex landscape of calcium signaling. Yet, their computational modeling has lagged behind that of neurons, leaving fundamental questions about how morphology shapes function. Here we present new results from a multiscale modeling framework that links nanoscopic calcium microdomains to whole-cell dynamics in cerebellar Bergmann glia. Using our open-source CellRemorph toolkit (Keto & Manninen, 2023) together with the NEURON simulator (Carnevale & Hines, 2006) and the ASTRO framework (Savtchenko et al., 2018), we generated a detailed yet computationally tractable full-cell astrocyte morphology. The morphology was based on previous structural characterizations of Bergmann glia (Grosche et al., 1999; Lippman et al., 2008), ensuring realistic representation of the fine branching architecture. In parallel, we carried out stochastic nanoscale simulations with particle- and voxel-based approaches to probe how fine-scale branching alters calcium transients. Our findings show that local morphological complexity strongly modulates IP3 receptor-mediated calcium dynamics, with branch thickness and connectivity altering transient amplitude and spread. When integrated at the cellular scale, these local effects accumulate into distinct global signaling patterns, demonstrating a direct morphological influence on whole-cell calcium dynamics. This work provides one of the first cross-scale computational analyses of cerebellar astroglia, offering new insight into how fine structure shapes calcium signaling. By bridging nanoprocesses and whole cells, our results highlight the functional significance of astrocytic morphology and provide a foundation for realistic predictions of morphology-function relationships in astrocytes. Acknowledgements: We are very grateful to Prof. Helmut Kettenmann for providing us the video file of Bergmann glia appendage, and to the Doctoral School at Tampere University.

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Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

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Title: Two-Photon Astrocyte Voltage Imaging Reveals State-Dependent Membrane Dynamics in Vivo

Authors: A. KIRUNDA[1], C. SMITH[2], R. KROEGER[1], N. HAKAM[1], Y.-Y. SHAN[3], M. A. GALDAMEZ[3], R. LAW[4], E. NEYHART[3], M. HU[5], *J. REIMER[1];
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Abstract: Astrocytes have historically been regarded as electrically uninteresting, with maximum fluctuations of only 1-2mV measured in somatic patch clamp recordings. However, due to their elaborate compartmental structure and low electrotonic space constant, somatic recordings may underestimate voltage fluctuations in the peripheral astrocyte processes. These processes are well-positioned to be influenced by ion fluxes in densely-packed neuropil, and they participate in electrogenic functions such as glutamate uptake and potassium clearance. Therefore, it is an open question whether peripheral processes experience larger membrane voltage dynamics than those visible from the soma. Using *in vivo* two-photon imaging with the genetically encoded voltage indicator, JEDI3hyp, we observed voltage fluctuations across astrocyte membranes that we estimate are nearly an order of magnitude larger than those previously observed using somatic patch-clamp techniques. Astrocyte depolarizations were correlated with large changes in local neural activity under various conditions, including isoflurane anesthesia, visual stimulation, transitions from quiet to active states, and during seizures in epileptic model mice. To eliminate any confounds due to imaging artifacts, we leveraged a novel quad-site imaging approach where we recorded from multiple spatially-separated fluorophores in the same cortical window that act as positive and negative controls for the astrocyte JEDI measurements. With these multi-site experiments, we estimate that astrocyte voltage fluctuations observed under isoflurane anesthesia are on the order of 10mV or more. Beyond the cytosolic calcium events that are routinely monitored to assess dynamic processes in astrocytes, our results suggest that membrane voltage may be an overlooked aspect of *in vivo* astrocyte physiology impacting their function in both health and disease.

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Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

Support: NINDS F32NS117776
Chan Zuckerberg Initiative

Title: Dysregulation of astrocyte-secreted pleiotrophin contributes to neuronal structural and functional deficits in Down Syndrome

Authors: *A. BRANDEBURA[1], A. PAUMIER[2], Q. ASBELL[2], T. TAO[2], M. MICAEL[3], S. SANCHEZ SANDOVAL[4], N. J. ALLEN[2];
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Abstract: Astrocytes perform fundamental functions in the establishment of the neural circuitry. One prominent mechanism by which astrocytes guide neural circuit formation is via the release of a variety of secreted proteins that act as guidance molecules to modulate processes such as dendrite branching and as synaptogenic molecules. Imbalances of these molecules during development may result in improper connectivity that manifests as a variety of neurodevelopmental disorders (NDDs), including Down Syndrome (DS). DS is characterized by excitatory-inhibitory imbalance, decreased dendritic spine density and reduced dendritic complexity. Prior work demonstrated that astrocytes in DS have aberrant protein secretion patterns, which may contribute to circuit deficits. From this dataset we identified the candidate protein Pleiotrophin (Ptn) to test for its functional relevance to DS. Ptn was >4-fold down-regulated at the secretory level from cultured astrocytes isolated out of the Ts65Dn mouse model of DS and is enriched in astrocytes during development. Therefore, we developed the hypothesis that if decreased Ptn secretion from astrocytes was contributing to neural circuit deficits in DS, then Ptn knockout (KO) mice should have overlapping phenotypes with Ts65Dn mutant (Mut) mice. Secondly, we hypothesized that overexpressing Ptn in astrocytes in Ts65Dn mice would improve the dendrite and synaptic deficits observed. We performed analysis of dendrite complexity, spine density and excitatory synapse number in Ptn KO and Ts65Dn Mut mice compared to their wildtype (WT) counterparts in the visual cortex (VC) at P30 and P120. We found that Ptn KO mice had highly overlapping phenotypes with Ts65Dn mice. We then used a blood-brain-barrier permeable AAV to overexpress Ptn in Ts65Dn astrocytes throughout the brain. The virus was delivered at two months of age and the mice were collected for analysis at four months. We observed that Ptn overexpression fully restored dendrite outgrowth and spine density in both the VC and the hippocampus (HP), two brain regions affected in DS. We showed using in vitro neuronal cultures that Ptn promotes dendrite outgrowth via the Alk receptor. Finally, we found that Ptn overexpression improved short-term plasticity deficits in the HP of Ts65Dn mice, and this was accompanied by rescue of reduced vesicular glutamate transporter

levels, a marker of excitatory synapses. These findings demonstrate that reduced levels of Ptn in DS have functional impacts on circuit formation and function and highlights that astrocytes can be targeted to deliver synaptogenic molecules such as Ptn to improve aberrant circuit wiring in DS, and potentially other NDDs.

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Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

Title: Astrocytic calcium dynamics under neuromodulator drive: an integrated imaging-modeling framework with implications for ALS

Authors: *R. AZAB[1], E. URDAPILLETA[2,3], R. BARAVALLE[3,4], C.-Y. CHANG[5], M. DE PITTÀ[6], A. DRANOVSKY[7,8], S. DURA-BERNAL[3,4,9];
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Abstract: Astrocytes are central regulators of excitatory neurotransmission, particularly in the cortex,where they couple intracellular calcium signaling to the release and uptake of glutamate, aprocess known as gliotransmission. Astrocytes not only modulate glutamate clearance through high affinity transporters localized to the membrane, i.e., glutamate transporter 1 (GLT-1/EAAT2), they also enable calcium dependent vesicular and non-vesicular glutamate release. As a result, astrocytes critically shape neural circuit dynamics, namely, synaptic plasticity, excitatory tone, and network homeostasis. In healthy brain states, astrocyte mediated uptake effectively regulates glutamate transients through spatiotemporal precision. However, pathophysiological states, such as amyotrophic lateral sclerosis (ALS), demonstrate impaired astrocytic calcium signaling, which tends to foster excitotoxic cascades and progressive motor neuron degeneration. Whether distinct calcium signaling motifs can “encode” neuromodulator identity, and how such “encoding” may be mapped onto the glutamatergic output under pathophysiological context remains unknown- a gap that obscures potential avenues for exploring neural circuit and synaptic adaptability in motor neuron diseases. To address this question in depth, we combined in vitro slice imaging with a biophysically constrained reaction

diffusion model of astrocytes using NetPyNE/NEURON. Using dual color calcium reporters, we imaged astrocytic calcium dynamics during neuromodulator application in vitro and analyzed responses across amplitude, temporal kinetics, and spatial synchrony. The experimentally derived population level signatures provided empirical parameters to calibrate our in-silico model. This model successfully simulated the intracellular pathways coupled to calcium dependent glutamate release (i.e., IP3 mediated calcium release, SERCA pump kinetics, and mitochondrial buffering) and extracellular diffusion of relevant molecules, effectively reproducing the experimentally observed calcium waveforms. Our multimodal framework characterizes the mechanisms through which astrocytic calcium dynamics govern excitatory signaling and has potential to identify preliminary targets in neuron-glial networks for therapeutic interventions. Future work will extend this framework to ALS associated excitotoxicity, where the interplay of impaired astrocytic calcium signaling and compromised glutamate clearance represents a central driver of motor neuron degeneration.

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Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

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Program #/Poster #: LBP060.10/LBP086

Topic: B.09. Glial Mechanisms

Title: Investigating region-specific astrocyte susceptibility in neurodegenerative diseases

Authors: *S. A. E. GARDNER[1,2], I. ILYASHOV[2], M. BAFFUTO[2], C. PRESSL[2], N. HEINTZ[2]; [1]Graduate Studies, Rockefeller University, New York, NY; [2]Laboratory of Molecular Biology, Rockefeller University, New York, NY

Abstract: Huntington's disease (HD) is a fatal inherited neurodegenerative disorder causing major neuronal loss, specifically in the striatal and cortical regions of the brain. The pathogenesis is driven by cell-type-specific CAG repeat expansion in the Huntingtin (*HTT*) gene in these regions, which causes dysfunction and selective vulnerability in neuronal cell types. However, previous studies have shown that astrocytes of the glia experience loss of function and develop various reactive profiles in HD despite not showing major somatic expansion like the neuronal cell types affected. This indicates that although the CAG expansions are a central feature of the disease, additional elements also drive cell death and toxicity occurring in vulnerable regions. Thus, region- and cell-type-specific factors beyond CAG length contribute to HD pathogenesis. Given their abundance, essential neuronal support role, and growing evidence of both functional impairment and reactive transformation in HD, astrocytes represent a unique cell type. Their region-specific and context-dependent contributions to disease vulnerability may reveal critical insights. Astrocytes in HD undergo region-specific transcriptional and epigenetic changes that drive their dysfunction and impact nearby neurons. It is necessary to characterize and uncover

the molecular drivers of astrocyte vulnerability and test their functional effects, and how they may differ across brain regions. Using isolated astrocyte-specific sequencing data from the striatum and primary motor cortex of HD and control postmortem tissue, we analyzed differential gene expression results to compare gene expression profiles of these two vulnerable regions and discover common and region-specific transcriptional changes in HD astrocytes. This allowed for the identification of targetable astrocytic genes or functional pathways that could modify HD progression. Some of these selectively altered astrocytic genes were then validated using in situ hybridization and immunofluorescence, providing spatial resolution and biological context of these transcriptional changes. From an epigenetic approach, analyzing our differential chromatin accessibility data as well as our histone post-transcriptional modification data for the striatum and primary motor cortex, identifies regulatory elements enhancing or repressing the transcription of astrocytic genes previously identified in driving susceptibility in HD. Ultimately, we aim to use these approaches to further study how astrocytes behave in disease to uncover new ways to protect the brain from damage in HD.

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Late-Breaking Poster

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Program #/Poster #: LBP060.11/LBP087

Topic: B.09. Glial Mechanisms

Title: Overexpression of PGRMC2 in Astrocytes Improved Cognitive Function in A Mouse Model of Alzheimer's Disease by Modulating Neuroinflammation

Authors: *T. ZHU;
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Abstract: Overexpression of PGRMC2 in Astrocytes Improved Cognitive Function in A Mouse Model of Alzheimer's Disease by Modulating Neuroinflammation
Authors Taiyang Zhu[1], Fang Hua[2] 1. Department of Neurology, Affiliated Hospital of Xuzhou Medical University, Xuzhou 221002 China 2. Division of Human Anatomy, College of Allied Health Science, Augusta University, Augusta, GA30912, USA
Disclosures Taiyang Zhu: None. Fang Hua: None.
Abstract Progesterone receptor membrane component 2 (PGRMC2), a member of the membrane-associated progesterone receptor (MAPR) family, has recently been implicated in neuroprotection. Persistent neuroinflammation is considered the third major pathological hallmark of Alzheimer's disease (AD). Here, we investigated the role of astrocytic PGRMC2 in modulating neuroinflammation and cognitive function in an AD mouse model. We used adeno-associated viral (AAV) vectors to induce overexpression of
PGRMC2 specifically in astrocytes of APPswe/PSEN1dE9 transgenic mice and C57BL/6J wild-

type mice. Cognitive performance was evaluated by Morris water maze and Y-maze tests. Brain structural changes were assessed using magnetic resonance imaging (MRI). Protein and mRNA expression were analyzed by Western blot, qPCR, immunohistochemistry, and immunofluorescence. We found that PGRMC2 expression was significantly upregulated in astrocytes of AD mouse brains. Astrocytic overexpression of PGRMC2 improved learning and memory performance, attenuated cortical thinning and hippocampal atrophy, and reduced neuronal loss, although it did not alter Aβ1-42 deposition. Mechanistically, PGRMC2 modulated the NFκB signaling pathway, inhibited the activation of neurotoxic A1 astrocytes, and promoted the polarization toward the neuroprotective A2 phenotype, thereby alleviating neuroinflammatory responses. These findings demonstrate that astrocytic PGRMC2 exerts neuroprotective effects in AD by regulating astrocyte polarization and neuroinflammation. PGRMC2 may represent a novel therapeutic target for Alzheimer's disease. **Keywords:** PGRMC2; astrocytes; Alzheimer's disease;

Disclosures: T. Zhu: None.

Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

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Program #/Poster #: LBP060.12/LBP088

Topic: B.09. Glial Mechanisms

Support: NICHD R01 HD107489
Powell Family Charitable Trust

Title: Neuroinflammatory Perspective on Folate Deficiency, Excess, and Astrogliosis

Authors: *A. MUSTAFA[1], K. ZARBALIS[2], R. GREEN[1];
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Abstract: Prenatal and lactational folic acid excess promotes astrocyte generation and activation in the offspring

Arshi Mustafa[1], Ralph Green[1,2], Konstantinos S. Zarbalis[1,2,3]
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Background: While folate intake during pregnancy and lactation is widely recommended to minimize the risk of neural tube defects and optimize infant micronutrient supply, the effects of this intervention beyond neurulation on brain biology and specifically glial biology of the offspring remains currently unknown. Previous studies have shown that excessive amounts of prenatal folic acid (FA) alters neurodevelopment and decreases the arborization of cortical projection neurons. Since neurons rely on astrocytes for optimal function and homeostasis, we

hypothesized astrocyte development and activation state may be also adversely affected by prenatal and early postnatal FA supply.**Method:** To examine this question, we provided mice with three different concentrations of FA in their diets, 2 mg FA/kg diet (control), 10 mg FA/kg diet (FA excess), and 20 mg FA/kg diet (FA superexcess), no folate (deficient), or an excess of folinic acid (11.7 mg/kg), in contrast to FA, a reduced, natural form of folate. We collected juvenile offspring and analyzed astrocyte distribution and activation in different forebrain regions by GFAP immunofluorescence analysis.**Results:** Our results indicate a substantial increase in the number of highly $GFAP^+$ astrocytes in cerebral cortex, white matter, and hippocampus in mice reared on FA excess and superexcess diets. In contrast, the total number of astrocytes and activated astrocytes were decreased in the folinic acid excess group while no significant effects were observed in folate deficient offspring. The prevalence of highly branched, hypertrophied, strongly $GFAP^+$ astrocytes in affected groups presents key features of astrogliosis, suggesting neuropathological outcomes associated with high FA exposure during early life.
Conclusion: Exposure to high amounts of FA during early brain development may present a risk factor to processes guiding generation, differentiation, and function of neurons and astrocytes in ways that adversely impact neural health and may predispose to neurodevelopmental disorders.

Disclosures: A. Mustafa: None. **K. Zarbalis:** None. **R. Green:** None.

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NIH/NINDS Grant R35NS122191
NIH/NIDDK Grant P30DK048520

Title: Dietary DHA deficiency increases microglia numbers in the brain during zebrafish development

Authors: *S. BOK, K. M. RANARD, B. APPEL;
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Abstract: The omega-3 fatty acid called docosahexaenoic acid (DHA) is a critical component of brain cell membranes and is an important nutrient for aspects of neurodevelopment such as neural migration and synaptogenesis. However, the Western-style diets currently consumed by many people lack adequate sources of DHA such as fatty fish and fish oil. Offspring rely solely on DHA transfer from the mother during development. Thus, low dietary intake of DHA during pregnancy can consequently lead to low DHA status in offspring, which has been associated with cognitive deficits and an increased risk for neurodevelopmental disorders such as autism

spectrum disorder (ASD). Importantly, the cellular and molecular mechanisms of DHA deficiency during development remain unclear. DHA status is known to impact the immune response, raising the possibility that DHA deficiency specifically affects microglia, the immune cells of the brain. Using a novel zebrafish model, we investigated how maternal DHA deficiency can affect microglia numbers in offspring. We fed zebrafish either a DHA deficient or DHA sufficient diet, then quantified the number of microglia in the brains of their offspring at 3 days post-fertilization using neutral red dye, which acted as a proxy for microglia. DHA deficient zebrafish larvae exhibited an increased number of microglia (n=18, 17.3 ± 1.51) compared to DHA sufficient controls (n=32, 12.6 ± 1.53) (p = 0.0210). These findings suggest that dietary DHA deficiency is sufficient to cause increased microglia numbers in offspring. Our results shed light on some of the cellular and molecular mechanisms behind DHA deficiency, contributing to our understanding of how DHA deficiency affects neurodevelopment.

Disclosures: S. Bok: None. **K.M. Ranard:** None. **B. Appel:** None.

Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

Support: NIH Grant AG075909
AFAR Kalman Fellowship
Parkinson's Foundation Stanley Fahn Junior Faculty Award

Title: Microglia Mitochondria: Mapping organelle status and influence on microglial function in aging and disease

Authors: *A. W. SCHALER[1,2], K. ESPINOZA[2], D. T. GRAY[3], L. M. DE BIASE[4];
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Abstract: Microglial capacity to adapt to local tissue needs is a hallmark feature of these cells. Yet, a full understanding of the intracellular machinery that allows them to flexibly adjust their cellular phenotype is lacking. Research has shown that macrophage ability to alter cellular phenotype is critically regulated by their mitochondria. Indeed, mitochondria are increasingly recognized as key intracellular signaling hubs, in addition to being ATP producers. However, little is known about microglial mitochondria *in vivo* and whether they play similar roles in regulating microglial capacity to alter cellular phenotype. Here, we utilize novel transgenic crosses and molecular biology and imaging-based approaches to analyze the relationship between mitochondria and key microglial attributes in physiological and pathological contexts that elicit prominent changes in microglial properties. Using transgenic mice with EGFP-labeled

mitochondria in microglia, we analyzed microglia in the nucleus accumbens (NAc) and the ventral tegmental area (VTA), regions where microglia show distinct cellular phenotypes and aging profiles. Confocal microscopy revealed regional differences in mitochondrial mass and aging-associated mitochondrial remodeling in 12-13 month (mo) and 16-18mo mice compared to 2-3mo mice. FACS-based analyses revealed decreases in microglial mitochondrial membrane potential beginning at 12-13mo, which were further reduced by 16-18mo. In response to an inflammatory challenge, systemic lipopolysaccharide (LPS) injection, microglial mitochondria were altered within hours of injection and microglial expression of inflammation-, trophic-, and phagocytosis-relevant genes was strongly correlated with expression levels of specific mitochondria-relevant genes. These findings support the idea that mitochondria influence basal microglia phenotype as well as phenotypic remodeling that takes place over hours to months. Moving forward, we are using RNAseq to investigate differences in microglia with high or low mitochondrial membrane potential across age and characterizing changes in microglia and microglial mitochondria in a preformed alpha synuclein fibril model of PD. Overall, this study provides foundational information about microglial mitochondria and their relationship to differences in cell phenotype that occur across brain region, during pathological insults, and during aging.

Disclosures: A.W. Schaler: None. **K. Espinoza:** None. **D.T. Gray:** None. **L.M. De Biase:** None.

Late-Breaking Poster

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Program #/Poster #: LBP060.15/LBP091

Topic: B.09. Glial Mechanisms

Support: NIA R01AG085531

Title: Modulation of microglia by L-type calcium channels Cav1.2 and Cav1.3

Authors: *B. PALLIYANA[1], C. S. CATUMBELA[2], S. C. HOPP[3];
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Abstract: Microglia, the resident macrophages of the brain, play a major role in immune surveillance and maintaining homeostasis. One of the key pathways that regulates the activity of microglia, is intracellular calcium signalling. Triggered by various extracellular stimuli, intracellular calcium signals modulate microglia responses and can also influence lysosomal and autophagy functions, including phagocytosis, acidification, trafficking and debris clearance.

Microglia dysregulation as well as dysfunction of lysosomes and impaired autophagy are notable features in pathogenesis of neurodegenerative diseases including Alzheimer's and Parkinson's diseases. Among the various potential sources of calcium influx, the L-type calcium channels (LTCCs) hold particular importance, as work from our group suggests that certain LTCC antagonists reduce microglia pro-inflammatory cytokine production, and can also reduce dystrophic neurite pathology in the 5XFAD mouse model of Alzheimer's disease. However, studies elucidating the functional role of LTCC in microglia are limited. We hypothesize that microglial phenotype is regulated by LTCCs, particularly the subunits Cav1.2 and Cav1.3. To study this, we utilized both *in vivo* and *in vitro* microglia-specific conditional knockout (CKO) models of Cav1.2 and Cav1.3. *In vivo*, we found that microglial CKO of Cav1.2 and Cav1.3 in adult mice did not significantly alter behaviour in the open field, novel object recognition, and Barnes maze tasks in the absence of immune stimulation. Future studies will examine how stimulation with lipopolysaccharide (LPS) alters sickness behaviour in Cav1.2 and Cav1.3 CKO mice. *In vitro*, we found that CKO of Cav1.2 and Cav1.3 in neonatal microglia altered some responses to LPS. Quantitative PCR revealed that expression of the lysosomal cysteine protease, cathepsin B (*Ctsb*) was suppressed by LPS, and a 3-way ANOVA revealed an interaction between LPS and Cre treatment. Additionally, LPS increased expression of the pro-inflammatory cytokine gene, *Il1b.* Overall, the current results suggest that microglial Cav1.2 and Cav1.3 have a limited role in regulating microglia phenotype, although additional work is required to understand how LTCC antagonists modulate microglia phenotype and function.

Disclosures: B. Palliyana: None. **C.S. Catumbela:** None. **S.C. Hopp:** None.

Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

Support: NIH/NINDS: R35NS132326

Title: Cortical microglia promote noradrenergic signaling to maintain wakefulness

Authors: *Y. LIANG;
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Abstract: Microglia are essential for maintaining brain homeostasis, including the sleep-wake cycle, but the underlying mechanisms remain unclear. Here, using in vivo two-photon imaging (in both head-fixed and freely moving mice) with electroencephalogram-electromyogram (EEG-EMG) recording, we investigated microglial process dynamics and their interactions with locus coeruleus (LC) noradrenergic (NE) axons in the frontal cortex across sleep-wake states. During sleep or chemogenetic suppression of LC neurons, microglia enhanced their surveillance ability and increased interactions with LC-NE axons. Correlative electron microscopy at nanometer

resolution identified structural contacts between microglial process endings and NE boutons. Mechanistically, microglia-bouton interactions are partially mediated by the ATP-P2Y12 signaling and enhance Ca^{2+} signaling in NE axons, independently of the sleep-wake state. These findings suggest that microglial interactions with NE axons promote cortical norepinephrine transmission and maintain stable wakefulness.

Disclosures: Y. Liang: None.

Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

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Topic: B.09. Glial Mechanisms

Support: NIH 3K12GM081266-15S1
Weill Neurohub Fellowship

Title: Type I interferon signaling mediates microglial engulfment in the developing zebrafish brain

Authors: *L. K. RANDOLPH[1], M. GIRGUIS[2], A. V. MOLOFSKY[3];
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[2]Psychiatry and Behavioral Sciences, University of California, San Francisco, Fullerton, CA;
[3]Psychiatry and Behavioral Sciences, University of California, San Francisco, San Francisco, CA

Abstract: Type I interferon signaling is activated in response to viral infection, limiting viral replication and promoting the clearance of infected cells. Our laboratory has discovered that type I interferon-responsive microglia are also critical for healthy brain development in the absence of viral infection (Escoubas, Dorman, *et al*., *Cell*, 2024). These microglia are highly phagocytic and frequently engulf whole neurons. Whether type I interferon-responsive microglia engulf only neurons that have already initiated the process of cell death or whether they are able to selectively prune living neurons to fine-tune existing circuits remains an open question. Using time-lapse imaging to capture microglial engulfment of neurons in real time in the developing zebrafish brain, I have discovered that engulfment of non-apoptotic neurons ("phagoptosis") occurs throughout development, with more frequent phagoptosis events at later developmental timepoints. To determine how type I interferon signaling mediates microglial engulfment and phagoptosis, I have generated novel zebrafish lines for interferon gain- and loss-of-function. I found that a loss of type I interferon signaling results in an accumulation of neuronal material inside microglia, suggesting that interferon signaling is required for efficient digestion of engulfed material. Interferon gain-of-function increases the overall number of microglia in the optic tectum region of the zebrafish brain. To determine how phagoptosis is impacted, I am currently performing high-resolution time-lapse imaging using fluorescent markers for specific stages and types of cell death in these gain- and loss-of-function zebrafish lines. Together, the

findings from this work will illuminate how type I interferon-responsive microglia sculpt neural circuitry in both physiological conditions and in conditions involving heightened interferon signaling, such as early life viral infection and type I interferonopathies.

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Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

Support: NSF Grant 2150799
Schmitt Program in Integrative Neuroscience (SPIN)

Title: A two-photon fluorescence-recovery-after-photobleaching technique reveals microglia and age-dependent changes in extracellular matrix pore size

Authors: *S. PAUL[1,2], A. K. MAJEWSKA[3], E. BROWN[2];
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Abstract: Learning and memory depend on the dynamic movement of diffusible molecules and remodeling of dendritic spines — processes essential for synaptic plasticity and new neural connections.The brain's extracellular matrix (ECM) can act as a physical barrier to molecular and cellular motions. We hypothesize that microglia are key regulators of ECM structure because of their highly motile processes and production of ECM-degrading enzymes. To test this, we used acute cortical slices from *Cx3cr1*^{CreER}*Ai9-tdTomato* mice and employed a quantitative, two-photon fluorescence recovery after photobleaching (2P-FRAP) method that we developed and optimized to measure diffusive transport within the ECM. Our objective was to determine whether microglia actively modulate ECM hindrance as reflected in diffusion measurements.We first validated the 2P-FRAP assay *in vitro*. In free solution, 2 MDa FITC-dextran (hydrodynamic radius, R ~ 30 nm) recovered more slowly than 500 kDa dextran (R ~ 15 nm) when compared by the diffusion time constant, τ ($p < 0.001$). In 1% agarose gels, τ scaled with the probes' radius to its first power, but the entire tracer curve showed a uniform vertical upward shift relative to water measurements, consistent with increased hindrance in the gel matrix. A similar pattern was observed in acute cortical slices: τ increased approximately to the first power of R, and a vertical shift across tracers reflected substantial ECM-imposed hindrance. Because the tracer curve obtained in the brain ECM maintained the same linear relationship as observed *in vitro*, no distinct pore-size cutoff was detected within the tested tracer range (~4.5-30 nm), suggesting that the cortical ECM pore size in a healthy mouse brain exceeds our largest probe radius.If microglia actively reshape ECM architecture, then removing microglia should alter the average effective pore size and therefore shift diffusion measurements into our testable range. In addition, we

asked whether our method could detect previously reported age-related reductions in ECM pore size in other rodent studies. Indeed, our age-dependent analysis showed a 39% increase in τ for 2 MDa dextran in 12-week-old versus 4-week-old mice (mixed-sex cohort, n = 3-8, $p < 0.01$), while smaller tracers were not significantly different. Moreover, pharmacological depletion of microglia (>90% depletion with 290 mg/kg PLX3397 administered through chow for 6 days) in 4-week-old mice also selectively increased τ for the 2 MDa tracer by 39% (mixed-sex cohort, n = 3-8, $p < 0.05$). Together, these results are consistent with the conclusion that microglia contribute to shaping ECM pore structure during early cortical development.

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Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

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Topic: B.09. Glial Mechanisms

Support: NIA grant: U54 AG054349

Title: The Abi3S212F Alzheimer's Disease risk variant induces amyloid beta plaque remodeling and disrupts microglia-plaque dynamics

Authors: *C. A. BUTLER[1], M. KI[2], G. MILINKEVICIUTE[1], S. KAWAUCHI[3], H. LIANG[4], A. GOMEZ ARBOLEDAS[5], D. DUONG[6], N. T. SEYFRIED[7], A. J. TENNER[8], F. M. LAFERLA[9], A. MORTAZAVI[4], V. SWARUP[10], G. MACGREGOR[1], K. N. GREEN[11]; [1]University of California, Irvine, Irvine, CA; [2]University of California Irvine, Irvine, CA; [3]IMIND/TMF, University of California, Irvine, Irvine, CA; [4]UC Irvine, Irvine, CA; [5]UCI MIND, University of California, Irvine, Irvine, CA; [6]ARC proteomics, Atlanta, GA; [7]Human Genetics, Emory University, Atlanta, GA; [8]Neurobiology and Behavior, The Regents of the University of California, Irvine, Irvine, CA; [9]UC Irvine, Univ California, Irvine, Irvine, CA; [10]Neurobiology and Behavior, University of California, Irvine, Irvine, CA; [11]Neurobiology and Behavior, University of California, Irvine, CA

Abstract: The microglial gene *ABI3* has been implicated in Alzheimer's disease (AD) risk, with the ABI3^{S209F} variant being associated with increased risk for developing Late-Onset AD. However, the functional impact of human variants remains poorly understood. To address this, we generated a mouse model that has the same amino acid switch at the equivalent position in the mouse genome, S212F.

To determine the effects of the *Abi3*^{S212F} variant on amyloid pathology and microglial responses, male and female 5xFAD and 5xFAD/*Abi3*^{S212F} mice were aged to 4, 12, and 18 months, representing early, middle, and late disease stages. Amyloid burden was evaluated using thioflavin S (dense-core plaques) and the OC antibody (fibrillar Aβ). 5xFAD/*Abi3*^{S212F} mice exhibited reduced dense-core plaque deposition in cortex from 12 months and in subiculum at all

ages, while fibrillar Aβ was unchanged or selectively increased at 12 months. Soluble Aβ levels were unaltered between 5xFAD and 5xFAD/*Abi3*^{S212F} genotypes, suggesting age-dependent redistribution of Aβ from compact plaques into more fibrillar, potentially more, neurotoxic species.
Microglial responses to plaques were assessed by IBA1, CD68, and PU.1 staining. Microglial density and volume were preserved until 18 months, when both were significantly reduced in 5xFAD/*Abi3*^{S212F} mice, disproportionate to plaque loss. At this stage, microglial activation (CD68+) and number of plaque-associated microglia were markedly decreased in cortex and subiculum. These findings suggest that *Abi3*^{S212F} microglia may have deficits in recruitment, proliferation, reactivity to plaques and/or be more vulnerable to Aβ-induced cell death.
Supporting an effect on vulnerability to cell death, unbiased proteomics identified a specific interaction between *Abi3*^{S212F} and Gasdermin D (GSDMD), the key effector of pyroptosis. Consistent with this, 18-month 5xFAD/*Abi3*^{S212F} mice showed increased GSDMD+/IBA1+ microglia in the subiculum.
Together, these results suggest the *Abi3*^{S212F} variant results in a loss of function while also revealing a novel *Abi3*^{S212F} -GSDMD interaction that may promote plaque-associated microglial death. Collectively, our findings demonstrate that *Abi3*^{S212F} alters plaque composition, impairs microglial-plaque dynamics characterized by deficits in microglial survival and compaction activity. Ultimately providing new insight into how *ABI3* variants may contribute to AD progression.

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Late-Breaking Poster

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Topic: B.09. Glial Mechanisms

Support: NIH Grant RF1NS135652
NIH Grant RF1NS135652-01S1

Title: Microglia depletion attenuates immune cell chemotaxis after traumatic brain injury in aged mice

Authors: *V. VILLANUEVA, K. FORD, H. HAN, S. SCHWULST;
Surgery, Northwestern Univ., Chicago, IL

Abstract: Traumatic brain injury (TBI) afflicts over 3 million Americans every year. Patients over 65 years of age experience increased mortality and greater long-term neurocognitive

morbidity compared to young adults. Aged microglia produce chemoattractants leading to a selective recruitment of T-cells into the brain. Our previously published data shows an age-specific influx of CD8+ effector T-cells into aged brains after TBI correlating to worse neurocognitive outcomes. Therefore, we hypothesized that depletion of microglia would attenuate accumulation of T-cells in the injured brain after TBI in aged mice. Young adult (14-weeks) and aged (80-weeks) C57BL/6 male mice (N=40) underwent microglia depletion via PLX5622, a CSF1R inhibitor, formulated into standard rodent chow at 1200 ppm vs. sham depletion with a control diet. Microglia depletion was confirmed via flow cytometry. After depletion, mice underwent TBI via controlled cortical impact vs sham injury. Brains were harvested at 8 hours or 2 months post TBI. Flow cytometry was used to assess the immune cell infiltrate and cytokine levels were assessed with a Luminex assay. Data was analyzed using two-way ANOVA and Tukey's multiple comparison test. Microglia depletion led to significant reduction of IL-2 8 hours post-TBI compared to sham depletion (4.4pg/mL ± 0.3 vs. 2.5pg/mL ± 0.7, $p<0.002$). This correlated to a 90% reduction of CD8+ T-cell infiltration as compared to mice receiving the control diet ($p<0.0001$). IL2 stimulates growth, proliferation, and subsequent differentiation of T-cells. In addition, microglia depletion also led to significant reduction in the proinflammatory cytokines CXCL10, CCL3, CCL7, CCL2, CXCL2, and CCL4 at 8 hours post-injury. Each of these cytokines/chemokines have been associated with recruitment of inflammatory leukocytes after TBI. No significant differences in any of these cytokines was detected at 2 months post-injury. Suggesting that T-cell recruitment into the injured brain is an acute, age-specific, response. We hypothesized that microglia depletion would attenuate T-cell accumulation in the injured brain after TBI in aged mice. Our data shows a marked reduction in several chemoattractant cytokines in microglia depleted TBI mice correlating to a significant reduction in effector T-cells with the aged, injured, brain. In particular, IL2 and CXCL10 expression are known to be associated with T-cell responses. This gives novel insight into a potential mechanism for T-cell recruitment in aged TBI. Further understanding of microglia and T-cell interactions has therapeutic potential in reducing the long-term morbidity and inflammation in aged subjects post-TBI.

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Late-Breaking Poster

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Program #/Poster #: LBP060.21/LBP097

Topic: B.09. Glial Mechanisms

Support: NIEHS P30ES030283

Title: Zeb1, beta-catenin and axin2 signaling alterations in the cortex of the BTBR and Shank3 mouse models of ASD

Authors: *I. TUNCALI[1], R. JAGADAPILLAI[2], G. NORIEGA[3], A. IKRAM[1], E. GOZAL[4], N. NAGARAJAN[5], G. N. BARNES[6];
[1]University of Louisville, Louisville, KY; [2]Pediatric Research Institute, University of Louisville School of Medicine, Louisville, KY; [3]Baylor College of Medicine, Houston, TX; [4]Pediatrics, Pharm & Tox, Physiology, Dept of Pediatrics PRI / University of Louisville, Louisville, KY; [5]University of Louisville Department of Pediatrics, PRI, Louisville, KY; [6]Dept Neurol, University of Louisville School of Medicine, Louisville, KY

Abstract: Neuroinflammation is a growing area of interest in autism spectrum disorder (ASD) research. Wnt signaling plays a crucial role in neuroglial differentiation and previous studies report that Wnt hyperactivation is sufficient to induce ASD behavior in mice. Wnt activation requires active ß-catenin nuclear translocation. Axin2 targets ß-catenin to degradation except when bound to the glycolytic enzyme enolase 1 (Eno1). Studies in Shank3 KO and VPA mice showed that preventing Axin2 interaction with Eno1 promoted synaptic maturation and rescued social behavior, but whether this occurs in BTBR mice, an inbred ASD mouse model, is unknown. Zeb1, a transcription factor which binds to the promoter of Axin2, is associated with neuroglial development and synaptic maturation and has been implicated in ASD. We aim to uncover an Axin2-Eno1 association in BTBR mice and provide evidence for the role of Zeb1 in dysregulation of Wnt signaling in microglia of BTBR and Shank3 mice. We assessed ß-catenin, Axin2, Eno1 and Zeb1 expression in 3m/o male BTBR, Shank3, and C57 control mice, and subcellular localization and protein interaction in 3 m/o male BTBR and C57 mice. Immunofluorescent (IF) staining (n=3), western blot (WB) (n=3), subcellular fractionation (n=1), Axin2 immunoprecipitation (IP) followed by Eno1 WB (n=2), were performed on homogenized cortex, and RT-qPCR (n=3) was performed using mRNA isolated from fresh frozen cortex samples. All WB were developed using a Bio-Rad ChemiDoc imaging system and WB and IF were quantified with ImageJ software. Data were analyzed using unpaired t- tests with $p<0.05$ significance and standard ANOVA with Tukey correction for multiple comparisons with $p<0.05$ significance.WB of subcellular fractions showed increased nuclear ß-catenin and Zeb1 expression in BTBR. IF showed increased Zeb1 in both BTBR and Shank3 cortex, co-localizing with microglial TMEM119 in BTBR. These data suggest increased Wnt pathway activity in cortical microglia of BTBR. Axin2 mRNA was increased in the BTBR cortex, and IP showed enhanced association to Eno1 in BTBR cortex compared to C57. This association, similar to that described in Shank3 KO and VPA models, may suggest that Eno1 binding to Axin2 protects ß-catenin from degradation, enhancing Wnt signaling in BTBR. The details of this mechanism are currently unknown but suggest that Axin2-Eno1 interaction and Zeb1 regulation lead to enhanced Wnt signaling in cortical microglia. Further studies are needed to fully elucidate this signaling pathway, its impact in neural circuitry including synaptic maturation, developmental timeline and brain area-specific characteristics.

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Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

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Program #/Poster #: LBP060.22/LBP098

Topic: B.09. Glial Mechanisms

Support: Denardo Foundation

Title: Investigating the role of neuroligin 2 in oligodendrocyte development and myelination

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Abstract: During CNS development, oligodendrocyte precursor cells (OPCs) receive synaptic input from neurons, but the molecular mechanisms organizing these contacts and their impact on OPC fate remain poorly defined. Neuroligin-2 (Nlgn2), a synaptic adhesion molecule present at neuronal synapses, is expressed in OPCs and may play a key role in organizing neuron-OPC connectivity. Neuronal activity has been shown to be important for oligodendrocyte myelination and maturation. However, the functional relevance of Nlgn2 at neuron-OPC synapses is unclear, nor has its role in myelination been examined previously. We hypothesize that Nlgn2 facilitates the formation and maintenance of synaptic input onto OPCs, thereby influencing OPC maturation and myelination. To test this, we are using a conditional knockout mouse model ($Ng2^{-Cre}$; $Nlgn2^{Fl/Fl}$mice) and a combination of in vivo and in vitro methods to characterize how synaptic architecture, OPC differentiation, and early myelination are altered in the absence of Nlgn2 in OPCs. We confirmed expression of Nlgn2 in OPCs, and specific loss of Nlgn2 in OPCs using RNAScope experiments. We are conducting all experiments in P28 adolescent mice, counterbalanced by sex, with a sample size of at least 5 mice per experiment, and 3 technical replicates from each brain. We are using age-matched littermate $Nlgn2^{+/+}$ mice as controls. We used immunohistochemistry to assess oligodendrocyte maturation and myelination in the prefrontal cortex, a region with high expression of Nlgn2 in OPCs. We found that in the PFC of $Ng2^{-Cre}$; $Nlgn2^{Fl/Fl}$ mice, the percentage of immature and mature oligodendrocytes is decreased. In the same region, myelin immunodensity is also decreased and myelin coherency, an inverse measure of complexity, is increased. We have also examined changes in the nodes of Ranvier in $Ng2^{-Cre}$; $Nlgn2^{Fl/Fl}$ mice in white matter tracts and have found decreased expression of the paranodal marker Caspr in paranodes in Nlgn2 conditional mutants. Using deletion mutant rabies virus to trace monosynaptic connections between neurons and OPCs, we have found that loss of Nlgn2 in OPCs also resulted in a significant decrease in the number of neuron to OPC synapses. Finally, we are examining synapse formation to determine whether neuronal excitatory and inhibitory synapses are affected by Nlgn2 loss in OPCs, using in vitro neuronal cultures to

examine changes in neuronal synapse type, number, and synaptic protein expression. Together, these findings confirm a role for Nlgn2 in OPCs, as its loss results in defects in neuron to OPC synapse formation, maturation of oligodendrocytes, and myelination in early postnatal development.

Disclosures: A. Rafalovich: None. **W. Stroh:** None. **A. Hutchin:** None. **L. Tsou:** None. **F. Bussiere:** None. **D.S. Moura:** None. **L.A. Cocas:** None.

Late-Breaking Poster

LBP060: B.09. Glial Mechanisms

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP060.23/LBP099

Topic: B.09. Glial Mechanisms

Support: NIH R01 Grant 5R01MH126108

Title: Reduced proportion of oligodendrocytes in people with schizophrenia

Authors: *A. BURNETTE[1], Y. ZHU[2], H. NORTH[3], F. A. MIDDLETON[4], M. J. WEBSTER[5], C. S. WEICKERT[6], M. BECHLER[7], C. NIKOLAUS[2], J. BOYER[8];
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Abstract: Deficits in oligodendrocyte number and function likely underlie impaired fractional anisotropy(FA) and altered white matter tracts in schizophrenia. Reduced oligodendrocytes in the prefrontal cortex and hippocampus are found in people with schizophrenia. Since oligodendrocyte dysfunction can affect neuronal connectivity and contribute to impairments in learning, memory,and executive function, we aimed to further define oligodendrocyte impairment in schizophrenia using snRNA seq. We characterized 31 cell clusters from the rostral caudate and subependymalzone (SEZ) tissue and defined 8 clusters of oligodendrocyte precursor cells (OPCs) and mature oligodendrocytes. The proportion of mature oligodendrocytes was decreased in schizophrenia(27.1±2.1%), compared to controls (37.8±3.4%, z=-2.71, p=0.014). Similarly, Olig2+(normalized expression >1) cells were decreased (3.85±0.43% vs. 7.72±0.90%, z=-4.19,p=4.95E-04). Within mature oligodendrocytes, the reduced subtype had increased stress-responsive and metabolic transcripts (HSPA1A, TXNIP, ENO4), and reduced expression of myelination-associated transcripts (LIPA, ZDHHC9, PLPPR1), suggesting that stress-responsive oligodendrocytes may synthesize less myelin in schizophrenia. Conversely, the proportion of another less abundant oligodendrocyte subtype was increased in schizophrenia

(4.86±0.67%)compared to controls (2.67±0.92%), and marked by neurotransmission-associated mRNAs(SYT1, NRXN1, GRIK2). Within this cluster, we found increased mRNAs for signaling and early oligodendrocyte states (CNST, ITPR1, PDZD2). More oligodendrocytes with an“immature” phenotype may indicate a lack of proper development or a compensatory response in schizophrenia. Numerous Olig2+ nuclei were found along the human lateral ventricle by immunohistochemistry, but we did not detect a diagnostic difference in Olig2+ cells in the SEZ[t(27)=0.784, p=0.440]. The unchanged cell proportion confirms oligodendrocyte lineage cells are still present in the SEZ, but our transcriptomic data indicate subtype imbalances and functional shifts within oligodendrocytes. Thus, the decrease in oligodendrocytes may be within the caudate. These findings suggest a selective loss of myelination-associated oligodendrocyte subtypes; however, further work is needed to anatomically localize them and to understand their relationship to the putatively increased immature oligodendrocyte subtype in the basal ganglia of schizophrenia.

Disclosures: A. Burnette: None. **Y. Zhu:** None. **H. North:** None. **F.A. Middleton:** None. **M.J. Webster:** None. **C.S. Weickert:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH R01 PI. **M. Bechler:** None. **C. Nikolaus:** None. **J. Boyer:** None.

Late-Breaking Poster

LBP061: B.10. Neuro-Oncology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP061.01/LBP100

Topic: B.10. Neuro-Oncology

Title: Investigating Polycomb-driven epigenetic reprogramming of SOX2 pathway in glioblastoma multiforme

Authors: *A. COVINO[1,2], S. FERRETTI[3], E. BARONCHELLI[4], M. KUBACKI[1], A. SESSA[5], V. BROCCOLI[5,6];
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Abstract: Glioblastoma Multiforme (GBM) is the most common brain cancer in adults, with a very poor prognosis due to the limited efficacy of current treatments. Despite substantial advances in glioblastoma research, median survival remains 12-15 months, largely due to residual cancer stem cells (CSCs) that regenerate tumors and drive therapy resistance. Given this complex landscape and the pivotal role of the transcription factor SOX2 in GBM, we developed innovative strategies of epigenetic silencing that could affect its entire molecular pathway. Initially, we generated a synthetic SOX2 epigenetic silencer (SES) that binds to SOX2 targets and permanently silences them through stable modifications. Positive results from *in vitro* and *in*

vivo GBM models led to the development of a new variant, SES-YAF2, which combined the SOX2-binding region to the YAF2/RYBP domain from the non-canonical PRC1 to induce repressive epigenetic changes via Polycomb Repressive Complexes (PRCs). Specifically, PRC1 mono-ubiquitinates histone H2A at Lys119, while PRC2 tri-methylates histone H3 at Lys27-together orchestrating synergistic gene repression mechanism.SES-YAF2 was delivered via lentiviral transfection into SNB19 and classical CSCs (cCSCs) cell lines, followed by proliferation assay, gene expression analyses and CUT&Tag epigenomic profiling. Our results showed that lentiviral transfection with SES-YAF2 effectively reduced proliferation in SNB19 ($p<0.0001$) and cCSCs ($p<0.0001$) compared to controls. RNA-Seq analysis identified several direct SOX2 targets showing significant downregulation (e.g., HDAC9 (log2FC=-3.24 $p<0.0001$), JAG1 (log2FC=-1.6 $p=0.00023$), SNAI2 (log2FC=-1.9 $p<0.0001$), VIM (log2FC=-2.01 $p<0.0001$). Moreover, gene ontology analysis revealed that critical oncogenic regulators were also repressed (e.g., UBTF (ENCODE); NFE2L2 (CheA); SMAD4 (CheA); TGF-β pathway), suggesting a cascade-like effect on tumor-promoting transcriptional programs. Epigenomic CUT&Tag profiling demonstrated significant enrichment of H2AK119Ub at SOX2 targets in SES-YAF2-treated samples versus controls, with stronger increase at downregulated genes globally and within a part of the SOX2 subset. While further clarification is needed to confirm the precise role of Polycomb recruitment, these results highlight the potential of this strategy to reprogram tumorigenic transcriptional networks and impair GBM proliferation.In conclusion, our research focuses on repurposing the repressive capabilities of Polycomb group domains after fusion with DNA binders, for generating a new class of targeted epigenetic glioblastoma anti-tumoral factors.

Disclosures: A. Covino: None. **S. Ferretti:** None. **E. Baronchelli:** None. **M. Kubacki:** None. **A. Sessa:** None. **V. Broccoli:** None.

Late-Breaking Poster

LBP061: B.10. Neuro-Oncology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP061.02/Web Only

Topic: B.10. Neuro-Oncology

Title: Integrating imaging, genomics, and machine learning to predict language deficits in diffuse glioma

Authors: *A. DADA[1], S. KRISHNA[2], D. BRANG[3], S. HERVEY-JUMPER[4];
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Abstract: Background: Diffuse gliomas frequently invade language-critical cortex, producing aphasia. Although these regions remain active in speech processing, their ability to encode

information is impaired, and the molecular drivers are poorly understood.
Objective: To identify imaging and genomic predictors of aphasia in patients with supratentorial glioma.
Methods: We evaluated 88 adults (median age 59; 38% female) with newly diagnosed WHO grade 2-4 gliomas who underwent targeted next-generation sequencing and Quick Aphasia Battery (QAB) testing (2017-2021). Support vector regression lesion-symptom mapping (SVR-LSM) identified voxels where tumor involvement correlated with QAB performance. A random forest model integrating radiomic, genomic, and clinical data ranked predictors of language deficits; key features were validated with multivariable regression. Single-nucleus RNA sequencing (snRNA-seq) from resected tumors clarified gene expression patterns.
Results: SVR-LSM localized a 61,745-voxel cluster in the left superior temporal gyrus where tumor overlap predicted poor QAB scores. Machine learning analysis highlighted three radiographic variables—T1 contrast enhancement, T2 FLAIR hyperintensity, and lesion volume in this cluster—and seven genomic alterations. ARID2 mutation (3/88) was the strongest molecular predictor, linked to significantly reduced language performance (QAB 6.6 ± 1.4 vs. 9.1 ± 1.3; $p = 0.01$). Multivariable analysis confirmed ARID2 status ($\beta = -1.42$; 95% CI -2.63 to -0.21; $p = 0.02$) and contrast-enhancing voxel burden ($\beta = -0.08$ per 100 voxels; $p < 0.001$) as independent predictors. snRNA-seq revealed prominent ARID2 expression in proliferating tumor cells, suggesting chromatin remodeling dysregulation contributes to cortical network failure.
Conclusion: An integrated radiogenomic model identifies ARID2 mutation and localized contrast-enhancing tumor burden as robust predictors of glioma-associated aphasia. These findings nominate ARID2 as a mechanistic driver of language impairment and provide actionable biomarkers for surgical planning and targeted therapies to preserve cognition.

Disclosures: A. Dada: None. **S. Krishna:** None. **D. Brang:** None. **S. Hervey-Jumper:** None.

Late-Breaking Poster

LBP061: B.10. Neuro-Oncology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP061.03/LBP101

Topic: B.10. Neuro-Oncology

Support: SECIHTI Grant CBF2023-2024-1982

Title: Effect of temozolomide and photodynamic therapy combination with TiO_2-FA-ZnPc nanoparticles in glioblastoma cell lines.

Authors: *C. RODRÍGUEZ-PÉREZ[1], S. RODRIGUEZ[2], G. JARDON[3], M.-R. MANRIQUEZ[4], E. ORTIZ[1];
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Abstract: Glioblastoma (GB) is an aggressive and lethal brain cancer with high molecular and cellular heterogeneity, which often exhibit recurrence after surgical resection and resistance to conventional chemotherapeutic and radiologic management. Temozolomide (TMZ) is an alkylating drug used to treat GB, however, 50% of patients do not respond. Photodynamic therapy (PDT) is a non-invasive medical procedure, that consist in the activation of photosensitizers with light. The aim of this study was to analyze the effects of titanium dioxide (TiO_2)-Zinc phthalocyanine (ZnPc) nanoparticles (NPs) functionalized with folic acid (FA) in combination with TMZ on human GB cell lines, one resistant (LN18) and another sensitive (U251) to TMZ. The cytotoxicity of TiO_2-FA-ZnPc was evaluated with MTT and trypan blue assays at 24h and 72h, resulting biocompatible in the range of 1-100 µg/mL. Photoactivation was performed by irradiating cells with ultraviolet (UV) light for intervals of 30s at distance of 10 cm, alone or in presence of TMZ, previous NPs incubation for 10min, the phototoxicity was enhanced with TMZ. After, levels of Ki67 and caspase-3 were detected by western blot, observing a reduction in first one and an increase in the second, when cells were treated in combination. PDT with TMZ showed synergistic antiproliferative and proapoptotic effects in both GB cell lines. These preliminary results opening the possibility of use it in clinical as an alternative to conventional treatments.

Disclosures: C. Rodríguez-Pérez: None. **S. Rodriguez:** None. **G. Jardon:** None. **M. Manriquez:** None. **E. Ortiz:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.01/LBP102

Topic: G.01. Neuroethology

Support: Fondation pour la Recherche Médicale, grant number SPF202209015738, to EV

Title: Seeing in the dark: Neuronal representation of water currents in the optic Tectum of the blind cavefish *Astyanax mexicanus*

Authors: *E. VINEPINSKY[1], S. NOURIN[1], M. PETRACCONE[1], E. LLOYD[2], A. C. KEENE[3], G. SUMBRE[1];
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Abstract: Despite living in complete darkness, Astyanax cavefish can successfully prey on small, moving organisms. This ability is believed to be based on the lateral line, which enables them to detect the location of prey in the absence of vision. Despite years of investigation into the evolution of the lateral line and other sensory systems, the neuronal processing principles of the lateral line in the Astyanax brain remain unknown. Using transgenic larvae expressing GCaMP6s from the Pachón cave and surface-fish populations (generated by Keene Lab), we

investigated the representation of small water currents sensed by the lateral line. We imaged activity in the optic tectum, the primary visual area in the fish brain, while delivering small water-current stimuli. Despite eye loss in cavefish, the tectum shows only ~20% reduction in size, and its spontaneous activity shows no difference from that of surface fish.We found a unique mapping of the lateral line in the tectum of blind cavefish. Small water current stimuli presented in front of the fish resulted in neuronal activation of the medial-ventral part of the tectum. Moving the stimuli laterally shifted the center of mass of the neuronal responses along the tectal axis, which corresponds to the retinotopic axis in surface fish and zebrafish. Furthermore, this tectal lateral-line map is also found in the Astyanax surface population, co-aligned to the visual retinotopic map. The lateral line-tectal map appears to be specific to the anterior lateral line, as we did not find any neuronal response in the tectum to water jets along the body and tail of the larvae. To ensure the relevance of this map to prey capture, we examined cavefish with lesions in the tectum while they were hunting for food. Our results indicate that lesions of the tectum indeed impaired prey capture behavior. In addition, retrograde labeling of the tectum shows direct connections to the medial octavolateralis nucleus (MON), which is the first brain region that receives lateral line inputs. This direct connection has not been described so far.Therefore, we hypothesize that the unique mapping of the anterior lateral line in the optic tectum is what allows Astyanax to hunt in the dark. This ability, present in both morphs, enabled Astyanax mexicanus to survive the initial transition into its new dark cave habitats, making it the only fish species to populate these dark caves. Such a pre-existing ability to feed in complete darkness might be required for fish to evolve into a cave-dwelling form. This can explain why no other fish, except Astyanax, is found in the eastern Mexican cave system and why only a limited number of fish species have undergone this evolution around the world.

Disclosures: E. Vinepinsky: None. **S. Nourin:** None. **M. Petraccone:** None. **E. Lloyd:** None. **A.C. Keene:** None. **G. Sumbre:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.02/LBP103

Topic: G.01. Neuroethology

Support: HFSP

Title: Evolution of neuronal computations underlying navigation.

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Abstract: Navigation is the capacity of animals to recognize their spatial location and orient themselves to move within an environment. This is a crucial process for survival. Although

substantial progress has been made in understanding the navigation system of vertebrates, how do navigation systems evolve to adapt to drastic changes in the environment is unknown. To address this question, it is necessary to use an animal model living in habitats with significant different constraints. Astyanax mexicanus fish is a unique animal model to study evolution. This species exists in two distinct morphs: a sighted form found in rivers (surface fish), and several blind populations living in perpetual darkness of caves (cavefish). Despite displaying regressive traits (loss of vision and pigmentation), cavefish also show enhanced mechanosensory and chemosensory capacities, providing an unparalleled perspective on sensory and behavioral adaptations. However, the behavioural and neural circuit navigation principles in A. mexicanus, have never been studied. Our hypothesis is that the evolutionary adaptations to the dark environment have shaped the neuronal circuits and computations supporting navigation. Preliminary experiments using two photon microscopy have shown the presence of neuronal assemblies in the anterior hindbrain, a brain region known to harbor head direction cells in zebrafish. These assemblies show a different distribution of neuronal activity correlations between both morphs, with more positive and more negative correlations in cavefish than in surface morphs. Furthermore, we found that cavefish exhibit Head direction cells in the anterior hindbrain with lower resolution than surface morphs, but with higher consistency in firing to their preferred angle. This data suggest that evolution adapted the functional connectivity of the head direction system, by increasing the excitatory synaptic connections and adding inhibitory synapses. This rewiring of the functional connectivity of the head direction system may have improved the circuit's robustness at the expense of resolution.

Disclosures: J.P. Casanova: None. **E. Vinepinsky:** None. **G. Sumbre:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.03/LBP104

Topic: G.01. Neuroethology

Support: NIH Grant R01NS128500
NIH Grant NIH P40OD018537

Title: A novel cold-sensing mechanism in the Drosophila anterior

Authors: *A. XU[1], H. SON[2], X. BAI[3], R. LI[1], E. A. RONAN[4], G.-H. KIM[2], B. YE[5]; [1]University of Michigan, Ann Arbor, MI; [2]Mechanical Engineering, Ulsan National Institute of Science and Technology, Ulsan, Korea, Republic of; [3]Molecular and Integrative Physiology, University of Michigan, Ann Arbor, MI; [4]Biologic and Materials Science, University of Michigan, Ann Arbor, MI; [5]Cell and Developmental Biology, University of Michigan, Ann Arbor, MI

Abstract: The sensation and avoidance of noxious temperatures is essential for survival. While heat sensation has been extensively studied, much less is known about cold sensation, mainly due to the lack of technologies that can lower temperatures with high speed and precision. To address this issue, we have engineered devices that can deliver thermal stimuli rapidly and precisely without mechanosensory input. Here, we use *Drosophila* larvae as a model to investigate cold sensing. By implementing custom-built thermoelectric devices capable of delivering rapid and precise thermal stimuli, we find that cold applied to the larval anterior end elicits the most robust avoidance behaviors. We identify a novel subset of cold-sensitive neurons, the anterior Class III dendritic arborization (aC3da) neurons, as necessary and sufficient for anterior cold avoidance. Optogenetic inhibition of aC3da significantly reduces cold-evoked anterior avoidance behavior, whereas optogenetic activation of aC3da is sufficient to elicit robust anterior avoidance responses. Furthermore, exposing the larval anterior to cold temperatures elicits robust calcium responses within aC3da, demonstrating that aC3da are cold-sensitive. To identify the cold-sensing receptors expressed in aC3da neurons, we implemented a candidate gene approach. Surprisingly, genetic mutations and RNAi-mediated knockdowns of a kainate-type glutamate receptor, not known as thermosensors, in aC3da neurons affected anterior cold responses. Loss-of-function mutations or RNAi knockdown of the receptor in aC3da neurons impaired cold sensitivity on the behavioral and neuronal level, and heterologous expression of the gene conferred cold sensitivity to normally temperature-insensitive cells, demonstrating that the receptor is indeed a cold sensor. Our study characterizes acute cold sensation in *Drosophila* larvae at the behavioral, neuronal, and molecular levels, revealing a previously uncharacterized anterior cold-sensing mechanism that may be evolutionarily conserved to promote temperature-based avoidance and survival across organisms.

Disclosures: A. Xu: None. **H. Son:** None. **X. Bai:** None. **R. Li:** None. **E.A. Ronan:** None. **G. Kim:** None. **B. Ye:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.04/LBP105

Topic: G.01. Neuroethology

Title: The role of an RNA-binding protein in the *Caenorhabditis elegans* motor circuit for backward locomotion

Authors: *R. C. HE[1], T. AHAMED[2], M. ZHEN[1,3], J. CALARCO[1];
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Abstract: RNA-binding proteins play critical roles in RNA metabolism as cell type- and developmental stage-specific regulators. In the nervous system, the structural development and

functional specialization of neural networks are strongly influenced by co- and post-transcriptional regulation of mRNA. While many RNA-binding proteins have been implicated in neuronal development and neurological conditions, their precise function at the circuit level remains poorly understood.
Using the locomotory circuit of *Caenorhabditis elegans* (roundworm) as a model, I am investigating how the RNA-binding protein MBL-1 regulates circuit properties and function. MBL-1 is a homolog of the human Muscleblind-like protein family, which are developmentally programmed regulators of RNA metabolism whose dysfunction contributes to neuromuscular diseases.
My work has uncovered a previously unrecognized locomotory phenotype in *mbl-1* loss-of-function mutants. MBL-1 knockout animals fail to initiate body waves from tail to head during backward locomotion.This phenotype indicates a defect in the neural circuits dedicated to backward behavioural state.I have generated transgenic strains expressing MBL-1 fused to a fluorescent protein and a chemically inducible degron tag. These strains enable temporally and spatially controlled protein depletion through a ubiquitin-mediated degradation system, allowing me to determine the neuronal subtypes and developmental stages critical for MBL-1 function in backward locomotion. The fluorescent tagging further confirmed high expression of MBL-1 in motor neurons and interneurons important for backward movement. Currently, I am in progress of expressing the ubiquitin ligase under neuronal subtype-specific promoters to achieve cell-type-specific depletion.
Together, my research characterizes the functional specificity of an RNA-binding protein in neural circuits that are essential for navigation and escape behaviours.

Disclosures: R.C. He: None. **T. Ahamed:** None. **M. Zhen:** None. **J. Calarco:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.05/LBP106

Topic: G.01. Neuroethology

Support: NIH Grant 5R01DC014989

Title: Anatomical and Electrophysiological Convergence of Parietal and Striatal Circuits Linked to Premotor Cortex During Skilled Behavior in Macaques

Authors: *S. BAUMANN[1], R. AFSAHI[1], M. KIM[1], J. P. RAUSCHECKER[2];
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Abstract: The dorsal stream model of auditory and speech processing suggests a critical role for parietal cortex and putamen in linking auditory input with motor output. While prior anatomical work has established direct connections from auditory regions to premotor cortex (PMC), the

intermediary substrates coordinating this flow remain underexplored. In the present study, we combined anatomical tract-tracing and electrophysiological recording to investigate these pathways in non-human primates. In the anatomical component, cholera toxin B subunit (CTB) tracers were injected into anterior (F2) and posterior (F4) divisions of the PMC in three adult rhesus macaques. Across all monkeys, retrograde labeling revealed dense clusters of CTB-positive neurons within the parietal cortex—including the operculum, posterior supramarginal gyrus (PFG), superior parietal lobule (SPL), lateral intraparietal area (LIP), and area VIP—as well as in the putamen and motor areas, highlighting robust cortico-cortical and cortico-striatal connectivity. Electrophysiological recordings - from areas where we found clusters of cells in our anatomy work - during an auditory-motor integration task revealed strong, concurrent activation of the same PMC subdivisions targeted by tracer injections (F2 and F4), alongside dorsal parietal cortex and putamen activity. Prominent oscillatory patterns in the dorsal parietal cortex suggested prediction-related processing, while synchronous PMC activation indicates functional engagement of the same motor circuits anatomically linked to auditory-associated parietal and striatal regions. These findings support a model in which parietal and striatal circuits serve as intermediary hubs between auditory and motor systems, facilitating predictive coding and sensorimotor integration during complex auditory-motor behaviors.

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Late-Breaking Poster

LBP062: G.01. Neuroethology

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Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.06/LBP107

Topic: G.01. Neuroethology

Support: NIH K99NS133031
Life Science Research Foundation Postdoc Fellowship sponsored by HHMI
HHMI

Title: Evolutionary expansion of the corticospinal system is linked to adaptive dexterity in Peromyscus mice

Authors: *K. TYSSOWSKI[1], J. D. COHEN[2], J. GUO[3], A. W. HANTMAN[4], H. HOEKSTRA[1]; [1]Harvard University, Cambridge, MA; [2]Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC; [3]University of North Carolina Chapel Hill, Chapel Hill, NC; [4]Cell Biology and Physiology, Neuroscience Center, UNC-CH, RCP, Chapel Hill, NC

Abstract: Evolutionary expansion in neuron number supports behavioral adaptations to animals' habitats. Corticospinal neurons (CSNs) are a classic example of this: an increase in the number of CSNs in the primate lineage is thought to underlie their exceptional dexterity. However, the role of CSN number in behavior has been difficult to assess due to the large evolutionary distance between primates and less skilled taxa with fewer CSNs. Here we use deer mice

(*Peromyscus maniculatus*) to overcome this challenge. We compared two closely related subspecies of deer mice: forest mice that evolved dexterous climbing to support a semi-arboreal lifestyle and prairie mice that are less dexterous. We find that forest mice have ~2x larger corticospinal tracts, and that this increase in volume is due to an increase in CSN number, particularly in secondary motor and sensory cortical areas (M2 and S2). Furthermore, in a reach-to-grasp test of dexterity, forest mice display higher success and greater grasping flexibility, using multiple grasp types compared to the stereotyped scooping motion of prairie mice, consistent with the idea that an increase in CSN number supports more dexterous movement. High throughput neural recordings during this task revealed a difference in the timing of activity in forest versus prairie mouse M2, but not M1: in forest mice, the peak of activity was shifted towards the time of grasp. Forest mice also outperform their prairie counterparts on an ecologically relevant climbing task, where they spend more time upright crossing a thin rod, move more quickly, and right themselves more quickly when they fall, suggesting a general increase in motor dexterity not restricted to hand use. To assess whether the increase in CSN number contributes to observed behavioral adaptations, we generated forest-prairie F2 hybrid animals with scrambled genomes, neural features, and behavior. We find that the F2 hybrids with larger CSTs perform better on the rod crossing task, suggesting that expansion of the CST likely supports the adaptive increase in climbing skill in forest mice. Together, our work establishes the forest-prairie deer mouse system as a novel model to investigate the role of neuron number expansion, and CSNs in particular, in dexterous movement.

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Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.07/LBP108

Topic: G.01. Neuroethology

Support: UCR Regents' Faculty Fellowship
Y.Giraldo Startup Funds

Title: Influence of spectral wavelength and light intensity on Drosophila orientation

Authors: *H. PAE[1,2], C. SAN[3], Y. GIRALDO[4,2];
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Abstract: Orientation is a complex behavior performed by many animals that requires integrating external and internal cues to maintain movement with respect to an object. Celestial

objects, such as the sun or the moon, serve as external references for many animals. In addition to these objects, sunlight provides varied visual cues, including differences in wavelength and brightness that can change depending on time of day and/or weather. When multiple types of visual information are available, how are cues prioritized by *Drosophila melanogaster* during orientation? Previously, we tested 2-5 day old female wild-type flies in a flight arena where a fly can rotate freely on its vertical axis and found that flies select a heading relative to a single green or UV LED and fly straight until the LED position changes, when they select a new heading. Additionally, when we presented flies with a dual green-UV stimuli, simulating multiple wavelengths in skylight, we found that flies preferred to use UV to orient. Here, we investigated the robustness of this UV preference during orientation as we varied LED intensities and the presentation order of different wavelengths. We first tested whether flies maintained a UV preference when presented with conflicting cues that would not occur in natural skylight. First, we presented flies with a green LED set 180° from a UV stimulus, and the fly was allowed to fly for 5 min. We then moved one of the LEDs, so that the green and UV stimuli were in the same azimuthal position, and recorded the fly's heading for 5 min (n=40). Similar to previous results, flies preferred to select and maintain their heading relative to UV. However, we found that this UV preference was dependent on photon flux: flies displayed a UV preference only when the UV flux was higher than green. In contrast, when the green flux was matched (n= 40) or higher than UV (n=37), flies used either wavelength to orient. Next, we tested if flies displayed a UV preference when initially presented with a single cue (green or UV) followed by the addition of the second wavelength 180° apart from the initial LED (n=40). This time, we found that flies preferred to maintain their initial heading regardless of wavelength, indicating that flies will use either wavelength to select their heading and will not change direction simply with additional visual information. Our findings suggest a conceptual model of cue hierarchy, where LED position appears to have the greatest effect on heading maintenance, followed by wavelength in an intensity-dependent manner. Our hypothesized model of cue processing provides insight into how different aspects of celestial cues are integrated by the nervous system to influence orientation.

Disclosures: H. Pae: None. **C. San:** None. **Y. Giraldo:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.08/LBP109

Topic: G.01. Neuroethology

Support: Electronics and Telecommunications Research Institute (ETRI) grant funded by the Korean government Grant 25YB1210

Title: Subthalamic nucleus broadband dynamics reflect behavior states in freely moving primates via a wireless electrophysiological recording system

Authors: *G. LEE[1,2], J.-Y. KIM[1], H. KIM[1], M. KIM[3], J. WON[3], K. LIM[4], C.-Y. JEON[3], S. Q. LEE[5], Y. LEE[3], H.-K. LEE[1], H. CHOE[2], C. JE[1];
[1]Brain Links Creative Research Section, ETRI, Daejeon, Korea, Republic of; [2]Department of Brain Sciences, DGIST, Daegu, Korea, Republic of; [3]National Primate Research Center, Korea Research Institute of Bioscience and Biotechnology, Cheongju, Korea, Republic of; [4]Futuristic Animal Resource & Research Center, Korea Research Institute of Bioscience and Biotechnology, Cheongju, Korea, Republic of; [5]Dept. of Mechanical Engineering, San Diego State University, San Diego, CA

Abstract: In Parkinson's disease (PD), beta band(12~30Hz) power of the subthalamic nucleus (STN) has been associated with motor suppression. It has been widely utilized as a closed-loop deep brain stimulation (DBS) biomarker. While beta band abnormalities of STN are well reported in PD, the band dynamics during spontaneous behavior in healthy individuals are poorly understood that can be utilized as a reference for DBS protocol. Characterizing normal STN dynamics provides reference values for calibrating DBS algorithms, and also enables computational modeling of STN function and the progressive pathophysiology of PD. We recorded STN local field potential (LFP) in a freely moving macaque to address this gap using a chronically implanted wireless recording system. LFP and behavior state were continuously acquired during spontaneous locomotion in a passage. For subsequent analysis, behavioral states(30fps, walking vs rest) were manually annotated and synchronized with LFP (8192Hz). The results showed that beta power in the STN was significantly correlated with motor state across all experimental sessions. Changes in beta power over time were weakly positively correlated with the delta-theta-alpha(1~4Hz/4~8Hz/8~12Hz) band and negatively correlated with the gamma-high gamma band(30~50Hz/50~100Hz). In particular, the theta-beta correlation coefficient was a sensitive reflection of the behavior state. In addition, beta power was higher in the rest state than in the walking state, and no consistent behavior state-related characteristics were identified in the lower frequency bands. Using a dimensionality reduction technique (t-SNE), we found that changes in beta power over time were sufficient to distinguish between walking and resting states. We confirmed that these physiological factors can affect STN broadband dynamics. This study suggests that broadband dynamics in the STN reflect the overall behavior states. Analyzing different frequency bands and correlation structures may provide an important basis for future adaptive neuromodulation.

Disclosures: G. Lee: None. **J. Kim:** None. **H. Kim:** None. **M. Kim:** None. **J. Won:** None. **K. Lim:** None. **C. Jeon:** None. **S.Q. Lee:** None. **Y. Lee:** None. **H. Lee:** None. **H. Choe:** None. **C. Je:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.09/LBP110

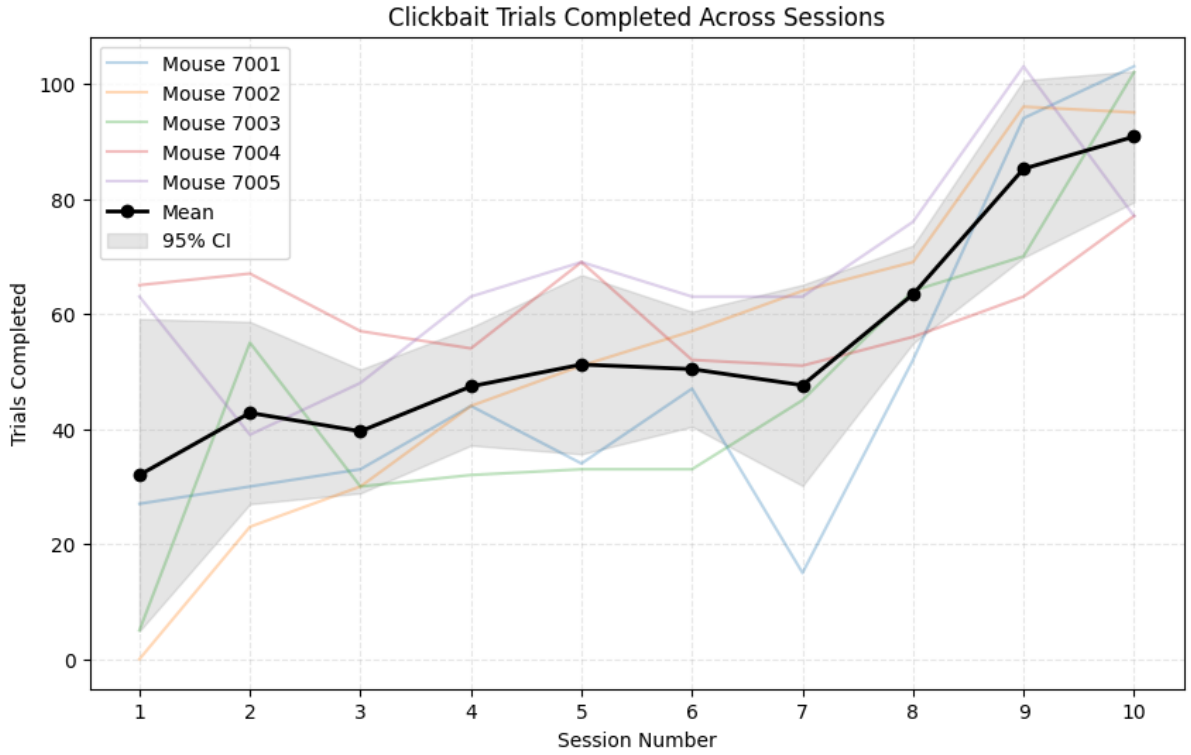
Topic: G.01. Neuroethology

Support: NIH grant R01NS123903

Title: The clickbait paradigm: an agent-controlled foraging task for freely-moving mice

Authors: N. HESS, J. O'NEILL, S. RAFILSON, S. JARAMILLO, *M. SMEAR;
University of Oregon, Eugene, OR

Abstract: Robust analysis of spatial coding in neural circuits requires animals to explore their environment both freely and uniformly, providing neural data from throughout the arena. Task-free paradigms must encourage uniform exploration, but traditional solutions such as scattered food pellets introduce sensory confounds, presenting an obstacle for researchers studying allocentric spatial coding in sensory systems. To address this problem in studying spatial coding in the olfactory system, we developed ClickBait, a novel closed-loop behavioral paradigm that promotes extensive spatial exploration without introducing olfactory or other sensory confounds. ClickBait utilizes real-time video tracking to monitor animal position, as water-restricted animals search for hidden target cells pseudorandomly distributed across the arena floor. When an animal enters a target cell, an audible click signals reward availability at a water port; the animal can then consume the reward at its leisure. After the animal finishes drinking, the next trial begins, and a new target cell is spawned at a pseudorandom location. Researchers can control target cell distribution patterns, thereby enforcing uniform exploration of the arena. In the present work, we recorded behavioral metrics across 10 daily sessions in chronically implanted, tethered, water-restricted mice (n=5). ClickBait leverages natural foraging behavior, and mice rapidly acquired the task within 1-3 sessions, demonstrating sustained performance improvements thereafter. ClickBait represents a methodological advance for spatial neuroscience research, leveraging natural exploratory behaviors to achieve comprehensive spatial sampling while allowing animals to behave agentically and naturalistically without strong researcher-imposed task demands. This work demonstrates ClickBait's reliability and validates a task- and stimulus-free paradigm ideal for investigating spatial representations in sensory systems.



Disclosures: N. Hess: None. **J. O'Neill:** None. **S. Rafilson:** None. **S. Jaramillo:** None. **M. Smear:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

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Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.10/LBP111

Topic: G.01. Neuroethology

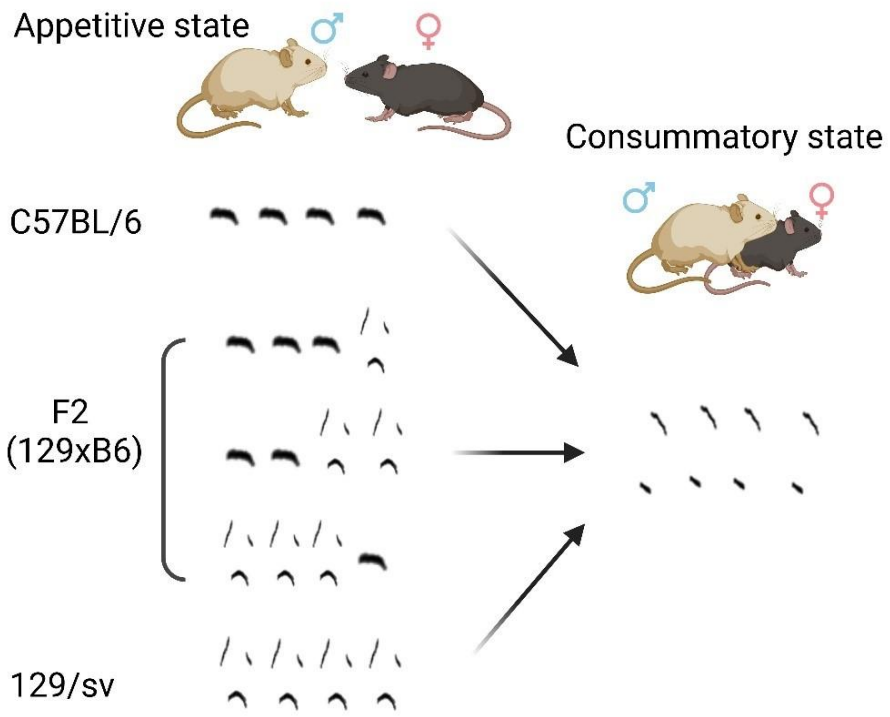
Support: NRF-2022R1A2C3013280
RS-2023-00266872
RS-2023-00249293

Title: Differential genetic background control state-dependent courtship ultrasonic vocalizations in mice

Authors: *S. NA[1], J. RYOO[2], C. KO[2], D. KIM[3];
[1]Korea Advanced Institute of Science and Technology, Daejeon, Korea, Republic of; [2]KAIST, Daejeon, Korea, Republic of; [3]Biological Sciences, KAIST, Daejeon, Korea, Republic of

Abstract: In male mice, courtship behaviors encompass distinct appetitive and consummatory phases, accompanied by ultrasonic vocalizations (USV) that vary with courtship progression and

exhibit strain-specific patterns. Despite these differences, how genetics contribute to state- and strain-dependent USV variations remain unclear. We examined USV syllable patterns during courtship in inbred C57BL/6J (B6) and 129S4/SvJae (129) mouse strains, along with their mixed-background F2 offspring. During appetitive behaviors, such as body and anogenital sniffing, B6 and 129 males produced distinct USV. F2 males emitted USV reflecting combinations of B6 and 129 patterns, correlative with the continuous similarity to each strain. In contrast, all groups emitted strikingly similar USV during mounting. These findings suggest that appetitive and consummatory phases are governed by distinct genetic mechanisms, shaped by evolutionary pressures for vocalization diversity during appetitive behaviors and conservation during consummatory behaviors, supporting adaptation to selection pressures that favor flexibility in mate attraction while ensuring consistency in mating success.



Disclosures: S. Na: None. **J. Ryoo:** None. **C. Ko:** None. **D. Kim:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

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Program #/Poster #: LBP062.11/LBP112

Topic: G.01. Neuroethology

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Searle Scholars Program
Pershing Square Foundation Innovator Fund
Esther A. & Joseph Klingenstein Fund
Cold Spring Harbor Laboratory
International Society for Neuroethology Konishi Research Award
George A. and Marjorie H. Anderson Fellowship

Title: Toward the neural code of a vocal innovation in the singing mouse

Authors: *X. ZHENG[1], C. HARPOLE[1], M. DAVIS[2], A. BANERJEE[1];
[1]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY; [2]Cold Spring Harbor Lab, Cold Spring Harbor, NY

Abstract: Animals display a remarkable variety of motor behaviors shaped over evolutionary time. Yet the neural mechanisms that give rise to this diversification remain less well understood in mammals. The Alston's singing mouse (*Scotinomys teguina*) offers a unique opportunity to investigate how neural circuits support the emergence of novel behaviors. These mice produce distinctive songs, consisting of loud notes arranged in a stereotyped rhythmic progression, used in long-range vocal exchanges. The orofacial motor cortex (OMC) modulates both the rhythm of these songs and their timing during social interactions. We recently reported that singing mice also produce ultrasonic vocalizations (USVs) during close-range interactions. Unlike songs, USVs are soft, less patterned calls that represent an ancestral vocal mode conserved across many rodents. Songs and USVs thus differ markedly in loudness, temporal structure, and social function, yet coexist within the same species. The midbrain periaqueductal gray (PAG) is essential for both behaviors, serving as a common substrate for the ancestral and the derived vocal modes. Here, we use high-density silicon probe recordings in freely behaving singing mice to examine neural activity in both the PAG and OMC during the production of songs and USVs. This approach allows us to assess the extent to which shared versus distinct circuit elements in these regions contribute to the contrasting features of the two behaviors—including their differences in loudness, temporal structure, and social usage. In parallel, we employ whole-brain viral tracing from PAG and OMC to map their input-output architecture. Together, these complementary approaches begin to reveal how vocal circuits are organized across the motor hierarchy in singing mice, providing a framework for understanding how novel behaviors such as the song emerge alongside ancestral ones.

Disclosures: X. Zheng: None. **C. Harpole:** None. **M. Davis:** None. **A. Banerjee:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.12/LBP113

Topic: G.01. Neuroethology

Support: Farouk Jabr Grant
University Research Board

Title: Post-synaptic facilitation and network dynamics underlying stimulus-specific combination sensitivity

Authors: Z. MERAABE, ***A. DAOU**;
American University of Beirut, Beirut, Lebanon

Abstract: Combination-sensitive neurons (CSNs) integrate multiple stimulus features to generate behaviorally meaningful responses. While such neurons are well studied in fast timescale systems such as bat echolocation, the mechanisms enabling extended temporal integration in species like songbirds remain poorly understood. Using a computational model, we show that syllable-specific neurons in the songbird auditory system function as coincidence detectors whose selectivity depends on both post-inhibitory facilitation and persistent network activity. This persistence serves as a "memory trace", allowing precise association of sequential syllables across hundreds of milliseconds. We propose that this dynamic interplay between intrinsic neuronal properties and convergent synaptic inputs gives rise to a higher-order "meta-combination sensitivity" enabling the auditory system to transform discrete acoustic events into temporally extended percepts. Our findings provide a mechanistic framework that bridges theories of coincidence detection with longer-timescale working memory, highlighting the importance of distributed network mechanisms for auditory temporal coding.

Disclosures: Z. Meraabe: None. **A. Daou:** None.

Late-Breaking Poster

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Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP062.13/LBP114

Topic: G.01. Neuroethology

Support: NSF GRFP

Title: Multimodal neural embeddings classify neighboring brain regions in the songbird arcopallium

Authors: ***J. BURKE**[1], Y. XU[1], C. L. HURWITZ[1], V. GADAGKAR[2];
[1]Columbia University, New York, NY; [2]Zuckerman Mind Brain Behavior Institute, Columbia University, New York, NY

Abstract: High-density silicon probes have transformed systems neuroscience by enabling simultaneous recordings from large numbers of neurons. The dense packing of low impedance contacts improves yield and localization of recorded units in large, well-defined brain areas. However, in small or poorly defined brain areas, identifying the precise location of recorded

units remains a challenge. Songbirds provide a good system for addressing this challenge because their song system areas are dense, nucleated, and histologically distinct, allowing reliable ground-truth identification. In the song system, the robust nucleus of the arcopallium (RA) is immediately surrounded by the less well-defined ventral portion of the intermediate arcopallium (AIV). While these neighboring regions have distinct roles in behavior—RA in song production, AIV in song evaluation—we wanted to explore whether they could be separated based on physiology alone. We performed high-density silicon probe recordings spanning RA and AIV simultaneously in anesthetized and awake adult male zebra finches during song playbacks. We found that both regions exhibited strong auditory responses under anesthesia, with divergent state-dependent modulation during wakefulness. However, auditory responsiveness alone was insufficient to reliably separate the two regions statistically. To overcome this, we applied a multimodal contrastive learning approach called NEMO (Neuronal Embeddings via MultimOdal learning), which jointly embeds spike waveform and spike train autocorrelations. Models trained on labeled spontaneous activity distinguished RA from AIV across animals and states, demonstrating that physiological features can serve as robust markers of brain region identity. The implications of this work are twofold. First, trained models could be used for real-time classification when histology is unavailable, such as during chronic recordings, allowing us to ask circuit-level questions about RA-AIV interactions during singing. Second, although validated in a context where histological ground truth is clear, this approach could extend to small or ill-defined nuclei where ground truth is less reliable. Even with limited training data (n = 3 birds), the model could achieve high accuracy (F1 > 0.9), demonstrating its potential to improve confidence in recordings from challenging areas. In songbirds, this could benefit studies of small areas such as avalanche (Av), nucleus uvaeformis (Uva), or female song system nuclei. More broadly, this approach offers a framework for classifying brain regions across species to help probe how neighboring brain areas support complex behaviors.

Disclosures: J. Burke: None. **Y. Xu:** None. **C.L. Hurwitz:** None. **V. Gadagkar:** None.

Late-Breaking Poster

LBP062: G.01. Neuroethology

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Program #/Poster #: LBP062.14/LBP115

Topic: G.01. Neuroethology

Support: JSPS 23H05428
JSPS 24H01560

Title: Species differences in time windows of auditory cortical neurons in songbirds

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Abstract: Multiple time scales for processing and integrating auditory information are important for recognizing details or global changes in sounds, which is crucial for vocal communication. In songbirds, auditory perception of songs differs between species. For instance, zebra finches (*Taeniopygia guttata*), a species with highly fixed song patterns, are sensitive to acoustic properties within a short time window (i.e., syllable structure), whereas Bengalese finches (*Lonchura striata* var. *domestica*), with more flexible and complicated song syntax, are more sensitive to a wider time window across the entire song structure (Okanoya, Tsumaki and Honda, 2000). Some behavioral studies suggest a trade-off between these recognition strategies. However, the neural properties and their composition in the auditory cortex underlying these species differences remain unclear. To examine the neural representation of species differences in song perception, we conducted extracellular recordings in the caudomedial nidopallium (NCM), a higher-level auditory cortical region involved in species recognition of songs and memorization of tutor songs, in adult Bengalese finches (BFs) and zebra finches (ZFs) under awake and body-fixed conditions. All experimental birds were raised in an aviary containing both ZF and BF breeding colonies. Song stimuli included the bird's own song (BOS), conspecific songs (CON), and heterospecific songs (HET: ZF or BF), with either the unmodified version or three manipulated versions of each: (1) Forward (FW), the unmodified song; (2) Local Reverse (LRV), in which syllables were reversed while preserving sequence order; (3) Order Reverse (ORV), in which syllable order was reversed while preserving local structure; and (4) Reverse (RV), in which the entire song was reversed. Except for BOS, all song stimuli were novel and were consistently used for all experimental birds. As a preliminary result, we identified two types of neurons whose detection frequency differed between the species: (i) neurons responding specifically to local acoustic features of syllables, which were more prominent in zebra finches, and (ii) neurons showing similar firing patterns between FW and LRV or between ORV and RV, which were more widespread in Bengalese finches. The latter population appears to respond to overall transition patterns in amplitude or frequency rather than to local syllable structure. These results suggest that species differences in the proportions of neuron types with sensitivity to various time windows may underlie species-specific auditory song perception.

Disclosures: Y. Shibata: None. **S. Yanagihara:** None. **K. Okanoya:** None.

Late-Breaking Poster

LBP063: G.02. Neuroendrocrine Processes and Behavior

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP063.01/LBP116

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH AIM-AHEAD Program Agreement NO. 1OT2OD032581

Title: A data-driving approach to uncover risk mechanisms and treatment barriers for opioid abuse among young females using OCHIN and MedStar data

Authors: *L. ZHANG;
Northern Arizona University, FLAGSTAFF, AZ

Abstract: Opioid abuse significantly contributes to and has profoundly harmful impacts on young adults at both individual and societal levels, yet research on young females often neglects the challenges they face in assessing opioid abuse treatment and rarely employs causal mediation analysis to address the complex pathways through which risk factors significantly affect abuse severity outcomes. To bridge the gap, a critical need exists to understand the complex causal pathways, particularly the mediating effects of comorbid conditions and systemic treatment barriers that exacerbate abuse severity. This study employs a novel integration of causal mediation analysis and machine learning to identify and quantify hidden risks driving opioid abuse (OA) among young female adults in rural areas. The two main research questions are: What are the key demographic , clinical, and geographic predictors of OA among young females? How do hypothesized mediators, such as mental health conditions, affect both predictors and OA severity, as well as the treatment effectiveness? The author draws on electronic health record data and examines 1,595,033 individuals from MedStar data (from year 2019 - 2022) at the baseline, from which the author identifies 858,636 individuals with mediated comorbid moderate/severe OA. To deepen understanding of mediator pathways, the author also incorporates additional variables such as anxiety index, health insurance coverage, provider distribution using statewide OCHIN data (2012- 2025), processing 3,350,187 unique patients after removing the duplicate to the analysis. Logistic regression and random forest models are employed to identify top predictors, while multiple regression and mediation models to forecast trends and disentangle indirect mediator effects. Key outcomes reveal that young females with comorbidities exhibit a nearly three - fold higher rate of moderate/severe OA than these without. Key demographic and clinical dynamic risk factors, including sex, age, back/neck pain, and cancer, remain significant predictors even after adjusting for mental health conditions. Supervised machine learning algorithms further highlight alcohol use, nicotine dependence, and geographic context (zip code) as top predictors of OA. As well, the mediation analysis aims to disentangle how hypothesized mediator indirectly influence OA severity as targeted outcome (In progress). Findings underscore the specific need for advancing treatment outcomes and clinical interventions, and provide data-driven framework for professionals to tailor prevention and OA treatment strategies effectively.

Disclosures: L. Zhang: 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.; AIM-AHEAD Research Fellowship Program Research funded by NIH.

Late-Breaking Poster

LBP063: G.02. Neuroendrocrine Processes and Behavior

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP063.02/LBP117

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Rank and Resilience - How Social Hierarchy Shapes Stress Vulnerability in Rats

Authors: *D. SRINIVASAN;
Centre for High Impact Neuroscience and Translational Applications (CHINTA), TCG CREST, Kolkata, India

Abstract: In social species, establishing a dominance hierarchy is crucial for accessing fundamental resources such as food, water, territory and mating partners. Stress has been proposed as a factor influencing an animal's position within this hierarchy, but the relationship between social rank and stress vulnerability remains understudied. Our study explores how social dominance impacts stress responses in adult male Sprague-Dawley rats. To investigate this, we compared the effects of stress on dominance behavior in two types of social contests:
First, between familiar rats—those housed together in the same cage—and second, between unfamiliar rats that had been housed separately. Initially, rats were assigned stable social ranks within their cage using the dominance tube test. Then, half of the rats were subjected to a 2-hour immobilization stress, and their dominance behavior within the cage was reassessed 1 and 10 days later using the tube test. We found that the stress exposure did not alter the pre-established dominance rankings among familiar cage-mates. However, in interactions with unfamiliar rats, the impact of stress was more evident. Unstressed dominant rats continued to win, while previously subordinate control rats, who typically lost to their dominant cage-mates, began winning in some competitions against stressed dominant rats. Notably, among the stressed groups, only subordinate rats showed persistent submissive behaviors and a significant decrease in dendritic spine density in the amygdala, while dominant stressed rats exhibited more resilient-like behaviors. These results suggest that an individual's social rank can influence their response to stress, with notable effects during encounters with unfamiliar animals. This study provides new insights into how social hierarchy can shape stress reactivity, contributing to our understanding of social anxiety and withdrawal in stress-related psychiatric conditions.

Disclosures: D. Srinivasan: None.

Late-Breaking Poster

LBP063: G.02. Neuroendrocrine Processes and Behavior

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP063.03/LBP118

Topic: G.02. Neuroendrocrine Processes and Behavior

Title: Pleasant odour is more effective in increasing the interpersonal attraction score in female subjects

Authors: *O. T. BAYAZIT[1], L. M. FERREIRA[2], M. SINAN[3];
[1]Physiology and Biophysics Department, Istanbul Aydin University Faculty of Medicine, ISTANBUL, Turkey; [2]Federal De Minas Gerais University, Minas Gerais, Brazil; [3]Physiology Department, Istanbul Aydin University Faculty of Medicine, Küçükçekmece, Turkey

Abstract: This study aimed to compare the effect of pleasant and unpleasant odor types on the interpersonal attraction score of the participants. Thirteen females (22±2.59 years old) and 12 males (24±2.12) participated in this study. The male and female pictures, ordered from high attractiveness score (HAS) to low (LAS) according to the London Face System, were presented to the subjects via a computer monitor. The subjects were asked to rate the attractiveness of each picture on a scale from 1 (not attractive) to 5 (very attractive). The girls found the LAS boy pictures more attractive under the pleasant odor ($p < 0.01$). The pleasant odor did not increase the attractiveness score of the HAS boy pictures in female participants. The pleasant odor increased the attractiveness score to both HAS and LAS girl pictures in male participants ($p < 0.05$). Interpersonal attraction is generally thought of as a positive emotional evaluation of another person. However, it is often assessed behaviorally or cognitively. The olfactory system helps translate the physicochemical properties of volatile molecules inhaled through the nose into the perception of odors, which have rich associative and hedonic properties. This study demonstrates that, although the human sense of smell is less developed than in other mammals, it plays a crucial role in mate selection. Especially, the pleasant odour has a significant effect on the attractiveness score in female subjects.

Disclosures: O.T. Bayazit: None. **L.M. Ferreira:** None. **M. Sinan:** None.

Late-Breaking Poster

LBP063: G.02. Neuroendrocrine Processes and Behavior

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP063.04/LBP119

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Wilczynski-Georgia Research Alliance Fellowship
Startup funds

Title: Cesarean birth alters mouse behaviors associated with the vasopressin system of the hypothalamic paraventricular nucleus

Authors: H. PRINGLE[1], K. STANKUS[1], S. GUEDEZ SUAREZ[2], ***A. CASTILLO-RUIZ**[1]; [1]Michigan State University, East Lansing, MI; [2]Georgia State University, Atlanta, GA

Abstract: Birth occurs at a time of intense remodeling of the brain via key neurodevelopmental processes, and therefore any deviations of the birthing experience could affect brain development. Indeed, we previously reported that Cesarean-born adult mice have fewer and smaller vasopressin (VP) neurons in the hypothalamic paraventricular nucleus (PVN) than vaginally-born mice. Because the VP system of the PVN regulates sociality, our previous findings suggest that Cesarean birth may alter mouse social behavior. To test this hypothesis, here we used two approaches. First, we recorded natural, in-cage behavior of adult mouse dyads of the same sex and birth mode (vaginal or Cesarean) for two hours during the early morning and night. Social behaviors (huddling, allogrooming) and non-social behaviors (locomotion, nest-

building, rearing, drinking, eating, self-grooming) were scored every 2 minutes for each mouse in the dyad. As expected, Cesarean birth reduced huddling behavior but this effect emerged in a sex and time dependent manner, with Cesarean-born males exhibiting less huddling than their vaginally-born counterparts during the night. Cesarean birth also affected locomotion and nest-building behavior, with Cesarean born mice showing increased levels regardless of sex and time of day. Remarkably, these are all behaviors associated with the VP system of the PVN. In the second approach, we exposed the same groups of mice to the sociability phase of the conventional three-chamber test, in which mice are given the choice to spend time in a chamber containing a same-sex social stimulus vs an empty chamber. We found no effects of Cesarean birth in this test. Thus, our naturalistic approach was more sensitive in detecting effects of Cesarean birth on behavior. Together with our previous findings, our present results suggest that Cesarean birth affects the neural circuitry of the VP system of the PVN. To further test this hypothesis, we are currently assessing VP innervation of brain regions linked to the altered behaviors observed here. Our studies are of clinical relevance given the widespread practice of Cesarean delivery across the world and epidemiological studies that hint that Cesarean-born humans are at increased risk for conditions characterized by social deficits (autism) and hyperactivity (ADHD).

Disclosures: H. Pringle: None. **K. Stankus:** None. **S. Guedez Suarez:** None. **A. Castillo-Ruiz:** None.

Late-Breaking Poster

LBP063: G.02. Neuroendrocrine Processes and Behavior

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Program #/Poster #: LBP063.05/LBP120

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH-IRACDA Postdoctoral Fellowship K12GM000680
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Title: Keypoint analysis of natural social interactions reveals that an Oxtr SNP associates with social observation of strangers in female prairie voles

Authors: *S. LEE[1], S. AGEZO[1], A. J. BOENDER[1], L. J. YOUNG[2], G. BERMAN[1], R. C. LIU[1]; [1]Emory University, Atlanta, GA; [2]Emory University, Decatur, GA

Abstract: The oxytocin receptor (OXTR) is highly conserved across species yet often distributed in a species-specific way across brain areas implicated in the ethological response to salient social cues. OXTR's actions have been thought to generally promote prosocial behavior, but recent studies suggest more subtle context-dependent effects on specific aspects of social behavior. In fact, even within a species, individual variability in the distribution of OXTRs has

been linked to *Oxtr* single nucleotide polymorphisms (SNP) that forecast different levels of sociability, yet how such genotypic variation correlates with phenotypic differences in specific social behavioral actions is still poorly understood. Here, we leveraged pair bonding behavior in prairie voles (Microtus ochrogaster) to test whether an intronic *Oxtr* SNP (NT213739), which associates with nucleus accumbens (NAc) OXTR expression levels, shapes how females use specific social actions to engage with an opposite-sex conspecific. Female C/C or T/T voles cohabited with a wild-type male, and their initial interactions were quantified with markerless multi-animal keypoint tracking, manual curation, and supervised learning. Autoradiography confirmed higher NAc OXTR in C/C than T/T voles, yet both genotypes formed partner preferences after a 48 hour cohabitation, indicating that the ability to form bonds was not predetermined by the SNP. A systematic analysis of tracked keypoints then revealed a distinct C/C phenotype in stranger-directed "social observation," which was defined as stationary, head-oriented monitoring of another at ≥2 body lengths distance. C/C more so than T/T females engaged in social observation of a male when it was novel, regardless of whether the voles were freely interacting during the cohabitation, or more restricted due to separation barriers in the social preference tests, which greatly reduced overall social observation. Thus, we discovered that an intronic *Oxtr* SNP selectively biases, across contexts, stranger-directed social observation before familiarity develops, consistent with a model in which NAc OXTR expression mediates social salience and biases the transition from observation to approach. These results highlight the value of using endogenous variation to understand how OXTR acts in region-specific ways to shape subtleties in specific early social interactions.

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Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP063.06/Web Only

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: DGAPA-UNAM-PAPIIT-IA202724

Title: Anxiogenic effects of arginine vasopressin in mice with autism-like phenotype evaluated in the hole-board test.

Authors: *E. LUNA CASTAÑÓN[1], E. ROCHA GONZÁLEZ[2], E. CALLADO[3], O. R. HERNANDEZ PEREZ[4];
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Abstract: Arginine vasopressin (AVP) is a neurohormone released in the hypothalamus in response to changes in blood osmolarity, such as water deprivation (WD). In addition to its hemodynamic functions, AVP has been attributed with influences on behavior, including anxiety and changes in socialization. Anxiety is a symptom common in psychiatric disorders, one of which is autism spectrum disorder (ASD), which is defined by the DSM-5-TR by two main characteristics: stereotyped and inflexible behaviors and difficulties in socialization. Altered levels of AVP have been found in people with ASD. For the study of ASD, multiple animal models have been utilized, including the C57BL/6J strain of mice, which is recognized for its natural phenotype. For evaluating anxiety in rodents, the hole-board test has been employed. The present study aimed to assess anxiety-like behaviors in C58/J mice subjected to WD using the hole board test. We used a hole board with 16 holes with a diameter of 3 cm, and mice C58/J treated with 24 h of WD., during the test, we measured: nose-poke (NP) latency, time of NP, number of NP, periphery and center of the arena, distance travel and speed of movement, risk assessments (rearing) and freezing. We found differences in AVP secretion and an increase in anxiety-like behaviors in the HB test, reflected in increased speed and distance traveled in the arena. Additionally, we found differences between the strains in NP parameters, as well as an increase in rearing. We found an influence of AVP in the levels of anxiety during the hole board test using the C58/J strain; these results open the possibility of a relation between AVP and ASD.

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Late-Breaking Poster

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Program #/Poster #: LBP063.07/LBP121

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: JSPS KAKENHI 21H05242
JSPS KAKENHI 24K00513

Title: Inhibition of intermale aggressive behavior in oxytocin receptor or vasopressin receptor knockout prairie voles

Authors: *K. HASUNUMA, N. SATO;
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Abstract: The male prairie vole (Microtus ochrogaster) is a monogamous rodent that exhibits aggressive behavior toward unfamiliar conspecifics after forming a pair bond with a female partner. Pharmacological studies have demonstrated that oxytocin (OXT) and vasopressin (AVP) contribute to partner preference. Specifically, AVP has been implicated in aggressive behavior toward stranger conspecifics. More recently, the generation of gene knockout models has allowed to investigate the OXT and AVP functions during developmental stages not accessible

by pharmacological approaches. To further elucidate how OXT and AVP regulate aggressive behavior in prairie voles, we assessed aggressive behavior in oxytocin receptor knockout (OXTR KO) and vasopressin 1a receptor knockout (V1aR KO) male prairie voles. Aggressive behavior toward a male stranger, a female stranger, and a female partner was measured in a neutral arena following partner formation. In wildtype male prairie voles, aggressive behavior toward a male stranger was greater than that toward a female stranger or partner. Consistent with pharmacological findings, aggressive behavior toward a male stranger was reduced in V1aR KO male prairie voles. In contrast to previous pharmacological results, OXTR KO male prairie voles also showed reduced aggression, suggesting that OXT signaling contributes to the regulation of aggressive behavior in a manner that has not been revealed by pharmacological studies . These findings indicate that both OXT and AVP play crucial roles in mediating intermale aggressive behavior in prairie voles. Future studies should investigate the underlying neural networks and the specific contributions of OXT and AVP within these circuits.

Disclosures: K. Hasunuma: None. **N. Sato:** None.

Late-Breaking Poster

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Title: Dissecting defensive behaviors in mice: a multimodal approach with active place avoidance

Authors: *A. G. CHAMBARD[1], E. VALJENT[2], F. BERTASO[2], A. BESNARD[3];
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Abstract: Dissecting defensive behaviors in mice: a multimodal approach with active place avoidance.

Alexandre Chambard[1], Emmanuel Valjent[2], Federica Bertaso[2] and Antoine Besnard[1].
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For many decades, neuroscience has investigated defensive behavior mostly through the narrow lens of freezing in fear-conditioning tasks. However, it is now well established that defensive responses encompass a much broader range of behaviors, including avoidance and risk

assessment. This diversity inspired the concept of the threat imminence continuum, which ranks defensive strategies according to the proximity and intensity of danger.Yet, this continuum remains largely theoretical.
A global demonstration within the same animals and within the same task is still missing. Such an approach would allow the field not only to capture the full spectrum of defensive phenotypes, but also to measure the factors shaping their distribution along the continuum.
In this study, we applied pose estimation analysis to a repurposed defensive paradigm, the active place avoidance task, to investigate a broader range of defensive behaviors.After thoroughly validating our behavioral tracking and analytical pipeline, we observed substantial phenotypic variability across mice. This variability was not explained solely by sex or experimental condition, but rather by their interaction, leading to the emergence of several distinct subclusters of animals. Some of these clusters appeared stable across sessions, resistant to pharmacological manipulations, and dependent on the animal's own sense of agency.
Importantly, we were able to predict clusters based on the animals' behavioral responses to potential as well as perceived threats.Together, these findings provide the first experimental validation of the threat imminence continuum, demonstrating that it is influenced by factors such as biological and experimental parameters.
Crucially, this continuum differs between individuals and depending on danger states (potential, perceived and immediate), in accordance with the well-established definition of anxiety, fear and panic states.
We are now devising experiments aimed at uncovering the neural correlates of this phenotypic variability.

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Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP063.09/LBP123

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: P01AG071746

Title: Metabolic health pre-determines the beneficial molecular and cognitive outcomes of estradiol in ovariectomized rats.

Authors: *M. J. MAROTEAUX[1,2], A. F. DELARGE[1,2], L. COLAKOVIC[1], S. KAMENETSKY[3], K. R. SALEM[1,2], J. M. DANIEL[1,2,4];
[1]Psychology, Tulane University, New Orleans, LA; [2]Tulane Brain Institute, New Orleans, LA; [3]Physiology, Tulane University, New Orleans, LA; [4]Neuroscience, Tulane University, New Orleans, LA

Abstract: Research in preclinical models indicates that estrogens are neuroprotective positively impact cognitive aging. However, clinical data have been equivocal as to benefits of menopausal estrogen therapy to the brain and cognition. Variation in response to estrogen therapy in women suggests that pre-existing disease such as metabolic syndrome can modulate mechanisms of estrogen action. These alterations may consequently reduce, or reverse protections estrogens provide against cognitive decline. The current work uses a preclinical rat model to test the hypothesis that metabolic disease induced by high-fat diet (HFD) attenuates the enhancing effects of estradiol (E2) on hippocampal dependent memory. Additionally, we used bulk RNA-seq to determine effects of E2 on hippocampal gene expression under conditions of health and disease.

Adult female rats were trained on an 8-arm radial maze (RAM) paradigm, then fed either a high-fat diet (HFD) or control diet (CD) for 11 weeks. Following ovariectomy, rats received silastic implants containing E2 or vehicle (Veh) and were aged an additional 5 weeks before RAM testing at increasing delays (2, 4, 6 hrs). Results revealed that in CD-fed rats, E2 improved RAM performance relative to Veh, while conferring no benefit to HFD-fed rats.

Hippocampal RNA-sequencing in a parallel cohort revealed that E2 in CD-fed rats upregulated neuroprotective and developmental signaling genes while downregulating apoptotic, inflammatory, and mitochondrial stress pathways. By contrast, in HFD-fed rats, E2 induced broader transcriptional changes characterized by upregulation of structural remodeling pathways and downregulation of metabolic and synaptic transmission pathways involved in long-term plasticity, learning and memory. Interestingly, in HFD-fed rats, E2 resulted in downregulation of Esr1 expression and upregulation of IGF-1 binding protein-4. These results suggest a potential mechanism by which HFD attenuates E2 effects as in our previous work in healthy subjects, the ability of E2 to affect memory is dependent on interactions of ERα and IGF-1 signaling.

In summary, these findings support the hypothesis that E2 effects on memory and the hippocampus vary under conditions of health and disease. They underscore the importance of metabolic health in determining hormone therapy outcomes.

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Support: Young Investigator Grant 23958
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Title: β-Endorphin Buffers Against Social Stress-Induced Neural Threat Reactivity and Inflammation in Adolescent Females

Authors: *K. AFSHAR[1], J. GASSEN[2], S. MENGELKOCH[3], G. SLAVICH[4];
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Abstract: Experiences of social stress are strong activators of neural threat responses and inflammatory signaling - both of which are processes that have been implicated in the pathophysiology of depression and related diseases. β-endorphin, an endogenous opioid, is involved in stress regulation and homeostasis-restoring behaviors and may buffer against threat-related brain activity and inflammation. To investigate the role of β-endorphin levels in the inflammatory response to threat detection, adolescent females (N = 52) ages 12-16 (MAge=14.90, SD=1.35) underwent a social stress task, during and after which activity and connectivity in threat-related neural networks, as well as circulating β-endorphin and proinflammatory cytokines (including TNF-α, IL-1β, IL-6), were measured. We found that greater threat network activation - particularly the amygdala and its connections with the anterior cingulate cortex (ACC) and ventromedial prefrontal cortex (VMPFC) - was associated with an increase in proinflammatory cytokines, but higher β-endorphin levels either reversed or blunted these effects. These findings suggest that endogenous opioid signaling may act as a protective mechanism against the proinflammatory consequences of social stress, and elucidate mechanistic pathways involved in stress-related disease risk.

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Late-Breaking Poster

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH grant R01-DK118910.

Title: Repeated Intraoral Glucose Exposure Fails to Condition a Cephalic Phase Insulin Response to Isomolar Fructose in Rats

Authors: *A. NISI[1], M. ARNOLD[2], L. TORNES[3], C. WOODHAM[1], G. D. BLONDE[1], G. SANCHEZ-WATTS[3], A. G. WATTS[3], W. LANGHANS[2], A. C. SPECTOR[1];
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Abstract: Previously, we found that intraoral (IO) infusion of 1.0 M fructose (FRU) evokes a greater insulin response than intragastric (IG) infusion only 1-min after stimulus onset in rats. We speculated that this may represent a conditioned response due to prior glucose (GLU) exposure in the experimental design. Here we tested whether repeated 1.0 M IO GLU exposure conditions an orally stimulated insulin response to isomolar FRU. Male rats were implanted with IO and IG cannulas for stimulus delivery and a jugular vein catheter for blood sampling. Separate groups of rats (N = 12-15/group) were then exposed to water (WAT), GLU or FRU for 5 consecutive days, receiving 5 ml delivered in alternating 1-min ON/OFF cycles (1 ml/min) to avoid taste adaptation. Then, they were tested for their response to GLU and FRU infusions (1 ml/min) in sessions counterbalanced for stimulus and delivery site (IO vs IG), with each stimulus completed in two consecutive test sessions. Blood was collected at -4, -2, 1, 2, 3, 5, and 10 min for plasma insulin and glucose analysis. In the WAT-exposed group IO GLU produced a more rapid and robust insulin response than the IG infusion, reflected in the 3-min AUC ($p \leq 0.05$) thereby replicating prior findings. Although IO FRU evoked higher insulin levels than IG at 1-min, this was not evident in the 3-min AUC. We found no evidence of a conditioned insulin response in the GLU-exposed group; insulin levels after the IO GLU still exceeded the IG response ($p \leq 0.05$, AUC 3-min). IO FRU produced a larger insulin response than IG, but only at 1 min as in the WAT-exposed group. In the FRU-exposed rats, IO GLU triggered higher insulin levels than IG GLU ($p \leq 0.05$, AUC 3-min), and IO FRU produced a brief site effect at 1 min that was reflected in the 3-min AUC ($p \leq 0.05$). These effects could not be explained by differences in plasma glucose among groups. Notably, the 3-min AUC did not differ across exposure groups for either GLU or FRU, for both insulin and glucose levels, regardless of delivery site. Despite five IO episodes of GLU exposure, we found no evidence of a conditioned insulin response to the IO delivery of FRU or an enhanced insulin response to IO delivery of GLU, at least under our test parameters. Thus, the small and transient increase in plasma insulin after IO FRU delivery that exceeds that seen after IG infusion in our previous experimental design represents an unconditioned response. Accordingly, the canonical T1R2+T1R3 “sweet” taste receptor may possess some partial role in the oral stimulation of an insulin response to the sugars tested.

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Late-Breaking Poster

LBP063: G.02. Neuroendrocrine Processes and Behavior

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Topic: G.02. Neuroendrocrine Processes and Behavior

Support: HJM0776/20-I

Title: Neuroendocrine axis involved in cardiovascular regulation across lifespan in women

Authors: *A. ROBLES-CABRERA;
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Abstract: AbstractThe autonomic nervous system and the endocrine system regulate cardiovascular physiology, and their alterations, as occurs in type 2 diabetes mellitus, are related to the development of cardiovascular complications. Sex hormones are major regulators of both cardiovascular and nervous tissue, and during postmenopause, the lack in hormone production can increase the risk for cardiovascular and autonomic diseases, even more in metabolic impairment such as in T2DM However, the evidence regarding whether sex hormones are related to autonomic activity is inconclusive. The goal of this paper was to evaluate the correlation between sex hormones and cardiac autonomic activity, as assessed by heart rate variability (HRV), women with well-controlled type 2 diabetes (T2DM) and healthy women as the control group.Subjects and methodsIn this study, four groups of women were designated according to their health status (control or T2DM) and fertility status (premenopausal or postmenopausal). Five serum sex hormones were measured (estradiol, progesterone, testosterone, LH and FSH), and time-domain and frequency-domain HRV indices were determined during three conditions: supine position, active standing, and rhythmic breathing. For the complete sample (n=118), bivariate Pearson correlations and linear multiple regressions were used to analyze the relationship between sex hormones, HRV indices, and other independent variables, such as glycemia and age. A p-value <0.05 was considered as significant.ResultsThere were no differences in sex hormones or HRV indices when comparing the healthy and T2DM groups. All bivariate Pearson correlations were significant between sex hormones and HRV indices; estradiol, progesterone, and testosterone have positive correlations; meanwhile, LH and FSH were negative in the time-domain (SDNN, RMSSD, pNN20) and frequency domain (PLF and PHF) indices. Regression models adjusted for mean heartbeat intervals confirmed an association between all sex hormones and HRV indices. Estradiol maintained significance in the regression models for specific HRV indices during supine and active standing conditions even after adjusting for age and glucose levels.ConclusionsAll sex hormones correlate with HRV indices. Regression analysis confirms that this correlation is independent from the mean heartbeat interval. However, in regression models adjusted for age and glucose levels, only estradiol was found to be significant, and should be considered an important variable related to cardiovascular and autonomic balance in T2DM women and may provide crucial information to improve cardiovascular risk algorithms.

Disclosures: A. Robles-Cabrera: None.

Late-Breaking Poster

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Title: Suckling evokes and maintains milk letdown via "starter" oxytocin neurons

Authors: *Y. TANG[1], R. NIU[1], Q. KRABICHLER[2], F. ALTHAMMER[3], S. CHEN[4], E. VAN DEN BURG[1], Y. LI[5,6], V. GRINEVICH[2,7], R. STOOP[1];
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Abstract: The pulsatile release of oxytocin (OT) that governsmammalian lactation is a hallmark of neuroendocrine regulation, yet the neuralcircuit initiating and synchronizing this process has remained elusive. Here,we identify a distinct population of parvocellular oxytocin (ParvOT) neurons inthe paraventricular nucleus (PVN) as the essential 'starter cells' for the milklet-down reflex.We retrogradely labeled ParvOTs through their axonalprojections to the supraoptic nucleus (SON) using a dual viral approach(CAV-Cre in SON and pOT-DIO-GFP/GCaMP/ChR2/Gi in PVN). Anatomical analysisrevealed that projections from ParvOTs to magnocellular oxytocin (MagnOT)neurons in the SON are significantly increased in lactating dams. Using thesame viral approach, we opto-tagged ParvOTs, combined with optrode recordingsand fiber photometry, and found that ParvOT activity consistently precededMagnOT bursts. Each bursting event showed synchronized activation patternsacross MagnOTs, though frequency and duration varied from event to event.Activation levels of ParvOTs, MagnOTs, and OT release allcorrelated with the number of suckling pups, demonstrating a precisesomatosensory tuning of the OT system. Confirming the essential role ofParvOTs, their selective chemogenetic silencing completely abolished MagnOTbursting, suppressed OT release, and prevented milk delivery to the pups.Conversely, when lidocaine applied to the nipples blocked pup suckling andsilenced ParvOTs, optogenetic activation of ParvOTs was sufficient to reinstatebursting and restore OT release.Insummary, we identify a local hypothalamic circuit in which ParvOTs drive MagnOTbursts during lactation, thereby orchestrating oxytocin release and enablingmilk ejection.

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Late-Breaking Poster

LBP063: G.02. Neuroendrocrine Processes and Behavior

Location: SDCC Hall B

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Program #/Poster #: LBP063.14/LBP128

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: Field Spicer Fellowship In Research (Internal Grant for Undergraudate Research)

Title: Nervous system impacts of Bisphenol-S exposure on development, growth, heat stress responses and behavior of the nematode (Caenorhabditis elegans)

Authors: *G. M. LANGE[1], N. JAMES[2], A. GANDHI[1], X. GUIMBA[1], H. STEMPLE[2]; [1]Saginaw Valley State Univ., University Center, MI; [2]Saginaw Valley State Univ., Saginaw, MI

Abstract: Previous work in our lab has established that Bisphenol-A exerts neurobehavioral impacts on the nematode, Caenorhabditis elegans. Bisphenol-S is a chemical agent found in many plastics used in everyday life. It has become a common substitute for Bisphenol-A in plastic production since Bisphenol-A has been implicated as a potent endocrine disrupting pollutant. Unfortunately, Bisphenol-S can and does leech from plastics and also enters the environment where it is inadvertently ingested by organisms. Therefore, this variant bisphenol also warrants study as a potential endocrine disruptor. Environmental osmolarity is a type of neurosensory stimulus for many organisms. While behavioral responses to osmotic change are important for maintaining intracellular osmotic stability, mechanisms shaping the development of these behaviors are not fully understood. In natural environments inhabited by the nematode, Caenorhabditis elegans, changes in environmental osmolarity occur frequently. Data about potential effects of dual stressors of osmotic change and Bisphenol-S exposure are scant. In this research, we developed novel experimental designs in which we provided environmental choice to Caenorhabditis elegans. We present findings of our research examining how these dual environmental stressors impact the nervous system, development and morphology of this nematode. In this research we compare wild type and OSM mutant strains of the nematode in two different environments and examine our results relative to Bisphenol-S exposure. Our statistically significant results show that Bisphenol-S is a strong chemoattractant for these nematodes. We speculate on how Bisphenol-S may mimic an important endogenous neuroendocrine chemical signal in these nematodes.

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Late-Breaking Poster

LBP064: G.03. Stress and the Brain

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Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: College of Arts and Sciences, Quinnipiac University

Title: Maternal Separation Alters Occludin and JAK/STAT3 Expression in the Meninges of Female Rodents.

Authors: J. MATHEWS[1], S. AZERRAD[2], H. JACK[3], P. SACK[4], *A. J. BETZ[5];
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Abstract: Early life stress (ELS) in humans contributes to the development of psychiatric mood disorders such as Generalized Anxiety Disorder and Major Depressive Disorder in adulthood. Consistent with these findings, animal models have demonstrated that ELS induces long-term behavioral, physiological, and neural changes. Maternal separation (MS) in rodents is a widely used model for studying the effects of ELS. While MS has been shown to alter behavior and neural function, little is known about its impact on the meninges, a key regulator of brain homeostasis and blood-brain barrier (BBB) integrity, particularly in females. The objective of this study was to investigate the role of circulating pro-inflammatory cytokine IL-6 and meningeal integrity in female rodents. MS exposure elevated circulating IL-6 levels and increased STAT3 activation, suggesting IL-6 involvement in the JAK/STAT pathway. In parallel, occludin, a tight junction protein critical for BBB permeability, was reduced following MS. These molecular alterations were accompanied by heightened anxiety-like behavior, as evidenced by reduced open-arm exploration in the elevated plus maze. Together, these findings suggest that ELS compromises neurovasculature integrity in females through IL-6 signaling and meningeal barrier dysregulation, contributing to anxiety-like behavior.

Disclosures: J. Mathews: None. **S. Azerrad:** None. **H. Jack:** None. **P. Sack:** None. **A.J. Betz:** None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.02/LBP130

Topic: G.03. Stress and the Brain

Support: STI2030-Major Projects 2021ZD0200204
Key Laboratory of Computational Neuroscience and Brain-Inspired Intelligence (Fudan University), Ministry of Education, China
National Natural Science Foundation of China 82271583
National Key Research and Development Program of China 2018YFA0701400
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Title: Distinct neural moderators of resilience and vulnerability confer heterogeneous outcomes following early-life adversity

Authors: *H. FAN[1,2], B. BECKER[3], J. ZHANG[1];
[1]Institute of Science and Technology for Brain-Inspired Intelligence, Fudan University, Shanghai, China; [2]Department of Brain Sciences, Imperial College London, London, United Kingdom; [3]Department of Psychology, The University of Hong Kong, Hong Kong, China

Abstract: The brain may actively moderate the impact of early-life adversity (ELA) on psychopathology—conferring protection or vulnerability and contributing to heterogeneous outcomes—yet prior studies have not clearly clarified how different ELA types are moderated, have relied on single neuroimaging modalities, and have been hypothesis-driven, overlooking many potential moderators. We used multimodal neuroimaging and moderation analyses in the Adolescent Brain Cognitive Development Study (N≈11,800, ages 9-10), testing >1,500 structural, diffusion, resting-state, and task fMRI features as moderators of three ELA types—familial interpersonal (IFA), non-familial interpersonal (NFIA), and non-interpersonal (NIA)—on transdiagnostic psychopathology. Linear mixed-effects models assessed brain×adversity interactions, classifying features as protective or vulnerability factors based on interaction direction. After Bonferroni correction, 57 features emerged (34 protective, 23 vulnerability), spanning multimodal cortical, subcortical, and network-level systems. Protective factors clustered in limbic, sensory integration, and regulatory circuits [amygdala, parietal cortex, and anterior cingulate cortex (ACC)], whereas vulnerability features concentrated in frontotemporal regions. Moderators were ELA-specific: NIA was mainly in allostatic interoception; NFIA involved both allostatic interoception and high-order social cognition, emotion regulation, cognitive control, and reward systems; FIA yielded only one vulnerability factor, suggesting it may override compensatory mechanisms. Notably, the ACC was particularly salient, encompassing cross-modal moderators and exhibiting bidirectional influence. Linking neural moderators to clinical trajectories, ordinal logistic regression showed subsets predicted psychiatric progression over 2 years. To capture cumulative effects, we developed a Relative Resilience Index (RRI) quantifying the whole-brain balance of protective versus vulnerability factors; higher RRI scores predicted reduced longitudinal psychiatric risk (OR 0.69, 95% CI [0.49-0.96]). Our findings indicate that moderation models can identify robust, ELA-specific multimodal neural moderators, revealing distinct neurobiological mechanisms underlying heterogeneous outcomes. The RRI characterizes individual brain resilience, enabling individual-level risk stratification and complementing actionable single-brain features. Overall, this work provides mechanistic insight into the differential effects of ELA on youth mental health and highlights neural targets for early intervention.

Disclosures: H. Fan: None. **B. Becker:** None. **J. Zhang:** None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

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Program #/Poster #: LBP064.03/LBP131

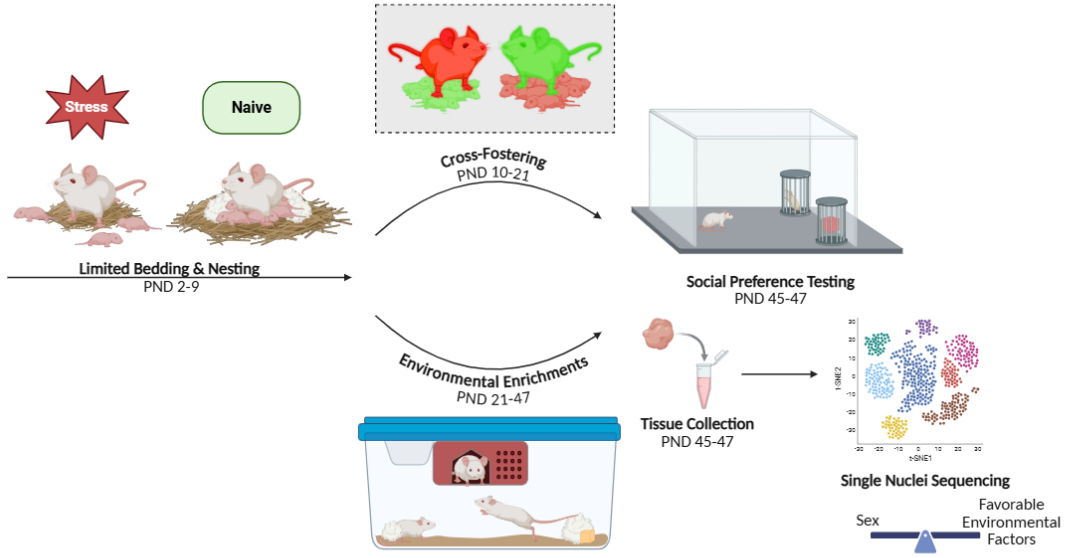
Topic: G.03. Stress and the Brain

Support: P20 GM109097/GM/NIGMS NIH HHS/United States

Title: Sex and enrichment dependent behavioral and transcriptomic signatures underlying early life stress

Authors: *A. DODGE, A. JEFFERS, M. HOCHSTETLER, S. CHAKRABORTY, S. MITRA; Oklahoma State University- Center for Health Sciences, Tulsa, OK

Abstract: Adverse childhood experiences (ACEs) profoundly shape brain and behavior, yet their consequences on adolescent social development, a critical window for establishing long-term social trajectories, remain largely unexplored. Using the limited bedding and nesting (LBN) paradigm in Sprague-Dawley rats to model early-life stress, we demonstrate for the **first time** that ACEs produce sex-specific and divergent alterations in adolescent social preference, with females showing reduced sociability and males exhibiting heightened social interactions. Remarkably, environmental enrichment selectively rescued sociability in females, revealing a sex-influenced capacity for behavioral plasticity following early life stress. Cross-fostering experiments confirmed the robustness of these outcomes, dissociating maternal lineage from environmental adversity. To uncover the cellular basis of these behavioral phenotypes, we performed the **first** single-nucleus RNA sequencing analysis of the medial prefrontal cortex in an LBN model during adolescence, identifying cell-type-specific transcriptomic signatures that link early adversity to disrupted plasticity and social processing circuits. Together, these findings establish adolescence as a sensitive period for the manifestation of ACE-induced social deficits, uncover sex-biased vulnerabilities and resilience mechanisms, and reveal novel molecular targets for interventions aimed at restoring social behavior after early-life stress.



Disclosures: A. Dodge: None. **A. Jeffers:** None. **M. Hochstetler:** None. **S. Chakraborty:** None. **S. Mitra:** None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.04/LBP132

Topic: G.03. Stress and the Brain

Support: NIH NIGMS P20GM103423

Title: Prefrontal parvalbumin DNA methylation, demethylation, and affective dysfunction outcomes following early life adversity and subanesthetic ketamine treatment

Authors: *Y. A. PENA[1,2], E. S. NOEL[2], S. ELLIS[2], A. LEMESHOVA[2], A. LIMBADA[2], J. A. HONEYCUTT[3];
[1]Psychological and Brain Sci., Dartmouth Col., Hanover, NH; [2]Neurosci., [3]Psychology, Bowdoin Col., Brunswick, ME

Abstract: Early life adversity (ELA) can lead to increased risk of affective disorders. There is a growing need to understand the biological mechanisms underlying ELA as a risk factor, and potential sex-specific behavioral outcomes that may be relevant to understanding therapeutic response. Parvalbumin (PV+) GABAergic interneuron dysregulation has been found following

ELA, and they are key in regulating responses to a potential threat. Our lab previously developed a novel analog to the Fearful Face Task to assess behavioral hypervigilance in rats. Similar to facial expressions, rats emit ultrasonic vocalizations (USV) to provide negatively-valenced social information. We leverage aversive rat 22 kHz USV playback in combination with the open field test (OFT), as well as the elevated zero maze (EZM), to assess hypervigilant behavioral outcomes following ELA and ketamine treatment. We set out to understand how ELA alters reactivity to a potential threat, how subanesthetic ketamine treatment might alter their response, and potential epigenetic mechanisms underlying the dysregulation of PV+ cells and sex-specific outcomes of untreated and treated animals. Six days after receiving a 10 mg/kg ketamine dose, ketamine-treated females spent more time in the center than their saline-treated counterparts during 22kHz playback but not silence. Saline-treated control males spent more time in center during silence but not during 22 kHz playback. ELA animals had higher total distance traveled in OFT than their saline counterparts regardless of sex and treatment. In the EZM, ELA-reared animals spend significantly less time in the open arms regardless of sex or treatment. Parvalbumin cell count was higher in ELA-reared animals in the prelimbic prefrontal cortex (plPFC), regardless of sex. Furthermore, DNA methylation and demethylation markers in plPFC PV+ interneurons were significantly impacted by ketamine treatment, rearing, and sex. These data provide evidence for anxiety-like behavioral outcomes following ELA, divergent sex-specific strategies in response to an ethological probe of potential threat reactivity, and altered parvalbumin - and its cell-specific methylation profile - in the prefrontal cortex.

Disclosures: Y.A. Pena: None. **E.S. Noel:** None. **S. Ellis:** None. **A. Lemeshova:** None. **A. Limbada:** None. **J.A. Honeycutt:** None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.05/LBP133

Topic: G.03. Stress and the Brain

Support: DoD W81XWH-13-1-0377
DoD W81XWH-20-1-0066

Title: Estrous cycle stage and female gonadal hormones on the day of trauma and outcome

Authors: *C. V. CHEN[1], I. LIBERZON[2];
[1]Texas A&M University, Bryan, TX; [2]Psychiatry, Texas A&M University, Bryan, TX

Abstract: Post-traumatic stress disorder (PTSD) is the fourth most common mental disorder. Interestingly, women are two to three times as likely as men to develop PTSD after a traumatic event. To determine whether estrous cycle stage or female gonadal hormones on the day of trauma might play a role on outcome, we used the widely accepted rodent model of PTSD, Single Prolonged Stress (SPS). In experiment 1, we tracked intact adult female Sprague Dawley

rats' estrous cycle, exposed them to SPS trauma (or not), and tested them on fear learning tests to determine severity of extinction recall deficits, a cardinal deficit in PTSD patients. In experiment 2, intact adult female Sprague Dawley rats were ovariectomized, injected with estradiol benzoate, progesterone, both or vehicle and exposed to SPS (or not), and later tested on fear learning behavioral tests. Findings indicate a role of estrous cycle stage and gonadal hormones on outcome after SPS trauma. Implication for current clinical practices will be discussed.

Disclosures: C.V. Chen: None. **I. Liberzon:** None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.06/Web Only

Topic: G.03. Stress and the Brain

Support: UNAM-PAPIT: IA205025

Title: Interaction between striatal cannabinoid CB1 and glucocorticoid receptors in procedural memory acquisition

Authors: *E. RENDON-OCHOA[1], G. LAMAR NAVA[1], G. GARCÍA MENDOZA[1], M. GONZALEZ LOPEZ[1], A. A. HERNÁNDEZ APARICIO[1], L. N. CEDILLO ZAVALETA[2], S. E. CRUZ-MORALES[1];
[1]Psycopharmacology. FES Iztacala. UNAM, Estado de México, Mexico; [2]FES Iztacala. UNAM, Estado de México, Mexico

Abstract: Stress can either facilitate or impair memory, depending on the phase and type of memory involved (1). Fifteen minutes of restraint stress (R) or striatal corticosterone (CO) injections have been shown to impair procedural memory acquisition (2), whereas striatal CO injections improve procedural memory consolidation (3). The molecular mechanisms underlying this phenomenon remain unclear. A current hypothesis suggests that CO may interact with different neurotransmitter systems, such as the noradrenergic or cannabinoid systems, leading to distinct effects on memory. During consolidation, CO interacts with the cannabinoid system to enhance memory consolidation (4). In this study, we investigated whether this interaction also occurs during memory acquisition. The selective cannabinoid CB1 agonist (WIN-55,212) or antagonist (AM-251) were administered directly into the striatum of rats subjected to fifteen minutes of R or CO injections ip (5 mg/kg) before training in the elevated T-maze task (ETM), a behavioral paradigm that assess both, procedural memory and anxiety. ETM task consists of four consecutive trials on day 1 (baseline, avoidance 1, avoidance 2 for memory, and escape 1 for anxiety) and two trials on day 2 (avoidance 3 and escape 2), during which the animal retrieves to avoid the open arms and remain in the closed arm. We found that 10 μM of WIN-55,212, as well as its combination with restraint stress (R + WIN) or CO injection (CO + WIN), impaired memory acquisition on day 1 compared to the vehicle (VEH). This effect was blocked by the

administration of AM-251 (1 μM) in both R (AM + R) and CO (AM + CO) conditions. In the retention phase (day 2), WIN, R + WIN, and CO + WIN groups performed significantly worse than the VEH, R + AM, and CO + AM groups, indicating amnesia in these groups. Taken together, these results suggest that striatal glucocorticoid receptors require the involvement of the cannabinoid system to mediate the effects of stress on procedural memory acquisition.

Disclosures: E. Rendon-Ochoa: None. **G. Lamar Nava:** None. **G. García Mendoza:** None. **M. Gonzalez Lopez:** None. **A.A. Hernández Aparicio:** None. **L.N. Cedillo Zavaleta:** None. **S.E. Cruz-Morales:** None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

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Program #/Poster #: LBP064.07/Web Only

Topic: G.03. Stress and the Brain

Support: NRF Grant RS-2023-00224823

Title: Enhancing Mindfulness-Based Cognitive Therapy (MBCT) with Real-Time Biofeedback for Stress Management: Preliminary Findings from a Randomized Controlled Trial

Authors: *H. LEE;
Seoul National University Hospital, Seoul, Korea, Republic of

Abstract: Background and Aims: Adherence to digital mental health interventions like Mindfulness-Based Cognitive Therapy (MBCT) is often limited, as users find mastering mindfulness challenging. This study aims to determine if real-time biofeedback from electroencephalography (EEG) and heart rate variability (HRV) can enhance the efficacy of MBCT for stress management in patients with mood disorders.Methods: In this single-blind randomized controlled trial (RCT), patients with mood disorders (major depressive or bipolar disorder) are assigned to one of two groups. The experimental group receives an 8-week MBCT program augmented with real-time EEG and HRV biofeedback designed to guide them toward a state of relaxation. The control group participates in the same MBCT program but without receiving biofeedback. The primary outcome is the change in the Perceived Stress Scale (K-PSS) score from baseline. Secondary outcomes include changes in depression (HAM-D) and anxiety (HAM-A). Assessments are conducted at baseline, and post-treatment (8 weeks).Results : A total of 95 participants (44 in the experimental group, 51 in the control group) were included in the final analysis. At baseline, there were no statistically significant differences between the two groups in socio-demographic characteristics or the severity of clinical symptoms as measured by the PSS, HAM-D, and HAM-A. Following the 8-week intervention, both groups showed a clinically meaningful reduction in stress, depression, and anxiety scores. However, the difference in the magnitude of this change between the two groups was not statistically significant. In the comparison of 8-week changes in EEG and HRV indicators, no statistically significant

differences between the groups were found for any quantitative biomarker. However, a trend towards a more positive change was observed in the treatment group's High Frequency (HF) power, an indicator of parasympathetic activity.Conclusion : Future long-term studies with larger sample sizes are warranted to verify the clinical and physiological effects of this program.

Disclosures: H. Lee: None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.08/LBP134

Topic: G.03. Stress and the Brain

Support: FONDECYT 1231012 Dr. Pablo Moya

Title: EAAT3 overexpression confers resilience to chronic stress: behavioral studies and redox state in mice model

Authors: *W. PLAZA-BRICEÑO[1], P. R. MOYA[2], R. SOTOMAYOR-ZÁRATE[3]; [1]Faculty of Sciences, University of Valparaíso, Valparaíso, Chile; [2]Fisiologia, University of Valparaiso, Valparaiso, Chile; [3]Instituto de Fisiología, Facultad de Ciencias, University of Valparaiso, Valparaiso, Chile

Abstract: Background: Depression is a debilitating mood disorder whose etiology remains unclear. Evidence links it to oxidative stress and glutamatergic dysfunction. Animal and human studies report decreased antioxidant activity and increased oxidizing agents. The glutamatergic hypothesis suggests that depression pathophysiology involves glutamate imbalance. Neuronal EAAT3 not only controls glutamate spillover but also transports cysteine, necessary for glutathione (GSH) synthesis. There is a regulatory effect of EAAT3 on GSH levels: EAAT3 knockout animals show decreased GSH levels, while EAAT3 overexpression leads to elevated GSH levels. These suggest EAAT3 plays a neuroprotective role against oxidative stress. Our aim was to determine if EAAT3 overexpression is a protective factor against oxidative stress and the manifestation of a depressive phenotype induced by unpredictable chronic mild stress (UCMS). Methods: Transgenic male mice overexpressing EAAT3 under CaMKIIα promoter and $EAAT3^{glo}$ controls were used. At postnatal day 60, four groups were formed: $EAAT3^{glo}$, EAAT3 CaMKII, $EAAT3^{glo}$ UCMS, EAAT3 CaMKII UCMS. UCMS is a stressor regimen in which two different stressors per day are applied for 5 weeks. During this period, body weight and coat state were registered. After UCMS sucrose preference and tail suspension tests were performed. Then, samples from prefrontal cortex (PFC), hippocampus (HPC) and striatum (ST) were collected to evaluate oxidative stress markers (GSH, malondialdehyde [MDA]).Results: Non-stressed animals gained weight normally but in UCMS group it is compromised. But EAAT3 CaMKII UCMS have significantly more weight gain than $EAAT3^{glo}$ UCMS. In non-stressed animals coat state was not affected. Its deterioration observed in stressed group was attenuated in EAAT3

CaMKII UCMS. Sucrose Preference Test showed non-stressed animals have normal preference to sucrose, but this preference is decreased in EAAT3^{glo} UCMS. Overexpression significantly increased preference for sucrose. Tail Suspension Test showed greater immobility in EAAT3^{glo} UCMS reduced by overexpression. Oxidative stress markers indicated that MDA levels remained unchanged in prefrontal cortex (PFC), hippocampus (HPC) and striatum (ST). In the other hand, we observed a basal reductor state in EAAT3 CaMKII but chronic stress diminished this status in HPC. Conclusion: Our results suggest EAAT3 overexpression confers resilience to chronic stress. But GSH levels in HPC and MDA levels in PFC, HPC and ST are not involved in resilience of EAAT3 overexpression mice. Future evaluation of GSH in PFC and ST, and glutamate levels using additional methods are necessary.

Disclosures: W. Plaza-Briceño: A. Employment/Salary (full or part-time); ANID scholarship 21220829. **P.R. Moya:** A. Employment/Salary (full or part-time); University of Valparaíso, Chile. 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.; FONDECYT 1231012. **R. Sotomayor-Zárate:** A. Employment/Salary (full or part-time); University of Valparaíso, Chile.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.09/LBP135

Topic: G.03. Stress and the Brain

Support: Staley Fellowship Award Wellesley College (MJT)

Title: Time longitudinal study of lifestyle factors associated with the human gut and vaginal microbiomes

Authors: H. CAO[1], Y. SUN[1], C. M. DEVENEY[2], A. G. COPE[3], M. M. R. S. WALTHER-ANTONIO[4], N. CHIA[5], C. W. PATTANAYAK[6], ***M. J. TETEL**[7];
[1]Data Science Program, Wellesley College, Wellesley, MA; [2]Psychology, Wellesley College, Wellelsey, MA; [3]Obstetrics and Gynecology, Mayo Clinic, Rochester, MN; [4]Obstetrics and Gynecology, Mayo Clinic, Roschester, MN; [5]Argonne National Labs, Lemont, IL; [6]Quantitative Analysis Inst, Wellesley College, Wellesley, MA; [7]Neuroscience, Wellesley College, Wellesley, MA

Abstract: The human microbiome has critical effects on human health and disease. It is well-known that the bacteria of the gut, or gut microbiota, profoundly affect metabolism, the immune system and brain function. In contrast, less is known about the contributions of the fungi in the vaginal mycobiome to women's health. Recent findings indicate that the vaginal mycobiome influences reproductive health, with *C. albicans* being the most abundant species and the leading cause of vulvovaginal candidiasis.

The present study explored the gut and vaginal microbiomes with a focus on the vaginal mycobiome and its associations with lifestyle factors, such as birth control, physical and sexual activity, and psychological well-being. Fecal and vaginal samples were collected daily from 78 college-age participants over 10-weeks and sequenced to identify the microbiota and mycobiome composition. Self-reports of menstruation and medication data were collected, and weekly DASS-21 surveys assessed mood and stress. In the vaginal mycobiome, *C. albicans*, *M. globosa*, and *M. restricta* were the top three dominant species, with Shannon Diversity varying with different dominant fungal species ($p<0.001$). Over the study period, non-athletes consistently showed higher *C.* albicans abundance compared to athletes ($p<0.05$). At the participant level, the abundance of *C. albicans* was higher for birth control users vs. non-users ($p=0.037$) and higher for sexually active vs. inactive individuals ($p<0.001$). There was a trend towards an association between the use of selective serotonin reuptake inhibitors (SSRIs) and higher *C. albicans* abundance, but the small sample size of SSRI users ($n=8$) precluded statistical significance ($p=0.2$). *C. albicans* abundance was associated with the vaginal bacterial community state types (CST), with a lower abundance in people with CST V (all pair-wise comparisons of CST V and other CST: $p<0.05$). Vaginal *Lactobacillus* abundance was associated with menstruation status ($p < 0.001$) but not SSRI usage ($p=0.1$). In the gut mycobiome, SSRI usage was possibly associated with higher *C. albicans* abundance, but again, a small sample size precluded statistical significance ($p=0.26$). This initial study of lifestyle factors and the vaginal mycobiome provides a foundation for future fungal analysis. Moreover, findings linking antidepressant use with both gut and vaginal microbiome provide important insights for women's health.

Disclosures: H. Cao: None. **Y. Sun:** None. **C.M. Deveney:** None. **A.G. Cope:** None. **M.M.R.S. Walther-Antonio:** None. **N. Chia:** None. **C.W. Pattanayak:** None. **M.J. Tetel:** None.

Late-Breaking Poster

LBP064: G.03. Stress and the Brain

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.10/LBP136

Topic: G.03. Stress and the Brain

Support: NIMH RO1MH096093
NINDS F99NS139535
Harvey Family Endowment
Zilkha Neurogenetic Institute
Beckman Institute at Caltech

Title: Multimodal comparison of olfactory bulb responses to predator threat using manganese-enhanced MRI and c-fos expression microscopy

Authors: C. M. PADILLA[1,2], *L. RIOS[2], R. E. JACOBS[3], E. L. BEARER[2,4], T. W. USELMAN[2];
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Sciences Center, Albuquerque, NM; [3]Zilkha Neurogenetic Institute, USC Keck School of Medicine, Los Angeles, CA; [4]Biology and Biological Engineering, California Institute of Technology, Pasadena, CA

Abstract: Longitudinal brain-wide MRI detects long-term changes to threat circuitry induced by predator odor, yet our understanding of lower-level neural contributions to these changes is limited. Cross modal comparison of neural activity detected by other methods with greater spatiotemporal resolutions can provide greater detail into how acute threat reshapes brain-wide circuits. Here, we compare neural activity of the olfactory bulb as detected by longitudinal manganese-enhanced MRI (MEMRI) with that detected by terminal c-fos immunohistochemistry (IHC). We hypothesize that cross-modal comparison would obtain more detail about long-term adaptations in neural activity of the medial DII olfactory bulb (m-DII) after predator odor exposure than either method could detect alone. MEMRI (100 μm^3) was acquired in adult mice ($n = 4$) before and 9 days after acute TMT exposure; each before and 24 hr after $MnCl_2$ injection (0.3 mmol/kg, IP). MR images were skull-stripped, intensity normalized and aligned. After MRI, mouse brains were processed for c-fos IHC. A separate cohort of threat-naive mice ($n = 5$) were processed similarly for c-fos IHC. A 3×3 grid of 100 μm squares was defined within the TMT-responsive m-DII olfactory bulb using micrographs of c-fos stained sections and MR images, from which c-fos+ cells were counted and voxel-wise MEMRI intensities measured. Activity differences between conditions were tested statistically in Python using mixed-effects models, and a cross-modal Pearson's correlation calculated. Paired analysis of MEMRI data revealed statistically increased intensities in threat-experienced versus naïve conditions (+4.6%, $p = 0.002$). Unpaired c-fos+ counts showed only a minor insignificant increase (+2%, $p \approx 0.84$). Both modalities exhibited qualitatively concordant directional changes (increased after threat), despite lack of statistical significance in c-fos. Cross modality correlations of the threat-experienced condition demonstrated a statistically significant relationship ($r = 0.37$, $p = 0.027$) where c-fos+ counts was a moderate predictor of MEMRI. Thus, longitudinal MEMRI detects persistent olfactory responses to predator threat with greater sensitivity than c-fos, whereas c-fos provides insight into likely sub-voxel signal contributions (number of cells versus degree of activity within a cell). Results suggest increased MEMRI signal is due to increased action potentials within a set number of neurons and not to recruitment of more neurons. Differing temporal resolutions may contribute to differences between modalities. Future studies will consider multi-region measurements for cross modal mapping of threat responses.

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Late-Breaking Poster

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Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP064.11/LBP137

Topic: G.03. Stress and the Brain

Title: Converging Behavioral and Hormonal Evidence of Fear Memory in Mice Following Odor Fear Conditioning

Authors: *V. LOPEZ[1], T. ARZUA[2], N. MIMOUNI[3], B. J. MARLIN[4];
[1]Columbia University, New York, NY; [2]Zuckerman Institute, Columbia University, New York, NY; [3]Neuroscience, Columbia University, New York, NY; [4]Columbia University Zuckerman Institute, New York, NY

Abstract: Fear conditioning is a widely used model for investigating the neural and physiological mechanisms that contribute to anxiety disorders such as post-traumatic stress disorder (PTSD). In PTSD, trauma-associated cues can trigger stress hormone release and defensive behaviors despite no immediate danger. In this study, we examined paired odor-shock fear conditioning in mice, with focus on whether re-exposure to a conditioned odor, without foot shock, was sufficient to elicit corticosterone release alongside behavioral avoidance. This approach provides a closer parallel to human PTSD, where reminders of trauma provoke physiological stress responses without new trauma exposure. Traditionally, rodent studies of fear conditioning emphasized behavioral outputs, such as freezing or avoidance, while human studies often emphasized physiological markers of stress such as cortisol release. Bridging these approaches by examining both behavior and stress hormones in rodents enhances the translational value of this paradigm. Recent work from our group showed odor-shock conditioning can bias the olfactory system itself, increasing odor-responsive sensory neurons in later generations; here, we test whether the same paradigm elicits hormonal stress responses. We implemented a three-day paired odor-shock paradigm in mice in which a 10-second odor (acetophenone) presentation was followed by a mild foot shock. Control groups included unpaired odor-shock exposure, odor alone, or home cage controls. On the final experiment day, mice were re-exposed to the conditioned odor in the absence of shock. Trunk blood was collected within ten minutes, and corticosterone levels were measured via ELISA. Behavioral responses (freezing) were recorded during odor-shock pairing, and avoidance was quantified by measuring distance from and time spent near the odor source during re-exposure. Mice in the paired condition exhibited significantly elevated corticosterone relative to home cage controls, alongside increased avoidance of the conditioned odor. To our knowledge, this represents one of the first demonstrations of odor-shock fear conditioning driving corticosterone release in mice (prior reports focused mainly on rats). Importantly, the stress response emerged following odor re-exposure alone, underscoring the power of conditioned cues to provoke behavioral and physiological fear responses even without ongoing threat. Together, these findings highlight odor-shock conditioning as a paradigm linking cellular, hormonal, and behavioral markers of fear, offering translational insight into mechanisms that may underlie cue-evoked symptoms of PTSD.

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Late-Breaking Poster

LBP064: G.03. Stress and the Brain

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Program #/Poster #: LBP064.12/LBP138

Topic: G.03. Stress and the Brain

Title: Uncovering the spatially resolved transcriptomic gene profile in the human dorsal raphe nuclei in major depressive disorder & anti-depressant treatment

Authors: *S. A. CODELUPPI-ARROWSMITH[1], Y. XIE[2], Z. LI[2], K. CASMEY[2], I. WAGNER[2], S. BARNETT BURNS[2], G. KRUCK[2], G. WARHAFTIG[2], D. ZURAWEK[2], C. NAGY[3], G. TURECKI[2];
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Abstract: Major Depressive Disorder (MDD) is a serious and potentially lethal mood disorder characterized by the presence of low mood, sense of helplessness and suicidal ideations. A majority of antidepressants used in clinical practice, act by altering serotonergic neurotransmission. Although serotonin is produced almost exclusively in the raphe nucleus, it remains a severely understudied region in neuroscience which is poorly characterized in humans with MDD and antidepressant use. Here, we aim to better understand the role of serotonin in MDD by studying the raphe nucleus. This study was performed using frozen human post-mortem midbrain and rostral pons samples from neurotypical individuals (n=4/ 50%♀). Brains were sliced to contain the DRN, mounted on slides and stained using an antibody targeting Tryptophan hydroxylase 2 (TPH2). We then followed the standard VisiumHD pipeline for which briefly includes probe hybridization, mounting on the VisiumHD Slides using the CytAssist (10x Genomics), probe release and library preparation. Upon completion of sequencing, resulting data was analyzed using Spacer Ranger pipelines and Seurat to determine key cell types and transcriptomic profiles. Our current early results demonstrate that the DRN contains a majority sertonergic neurons and there may be up to 15 subtypes of sertonergic neurons in the DRN. In addition, these neurons appear to be spatially organized, in our pilot work. Overall, this work provides the first transcriptomic map of the human DRN at a sub-cellular level using VisiumHD providing extensive insight into the understanding of the human serotonergic system

Disclosures: S.A. Codeluppi-Arrowsmith: None. **Y. Xie:** None. **Z. Li:** None. **K. Casmey:** None. **I. Wagner:** None. **S. Barnett Burns:** None. **G. Kruck:** None. **G. Warhaftig:** None. **D. Zurawek:** None. **C. Nagy:** None. **G. Turecki:** None.

Late-Breaking Poster

LBP065: G.04. Neuroimmunology and Neurovirology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP065.01/LBP139

Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH Grant R01 CA270372-01A1S1
ACS Gran RSG-22-024-01-CDP

Title: Gut-blood-brain axis disruption after commonly-used breast cancer chemotherapeutics: A comparative study in female mice.

Authors: *Y. A. VALENTINE[1], A. F. DUFF[2,1], B. E. ESCUE[1], M. T. BAILEY[2,1], L. M. PYTER[3,1];
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Abstract: BACKGROUND: Chemotherapy induces gut side effects (e.g., diarrhea) in 40-80% of U.S. breast cancer patients. Indeed, chemotherapy disrupts gut physiology, bacteriome, and metabolome. Recently, gut dysbiosis has been linked to brain and behavioral side effects (e.g., neuroinflammation and anxiety), which can occur through humoral communication. It is not yet known which chemotherapeutics are most disruptive to the gut microbiome, since most are administered in combination clinically. Here, mice were used to systematically investigate gut microbiome changes by 4 classes of chemotherapeutics commonly used to treat breast cancer [taxane (paclitaxel), alkylating agent (cyclophosphamide), platinum-based alkylating agent (cisplatin), or anthracycline (doxorubicin)]; circulating and central inflammatory mediators were assessed. Since preclinical studies have reported multi-organ system disruption due to platinum-based alkylating agents, we hypothesized that this chemotherapeutic class would induce the most severe and longest-lasting gut-blood-brain axis disruption. METHODS: Adult female C57BL/6 mice. (9-10/group), were administered repeated chemotherapeutic treatments or vehicle (i.p.) using clinically comparable regimens. Fatigue and anxiety-like behavior were assessed in an open arena. The gut bacteriome was assessed via 16S rRNA sequencing from fecal samples collected at baseline, 1 and 28 d after treatment. Targeted metabolomics was performed on cecal/colon contents, plasma, and brain tissues. Circulating and central inflammation was assessed in plasma and brain tissue via cytokine ELISA and RT-qPCR, respectively. RESULTS: Many novel inter-chemotherapeutic differences were observed. Notably, cisplatin and paclitaxel induced severe and long-lasting gut-blood-brain axis disruption. Doxorubicin and cyclophosphamide disrupted gut bacteriome composition at different timepoints post-treatment, 1 and 28 d post treatment, respectively. Cisplatin, paclitaxel, doxorubicin and cyclophosphamide disrupted host and microbial metabolism of tryptophan in the gut at one and/or both timepoint(s) after chemotherapy. Paclitaxel maintained increased circulating and central proinflammatory

mediators even at 28 d post-treatment. CONCLUSIONS: These results indicate that taxane and platinum-based alkylating chemotherapeutics may be most suitable for gut microbiota-targeted interventions to attenuate gastrointestinal, and possibly, behavioral side effects of treatment.

Disclosures: Y.A. Valentine: None. **A.F. Duff:** None. **B.E. Escue:** None. **M.T. Bailey:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Scioto Biosciences, Inc. **L.M. Pyter:** None.

Late-Breaking Poster

LBP065: G.04. Neuroimmunology and Neurovirology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP065.02/LBP140

Topic: G.04. Neuroimmunology and Neurovirology

Support: NIH R01MH128688

Title: Neural mechanisms underlying social behavior susceptibility to systemic inflammation

Authors: *P. X. DIAZ MUNOZ[1], H. T. LANOVOI[2], G. CEDENO[3], J. S. RICEBERG[4], I. CARCEA[5];
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Abstract: Inflammation contributes to the onset and severity of many psychiatric disorders, especially those with a social dimension. In mammals, inflammatory sickness reshapes social choices as a function of pre-existing relationships, yet the underlying mechanisms remain unclear. Systemic inflammation engages interoceptive neural circuits and local neuroinflammatory pathways, recruiting a distributed network of brain structures in response to immunogens such as the bacterial toxin lipopolysaccharide (LPS). We investigate if hierarchical social relationships gate susceptibility to LPS-treatment, and what interoceptive mechanisms mediate this susceptibility.We determined the social rank of adult male and female C57BL/6N mice (age 8-10 weeks) via the tube test, and then treated them with a single intraperitoneal injection of LPS (0.5 mg/kg) or saline. Two hours later, we measured social novelty preference in a three-chamber assay by quantifying distance and orientation toward a familiar cagemate versus a novel conspecific. LPS caused dominant but not subordinate males to increase investigation of familiar cagemates ('dominant LPS' vs 'dominant Saline', $p < 0.0001$; 'subordinate LPS' vs 'subordinate Saline', $p = 0.415$; $N = 39$). No effect of LPS on social novelty investigation was detected in females of either rank. In a different cohort, we performed immediate early gene activity mapping of interoceptive brain structures. We found that LPS activates capsular nucleus of the central amygdala (CeC) in dominant ($p = 0.0085$, $N = 9$) but not

subordinate male mice (p = 0.104, N = 10). Within CeC, ~40% of activated neurons express the receptor for oxytocin (OTR). CeC-OTR$^+$ cells integrate visceral signals and social information, and represent prime candidates for mediating rank-dependent shifts in social preference during inflammation. We therefore used fiber photometry calcium recordings to test whether CeC-OTR$^+$ activity aligns with rank-dependent susceptibility to inflammation. In preliminary data, saline treated dominant mice have increased activity in the proximity of novel mice compared to cagemates. LPS treatment reverses this pattern, increasing activity in the proximity of cagemates. We detected no clear patterns in the activity of CeC-OTR+ neurons in subordinates. These data demonstrate that CeC OTR$^+$ neurons selectively encode rank-dependent social preference changes under systemic inflammation and define CeC oxytocin signaling as a key mediator of social susceptibility to systemic inflammation.

Disclosures: P.X. Diaz Munoz: None. **H.T. Lanovoi:** None. **G. Cedeno:** None. **J.S. Riceberg:** None. **I. Carcea:** None.

Late-Breaking Poster

LBP065: G.04. Neuroimmunology and Neurovirology

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP065.03/LBP141

Topic: G.04. Neuroimmunology and Neurovirology

Support: National Institute of Mental Health (R01-MH115037 and R01-MH106497, G.B.C)
Jeongho Kim Neurodevelopmental Research Fund (G.B.C. and J.R.H.)
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the Simons Foundation Autism Research Initiative (G.B.C. and J.R.H)
the Picower Fellows (L.Y.)

Title: IL-1R-expressing dorsal raphe neurons mediate self-imposed social withdrawal during sickness

Authors: *L. YANG[1], M. L. ANDINA[1], M. WITKOWSKI[1], I. R. WICKERSHAM[2], J. HUH[3], G. CHOI[1];
[1]Picower Institute for Learning and Memory, MIT, Cambridge, MA; [2]McGovern Institute for Brain Research, Massachusetts Institute of Technology, Cambridge, MA; [3]Immunology, Harvard Medical School, Boston, MA

Abstract: Social interactions, while essential for survival and fitness of individuals and species, also increase the risk of disease transmission. When exposed to pathogens, animals must balance the benefits of social contact against its costs. Across species, infected individuals often exhibit social withdrawal- an adaptive response believed to protect group health by isolating the sick and limiting pathogen spread. How such behaviors are orchestrated by the nervous system and

mediated at the molecular level remains largely unclear. To identify molecules that induce social withdrawal, we screened intracerebroventricularly delivered cytokines, immune-derived factors that can act as neuromodulators linking the immune and nervous systems. Among those tested, only interleukin-1β (IL-1β), a cytokine rapidly upregulated during early infection, reduced social interaction and also induced locomotor hypoactivity. Mapping its receptor, IL-1R1, revealed a neuronal population in the dorsal raphe nucleus (IL-1R1^{DRN}) that expresses IL-1R1 and shows increased activity in response to IL-1β. Molecular profiling indicated that IL-1R1^{DRN} neurons are predominantly serotonergic. To selectively manipulate the activity of these neurons, we employed an intersectional genetic approach by crossing an IL-1R1-Cre line, a serotonergic neuron-specific Sert-Flp line, and a dual recombinase-dependent line expressing the chemogenetic tool hM3D(Gq) or hM4D(Gi). Chemogenetic activation of these neurons reduced social interaction, whereas inhibition reversed the IL-1β-induced social withdrawal without rescuing locomotor hypoactivity. These findings indicate that IL-1R1^{DRN} neurons are both sufficient and necessary for IL-1β-induced social withdrawal, independent of the sickness-induced hypoactivity. We next conditionally knocked out IL-1R1 in DRN neurons by crossing *IL1r1*$^{flox/flox}$ mice with Sert-Cre mice and validated that receptor expression in these neurons is required for IL-1β-induced social withdrawal. Monitoring social behaviors within animal cohorts further revealed that IL-1β-treated animals initiated self-isolation from cage mates, which was mitigated by inhibiting IL-1R1^{DRN} neurons, suggesting that IL-1β-induced social withdrawal is a self-imposed process. This mechanism also accounts for the social withdrawal observed during systemic inflammation induced by lipopolysaccharide (LPS) or Salmonella infection. Our findings show that IL-1R1^{DRN} neurons convey IL-1β signals to drive social withdrawal in sick animals, highlighting the role of neuro-immune interplay in shaping behavioral responses to immune challenges.

Disclosures: L. Yang: None. **M.L. Andina:** None. **M. Witkowski:** None. **I.R. Wickersham:** None. **J. Huh:** None. **G. Choi:** None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.01/LBP142

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: BYU College of Life Sciences

Title: Ketone bodies reduce spreading depolarization occurrence and impairment of mitochondrial respiratory capacity

Authors: *R. RICKS, T. POULOS, D. S. NEVERS, T. SHAFER, B. T. BIKMAN, R. PARRISH;
Department of Cell Biology and Physiology, Brigham Young University, Provo, UT

Abstract: Spreading depolarization (SD) is a stress response in the central nervous system distinguished by a slowly propagating wave of collapsing ionic gradients resulting in prolonged neuronal and glial depolarization. Recovery of ionic homeostasis presents an acute metabolic challenge directly related to degree of neuronal injury following SD. SD is implicated in various neuropathologies including seizure, migraine with aura, stroke, and traumatic brain injury, and as such, determining strategies for preventing SD and promoting brain recovery following SD is important for improving patient prognoses. The ketogenic diet (KD), characterized by high fat and very low carbohydrate intake, is a promising therapeutic strategy for ameliorating the occurrence and consequences of SD. Previous studies have demonstrated that KD reduces oxidative stress and inflammation, improves energy metabolism, and modulates ion channels and neurotransmitter balance. Data directly analyzing the impact of ketosis on SD prevention and recovery are limited. To investigate the potential protective effects of ketones against SD, we incubated neocortical brain slices with β-hydroxybutyrate (BHB), the main ketone body in circulation during ketosis, prior to SD induction. SDs occurred less frequently in slices incubated in high ketone aCSF (75% BHB, 25% glucose) compared to slices incubated in standard glucose aCSF, and the SDs that occurred in slices incubated in high ketone aCSF had significantly lower amplitudes. To gain insight into how ketone bodies might protect the brain during SDs, we first studied the impact of SD on mitochondrial fitness. Using high resolution respirometry, we found that SD significantly reduced the function of mitochondrial electron transfer system complexes as well as mitochondrial total respiratory capacity. In contrast, neocortical brain slices with access to BHB did not have significant alterations in mitochondrial fitness. These findings suggest that KD may have efficacy as a therapeutic strategy to prevent SDs and improve mitochondrial fitness during SDs, potentially enhancing recovery and minimizing long-term consequences.

Disclosures: R. Ricks: None. **T. Poulos:** None. **D.S. Nevers:** None. **T. Shafer:** None. **B.T. Bikman:** None. **R. Parrish:** None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.02/LBP143

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

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KHIDI grant RS-2024-00404132
KUCRF grant RS-2024-00466703
KBRI grant 21-BR-04-03
SNU grant 305-20240038

Title: Hindbrain cold-sensitive neurons orchestrate integrated homeostatic responses

Authors: *S. JUNG[1], M. LEE[2], S.-Y. KIM[3];
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Abstract: Thermoregulation is a fundamental physiological process critical for survival, yet how the brain represents peripheral cold sensory information and coordinates the diverse responses remains incompletely understood. Here, using activity dependent genetic labeling (Targeted Recombination in Active Populations, TRAP) in mice, we characterize cold-activated neurons in the external lateral parabrachial nucleus (abbreviated as PB^{Cold} neurons) as primary recipients of cold sensory input in the brain. PB^{Cold} neurons exhibit rapid and sustained activation to various cold stimuli, with response amplitude increasing progressively as temperature deviates from thermoneutrality. Functional inhibition of these neurons impairs essential cold-induced responses across multiple domains, including autonomic (brown adipose tissue thermogenesis and tail vasoconstriction), behavioral (cold avoidance), metabolic (cold-induced hyperphagia), and affective (dopamine release to rewarding cool stimuli) adaptations, and compromises survival under severe thermal stress. Conversely, targeted activation of PB^{Cold} neurons promotes warmth-seeking behavior and enhances food intake without causing weight gain, suggesting an elevation in energy expenditure that offsets increased caloric intake. Collectively, our findings establish PB^{Cold} neurons as a critical integrative center coordinating cold responsive adaptations, providing insights into central mechanisms of thermal homeostasis.

Disclosures: S. Jung: None. **M. Lee:** None. **S. Kim:** None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.03/LBP144

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: CAPES-Fulbright Full PhD Fellowship, grant CAPES call 05/2021 number 88881.625374/2021- 01

Title: Diet-context gates AgRP neurons involvement in Semaglutide-induced weight loss in female mice

Authors: *M. D. SILVA[1], R. COLLADO-PÉREZ[1], Z.-W. LIU[2], T. L. HORVATH[3];
[1]Yale University, New Haven, CT; [2]Comparative Medicine, Yale University School of Medicine, New Haven, CT; [3]Comparative Medicine, Yale Med Sch, New Haven, CT

Abstract: Diet context gates AgRP neuron involvement in Semaglutide-induced weight lossin female mice Semaglutide, a GLP-1 receptor agonist, induces durable weight loss, yet the central circuits mediating this effect remain unresolved. We tested whether hypothalamic agouti-related peptide (AgRP) neurons, key regulators of feeding and energy balance, are required for

semaglutide's actions *in vivo* and whether diet composition modulates this requirement. Mice (8-12 weeks, both sexes) received daily semaglutide (0.16 mg/kg, i.p.) or vehicle (PBS) for 2 or 15 days. In *Npy*-GFP slices, 2-day treatment increased sEPSC (4.2±1.8vs 12.3±5.7 Hz, $p<0.01$, n=15) and sIPSC frequency (4.5±2 vs 8.6±4.1 Hz, $p<0.05$),reduced *Npy* mRNA (100±5.8% vs 85±8.9%, $p<0.05$, n=6), and did not alter AgRP c-Fos(7.6±3.5 vs 8.1±4.7%, n=5), suggesting early neutral/inhibitory effects. After 15 days,semaglutide decreased sIPSCs (14.2±4.1 vs 9.8±3.2 Hz, $p<0.05$, n=15), increased *Agrp* (100±5.6% vs 387±188%, $p<0.001$) and *Npy* (100±4.2% vs 257±49%, $p<0.001$) gene expression, and elevated AgRP c-Fos (7.6±3.5% vs 20.1±6.4%, $p<0.01$), indicating sustained activation. To test necessity, we used AgRP-Sirt1 knockout mice (AgRP-Sirt1KO). Both WT and KO mice initially lost ~10% weight, but KO females fully rebounded after 3 days, unlike males. EchoMRI confirmed early fat loss followed by regain in KO females. Indirect calorimetry (14 days) showed reduced intake, energy expenditure, and RER equally in WT and KO females, despite rebound in KO animals. Semaglutide lowered glycemia and enhanced insulin in WT but not KO females after 15 days (79±6.4vs 104±2.1 mg/dL, n=8). Under 12-week HFD, KO mice maintained weight loss(WT=91±4.6% vs KO=88±1.6%, n=10). Acute HFD (3 days) also abolished KO rebound, whereas switching HFD-fed females back to standard diet reinstated AgRP dependence(WT=92±1.7% vs KO=98±4.7%, $p<0.05$, n=8). These findings demonstrate that AgRP neurons are required for sustained weight-loss and hypoglycemic effects of semaglutide in female mice on standard diet, but are dispensable under HFD. Diet composition thus dynamically gates AgRP necessity for GLP-1RA efficacy, reconciling divergent reports on the mechanism of action of semaglutide and informing translational strategies.

Disclosures: M.D. Silva: None. **R. Collado-Pérez:** None. **Z. Liu:** None. **T.L. Horvath:** None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.04/LBP145

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: NIH Grant 5R01NS119243-05
NIH Grant 5R01NS122782-05
Owen's Family Foundation
UVA Harrison Undergraduate Grant

Title: The role of perivascular and meningeal macrophages in modulating basal cerebral arteriole tone

Authors: *D. GUPTA, A. SURAM, A. GUPTA, S. ZEIAEI, W. A. MILLS III;
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Abstract: Myeloid cells, consisting of parenchymal-resident microglia and border-associated macrophages (BAMs), have been implicated in regulating cerebrovascular responses to hypercapnia, yet it remains unclear which myeloid populations modulate specific vessel types. In our previous work, we demonstrated that microglia are the exclusive myeloid cells localized to capillaries, whereas perivascular macrophages (PVMs) reside along larger arterioles and venules. Using focal and global elimination approaches, as well as genetic knockdown strategies, we found that microglia facilitate capillary vasodilation via the enzymatic action of cyclooxygenase-1 (COX1). Here, we extend these findings by combining two-photon imaging through a cranial window with global ablation using PLX3397 (660 mg/kg chow for eight days). Under these conditions, arterioles and venules where PVMs are localized exhibited significantly reduced diameters relative to baseline. Notably, even after an eight-day recovery period following drug withdrawal, vessel diameters failed to return to baseline, which we attribute to impaired PVM repopulation. These results support a role for PVMs in maintaining the resting basal tone of larger vessels. Consistent with prior observations, immunostaining confirmed that PVMs do not express COX1. Interestingly, however, we now show that meningeal macrophages express COX1 at levels comparable to microglia. Given prior reports that global COX1 loss impairs vascular responses to hypercapnia, our findings raise the possibility that meningeal macrophages provide the COX1-dependent signaling necessary for vasodilation under hypercapnic conditions. Together, these results reveal vessel-specific functions for microglia, PVMs, and meningeal macrophages in cerebrovascular regulation. Ongoing work is focused on confirming the contribution of meningeal macrophages to COX1-dependent hypercapnic vasodilation and further elucidating the COX1-independent mechanisms by which PVMs influence arteriolar and venular tone.

Disclosures: D. Gupta: None. **A. Suram:** None. **A. Gupta:** None. **S. Zeiaei:** None. **W.A. Mills:** None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.05/LBP146

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Title: Effect of intracranial pressure changes on waveforms from supraorbital and peripheral auricular arteries

Authors: *A. V. NESTERENKO[1], M. V. HOSSEN[2], R. H. SANDLER[1], H. A. MANSY[2]; [1]College of Medicine, University of Central Florida, Orlando, FL; [2]College of Engineering and Computer Science, University of Central Florida, Orlando, FL

Abstract: Intracranial pressure (ICP) is a critical metric used when managing strokes, TBIs, hydrocephalus, and other conditions. Standard methods of continuous ICP monitoring, intraparenchymal catheters, epidural transducers etc., are invasive and carry a risk of infection.

Previous non-invasive monitoring techniques have been unsuccessful. This study investigated the utility of supraorbital artery (SOA) and peripheral auricular artery (PAA) photoplethysmography to monitor changes in ICP during orthostatic tilt and hyperventilation, which increase and decrease ICP respectively. Through a continuous 6-minute recording on a tilt-table, we characterized SOA and PAA waveforms in 4 participants (2 male, 2 female, ages 19-21). Subjects were studied sequentially in four conditions: +45° head-up tilt (HUT), -45° head-down tilt (HDT), -45° post hyperventilation, and +45° HUT post HDT. Capnography ensured proper hyperventilation occurred and ECG provided context for the plethysmographic waveforms. In both HUT positions (Fig.1), we observed 2 peaks in the SOA and PAA, with a larger first peak, smaller second peak, and pronounced dicrotic notch; the R peak of the ECG intersected the descending troughs of the waveforms. In the HDT condition, the SOA and PAA waveforms had 3 peaks with amplitudes in ascending order; the R peak intersected the 2nd waveform peaks. The transient post-hyperventilation HDT condition had similar peaks to the HUT conditions. In all cases the SOA and PAA stayed in phase, with the same number of peaks, and similar relative amplitudes. These preliminary results suggest that SOA and PAA plethysmography, through number, relative amplitude, and ECG R-peak intersection, may sensitively reflect the relative ICP changes associated with HDT and hyperventilation and thus may prove useful as a noninvasive ICP monitor. Future studies will need to expand the number of subjects studied in clinical settings, comparing the findings to invasive monitoring methods.

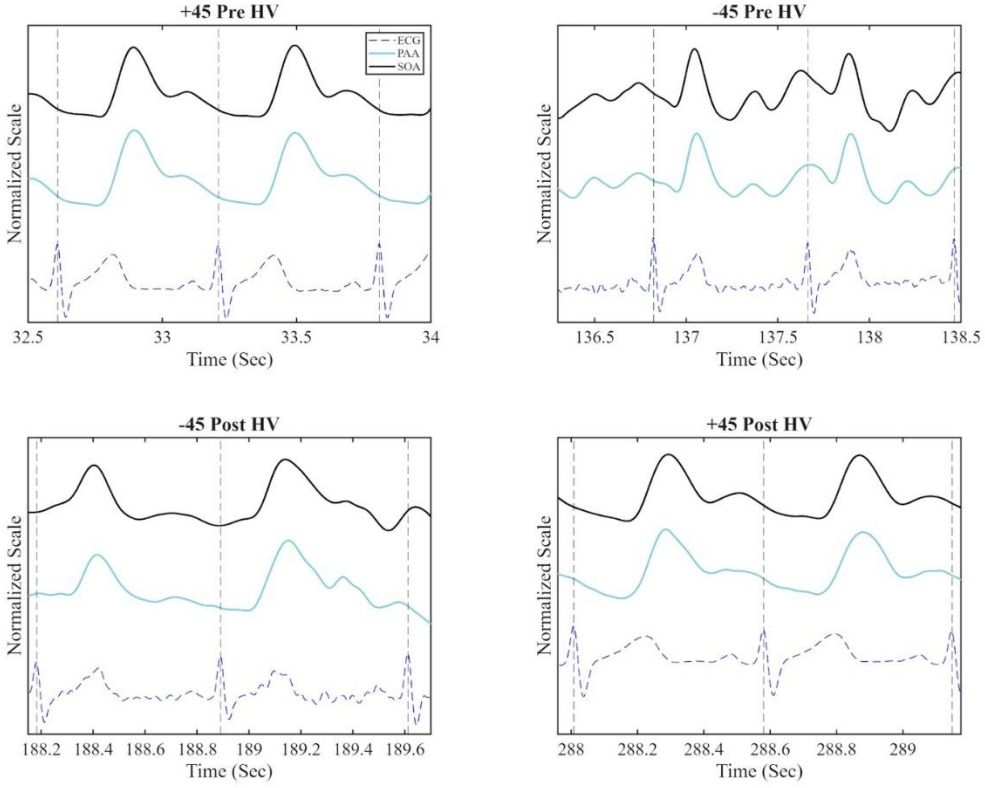

Figure 1. Two consecutive ECG, PAA, and SOA waveforms from the same subject in each of the four physiological conditions.

Disclosures: A.V. Nesterenko: None. **M.V. Hossen:** None. **R.H. Sandler:** None. **H.A. Mansy:** None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.06/LBP147

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Carney Innovation Award CC42000 GR500237

Title: Integrating longitudinal optical coherence tomography (OCT) and 2-photon microscopy (TPM) to resolve blood vessel network dynamics across timescales

Authors: *A. NAGAR;
Engineering, Brown University, Providence, RI

Abstract: Neocortical blood vessel networks conduct a wide range of functions critical to maintaining health, from waste clearance to oxygen delivery for neurons. These functions require vessel networks to form optimal flow graphs. Dynamic, ongoing activity in a wide range of input signals from cell types likely contribute to guiding this graph creation. Recent studies from our group and others have shown that OCT provides the unique ability to track changes in vascular networks over several months with a contrast-free signal. However, OCT has low temporal resolution and cannot image fast dynamics. TPM requires contrast agents (e.g., GCaMP) and is not as amenable to repeated measurement as OCT, but provides a detailed view of ongoing dynamics. To directly address this spatiotemporal gap, we are developing approaches for aligning contrast-free, high spatial coverage OCT imaging with TPM recording of fast calcium dynamics across the lifespan. Preliminary results demonstrate successful alignment of OCT maps with TPM regions of interest (N=4 mice). As a first step in understanding the development and dynamic updating of optimal network structure, we are investigating the propagation of signals through the network itself in the form of Endothelial Cell Calcium Events (ECCE). Endothelial calcium signals are a critical node of vascular input integration, driving processes critical to health (dilation, waste clearance), as and angiogenesis. During diseases like Alzheimer's, both blood vessel network structure and Endothelial calcium signaling are affected, with deleterious outcomes for brain health. However, the temporal relationship between disease progression, endothelial calcium signaling, and vessel network structure has neither been examined longitudinally nor in awake, behaving animals. Through a suite of custom analysis tools, we have made inroads towards measuring these signals as both waves and discrete events in awake, behaving animals. Our results demonstrate the feasibility of aligning OCT and TPM to track multiple measures of vessel network health across timescales in awake animals, toward the ultimate goal of correlating vascular network signaling and structure longitudinally across disease progression.

Disclosures: A. Nagar: None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.07/LBP148

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Support: Travel Grant from Italian Society of Pharmacology

Title: Unveiling the role of endothelial $K_v7.5$ channels in seizures

Authors: *C. CELENTANO[1,2], R. F. YOSHIMURA[2], M. TAGLIALATELA[1], V. BARRESE[1], G. W. ABBOTT[2];
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Abstract: Blood-brain barrier (BBB) disruption and consequent alterations of ion transport play a pivotal role in the onset and progression of many neurological diseases. Notably, a leaky BBB is a risk factor for epilepsy, and seizures can damage brain endothelial cells (ECs), thus exacerbating the disease. Our group recently demonstrated that voltage-gated potassium Kv7 channels (in particular, Kv7.1, Kv7.4 and Kv7.5) are expressed in brain ECs where they regulate barrier permeability. Moreover, we showed that Kv7.5 subunits were selectively reduced in brain microvessels (BMVs) from kainic acid-induced Status-Epilepticus (KASE) rats, and that pharmacological activation of Kv7 channels reduced EC damage induced by kainic acid (KA) in vitro, suggesting a critical role of Kv7.5 in the BBB. Therefore, in this study, we investigated the alteration of the BBB at rest and in response to seizures, as well as seizure susceptibility of Kv7.5 homozygous knockout (Kv7.5-KO) rats. Experiments were conducted on 6-10 week-old male rats (females were excluded due to differences related to estrous cycle). Permeability was evaluated by measuring fluorescein isothiocyanate (FITC)-dextran uptake in freshly isolated BMVs; results were normalized to vessel length. To generate KASE model, rats received repeated KA doses (5 mg/kg) every 30 min until reaching SE, established when animals experience ten ≥ stage 3 seizures within 1 h. Seizure severity was scored using the modified Racine scale. Animals were culled 24 h after reaching SE and brains were collected to isolate BMVs. BMVs from Kv7.5-KO rats displayed increased permeability by about 45% compared to wild-type (WT). Immunofluorescence (IF) on BMVs showed reduced Zonula Occludens 1 (ZO-1) signal and an increase of Kv7.4 (65 and 30% respectively) in Kv7.5-KO BMVs; no differences were observed for claudin 5 (CLN5). When exposed to epileptogenic stimuli, Kv7.5-KO rats required a lower KA dose than WT to reach SE (19 vs. 24 mg/kg), and showed decreased latency to the first stage 3 seizure (118 vs. 143 min). KA caused a 60% increase in FITC-dextran uptake in WT rats, while Kv7.5-KO rats permeability remained unchanged, possibly suggesting that maximum damage had occurred. IF showed reduced ZO-1 signal in both WT and Kv7.5-KO BMVs (60 and 30%, respectively) and CLN5 (49 and 60%, respectively); in WT rats exposed to KA, Kv7.5 was selectively downregulated while Kv7.4 expression was not

altered. Overall, these findings suggest that Kv7.5 channels influence BBB integrity and seizure susceptibility, highlighting their potential as therapeutic targets for epilepsy and other neurological disorders.

Disclosures: C. Celentano: None. **R.F. Yoshimura:** None. **M. Taglialatela:** None. **V. Barrese:** None. **G.W. Abbott:** None.

Late-Breaking Poster

LBP066: G.05. Brain Blood Flow, Metabolism, and Homeostasis

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP066.08/LBP149

Topic: G.05. Brain Blood Flow, Metabolism, and Homeostasis

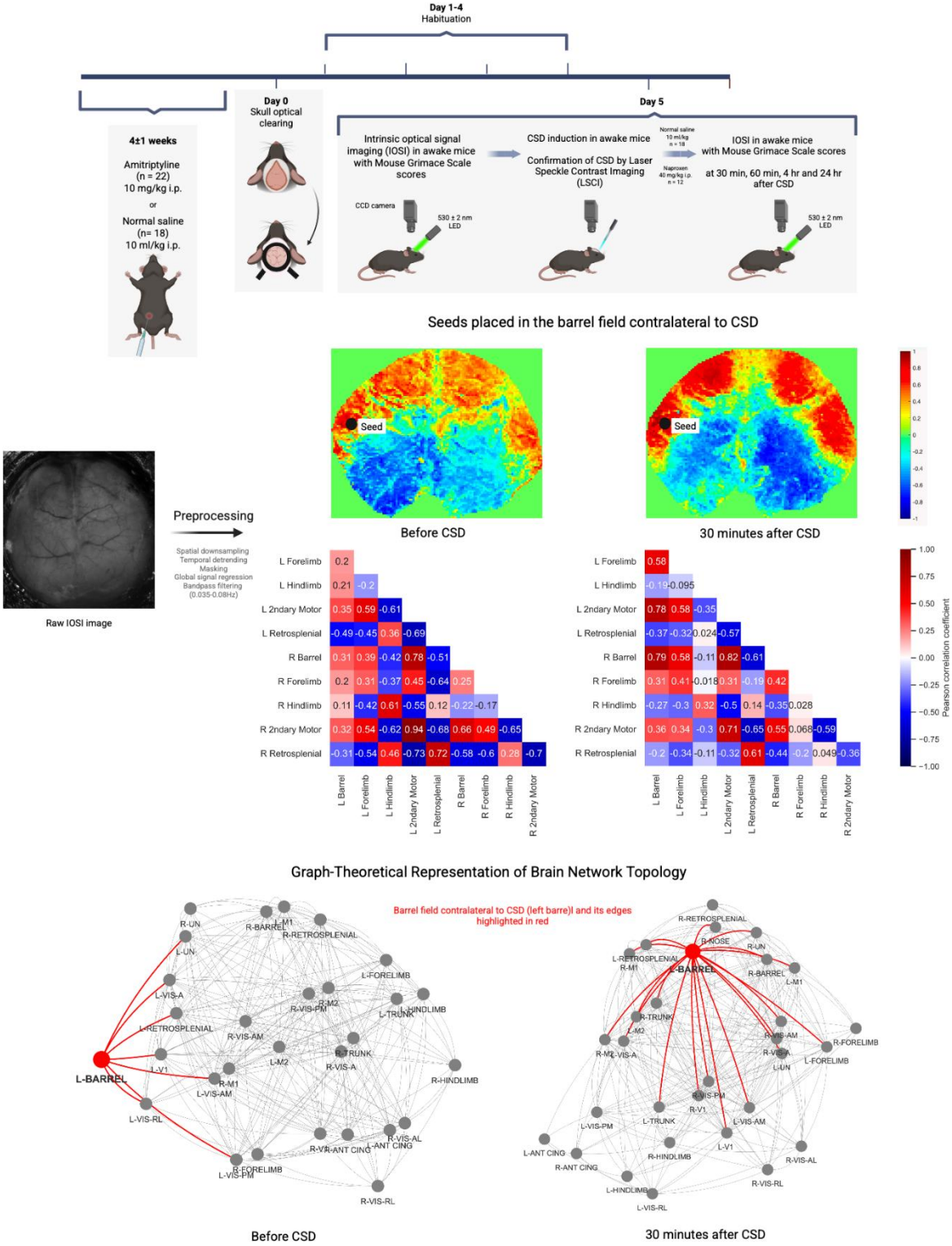
Support: Hacettepe University Scientific Research Projects Coordination Unit TDK-2023-20402

Title: Barrel field plays a hub-like role in the resting-state cortical network after spreading depression

Authors: *B. SOLGUN[1,2], B. DONMEZ-DEMIR[2], H. KARATAS-KURSUN[2], E. ERDENER[2]; [1]Hacettepe University, Ankara, Turkey; [2]Hacettepe University, Institute of Neurological Sciences and Psychiatry, Ankara, Turkey

Abstract: Resting-state functional imaging is increasingly utilized to study how cortical networks modulate and respond to pain. Migraine, a common headache disorder, can be experimentally modeled by cortical spreading depolarizations (CSD) in rodents, and barrel field, among other high-order cortical areas, receives trigeminal nociceptive signals after CSD. However, the impact of CSD on functional connectivity and network topology is not well understood. We used awake wide-field intrinsic optical-signal imaging (IOSI) on optically cleared intact skull windows to investigate the effect of CSD on bihemispheric resting-state functional connectivity and network topology. C57BL6-ChR2 mice received i.p. amitriptyline or normal saline for 4±1 weeks, and underwent skull optical clearing with 10% EDTA solution prior to imaging. We then performed IOSI under 530nm light to observe changes in total hemoglobin (HbT) concentration. Next, CSD was triggered optogenetically and confirmed by laser speckle contrast imaging. After CSD onset, to modulate headache, a subset of mice received i.p. naproxen, an analgesic medication. IOSI was repeated at 30 minutes, 60 minutes, 4 hours and 24 hours after CSD. Mouse Grimace Scale was scored at each timepoint for behavioral headache documentation. We observed distinct time-dependent changes in connectivity patterns after CSD, reversed by naproxen. Barrel field contralateral to CSD showed stronger connectivity with multiple regions in both hemispheres. In addition, functional connectivity within the barrel field contralateral to CSD also increased. Network analysis revealed increased closeness centrality, eigenvector centrality and degree centrality in the barrel field contralateral to CSD after CSD, reversed by naproxen. Moreover, amitriptyline, a prophylactic migraine medication,

increased CSD threshold, altered baseline connectivity and led to unique connectivity changes after CSD. This work highlights barrel field's role in cortical pain modulation and indicates alteration of network dynamics after CSD, and with migraine medications.



Disclosures: B. Solgun: None. **B. Donmez-Demir:** None. **H. Karatas-Kursun:** None. **E. Erdener:** None.

Late-Breaking Poster

LBP067: G.06. Autonomic Regulation

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP067.01/LBP150

Topic: G.06. Autonomic Regulation

Support: NIH Grant T32-GM007170
NIH Grant T32-GM148377

Title: Map of central neuronal activation in acute myocardial infarction

Authors: *C. N. WINSTON[1], C. BAUMER-HARRISON[2], M. R. HAYES[2], Z. ARANY[1]; [1]Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, Philadelphia, PA; [2]University of Pennsylvania, Philadelphia, PA

Abstract: Sympathetic overactivation associated with acute myocardial infarction (AMI) drives arrhythmogenesis, mortality, and the development of heart failure (HF), but the neural substrates of this autonomic dysregulation are poorly understood. In this study, we mapped the central neuronal response to AMI to provide insight into the involvement of brain circuits in AMI. We induced MI in 8-week-old male mice by surgically ligating the left anterior descending artery (LAD). Brains were collected 90 minutes after LAD ligation or sham operation (n = 5/group). We used c-Fos immunohistochemistry (IHC) to quantify neuronal activation in regions of interest. We observed robust activation in the caudal nucleus tractus solitarius (cNTS) and the ventrolateral medulla (VLM) with the number of c-Fos positive cells present in each region almost three times higher after MI than after sham operation ($p < 0.01$; Student's two-sample t-test). Increased activity was also observed in the dorsal motor nucleus of the vagus (DMV), the locus coeruleus (LC), and the paraventricular nucleus of the thalamus, and decreased activity was observed in the ventromedial hypothalamus (VMH) and the anterior hypothalamus (AH) after MI. The regions we identified are implicated in autonomic regulation and have polysynaptic connections with the heart. The cNTS is the primary central relay of cardiovascular afferent information. The VLM and the DMV are major sources of sympathetic and vagal outflow, respectively, to the heart. The LC contains noradrenergic neurons that project widely throughout the brain. Given the role of orexin in cardiac autonomic regulation and the evidence for orexinergic projections to each of these regions, we hypothesized that orexinergic neurons in the lateral hypothalamus (LH) may underlie the observed changes in AMI. We used a related closed-chest model, wherein the LAD is ligated without thoracotomy, to test this hypothesis. Brains were collected 60 minutes after closed-chest MI or sham operation (n=3/group), and IHC was performed for orexin and c-Fos. We found increased activation in the LH after MI ($p < 0.01$; Student's two-sample t-test). Additionally, the proportion of orexinergic neurons in the LH that were c-Fos positive was increased after MI, though larger samples are needed to confirm this

result. The anatomical findings from our study demonstrate activation of central autonomic regions in AMI and suggest the orexinergic system as a candidate driver of these changes. Future studies will identify the connectivity and functional relevance of orexinergic circuits implicated in AMI, as well as the neurochemical phenotype of activated neurons.

Disclosures: C.N. Winston: None. **C. Baumer-Harrison:** None. **M.R. Hayes:** None. **Z. Arany:** None.

Late-Breaking Poster

LBP067: G.06. Autonomic Regulation

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP067.02/LBP151

Topic: E.02. Somatosensation – Touch

Support: National Institutes of Health (R01DK133605)

Title: Pudendal Sensory Nerve Activity Modulates Voiding Efficiency in Aging Underactive Bladder

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Abstract: This study explored strategies to enhance voiding efficiency (VE) of old rats with an underactive bladder (UAB) phenotype by enhancing urethral sensory transmission. Efficient voiding depends on the urethra-to-bladder augmenting reflex (AR), a sensory-driven mechanism mediated by pudendal afferents that detect urethral fluid flow and distension, then strengthen bladder contractions and promote urethral relaxation. Our prior research showed that pudendal sensory function declines with age, increasing the intraurethral flow threshold needed to trigger AR, likely contributing to age-related voiding dysfunction. This sensory impairment offers a promising therapeutic target. Here, we aimed to restore VE by activating urethral afferents through bolus saline infusion in an aged UAB rat model.Aged female Sprague-Dawley rats (18-24 months) underwent suprapubic catheter implantation for intravesical bladder pressure recording and placement of EMG electrodes to monitor external urethral sphincter (EUS) activity under urethane anesthesia. Voiding trials were conducted under baseline conditions, followed by trials where a 100 µl saline bolus was infused into the bladder during voiding. VE was calculated as the percentage of infused bladder volume expelled per void.In aged rats with the UAB phenotype, fluid bolus infusion substantially improved VE, increasing from 38 ± 21% at baseline to 73 ± 16% ($p < 0.05$). To confirm that VE improvement resulted from the bolus activating pudendal sensory afferents that trigger the AR (rather than bladder afferents), 2% lidocaine was applied intraurethrally to block these afferents locally. Lidocaine completely abolished the VE improvement induced by bolus infusion, demonstrating that urethral sensory signaling through

pudendal afferents is essential for this voiding improvement.These findings provide direct mechanistic evidence that the activation of urethral sensory pathways enhances bladder emptying in aged rats with UAB, highlighting reduced pudendal sensory input as a key contributor to age-related voiding dysfunction. Future studies will prioritize the development of minimally invasive neurostimulation strategies that mimic urethral fluid flow-evoked sensory activation, offering a potential therapeutic approach for UAB in aging populations.

Disclosures: B. Afrashteh: A. Employment/Salary (full or part-time); Department of Rehabilitation Medicine, Division of Physical Therapy, Emory University, Atlanta, GA, USA. **Z.C. Danziger:** A. Employment/Salary (full or part-time); Department of Rehabilitation Medicine, Division of Physical Therapy, Emory University, Atlanta, GA, USA, Wallace H. Coulter Department of Biomedical Engineering, Emory University and Georgia Institute of Technology, Atlanta, GA, USA.

Late-Breaking Poster

LBP067: G.06. Autonomic Regulation

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Topic: G.06. Autonomic Regulation

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Hawaii Community Foundation MedRes_2023_00002772
National Institute on Minority Health and Health Disparities (NIMHD) U54MD007601
National Institute of General Medical Sciences (NIGMS) P20GM113134

Title: Cardioprotection in prediabetes via chemogenetic stimulation of hypothalamic oxytocin neurons

Authors: *A. NILSSON[1], K. J. SCHUNKE[2], D. S. MENDELOWITZ[3];
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Abstract: Diagnoses of prediabetes and metabolic syndromes are increasing at an alarming rate worldwide, often simultaneously. A significant consequence is high risk of cardiovascular disease, highlighting the need for cardiac-specific therapeutics for early intervention. It has been shown that targeting excitatory neurotransmission to brainstem cardiac vagal neurons via chemogenetic activation of hypothalamic oxytocin (OXT) neurons activates the cardiac parasympathetic system and provides cardioprotective effects in models of heart disease. We hypothesized that stimulating this neural network would offer cardioprotection in a rat model of prediabetes with cardiomyopathy. First, we induced prediabetes through prolonged high-fat, high-fructose feeding. Viral vectors were stereotactically injected into the paraventricular nucleus (PVN) of the hypothalamus in neonatal rats to express excitatory designer receptors

exclusively activated by designer drugs (DREADDs) in PVN OXT neurons, which were then chronically activated using the designer drug clozapine-n-oxide (CNO) for four weeks. Compared to non-treated disease animals after four weeks of CNO, treated animals exhibited improved cardiac diastolic function measured using echocardiogram and reduced left ventricular fibrosis, assessed with trichrome blue staining. Implanted telemetry revealed trending improvements in tachycardia and heart rate variability. Importantly, these cardioprotective benefits in treated animals occurred with no changes to systemic indices of prediabetes. Transcriptional analysis of left ventricular tissue suggests involvement of metabolic pathway (Pdk4, Pdp1, Hk2) and ion handling (Sln, Atp1a2, Atp1a4) preservation in treated compared to diseased animals. These results demonstrate the benefits of stimulating the PVN OXT network to counteract prediabetic cardiomyopathy, independent of systemic prediabetes. These neurons and their downstream networks appear to be a promising therapeutic target for activating protective parasympathetic-mediated cellular pathways within the heart during prediabetic cardiomyopathy.

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Late-Breaking Poster

LBP067: G.06. Autonomic Regulation

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP067.04/LBP153

Topic: G.06. Autonomic Regulation

Support: ZIA DK075057
ZIA DK075063
ZIA DK075064
ZIA DK075168
ZIA DK075087-07
ZIC DK070002

Title: Thermoregulatory roles of preoptic area histamine H_1 receptor-expressing neurons

Authors: *R. A. PIÑOL[1], A. VALERI[2], C. XIAO[1], S. KULKARNI[3], O. GAVRILOVA[1], A. LUTAS[4], M. J. KRASHES[5], M. REITMAN[6];
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Abstract: Endothermy defines two whole classes of vertebrate animals. We know surprisingly little detail on how the brain regulates this critical feature. The first line of body temperature regulation is behavior and includes, in mice, nest building, huddling and thermal preference. Physiological processes include thermogenesis and vasomotion. The hypothalamus' preoptic area (POA) is a key node in neural circuits controlling thermoregulatory behavior and

physiology. Many single gene populations spanning the POA subregions have been probed for their role in thermoregulation. Only a few POA populations increase Tb upon activation, canonically through sympathetic activation of brown adipose tissue, which is recruited by cold exposure. Histamine exerts its peripheral and central nervous system actions through its four receptors. There is an evolutionary conserved connection between circadian rhythm, body temperature regulation and histamine. In the POA, in the anterior hypothalamus, histamine H_1 receptor activation can increase body temperature and extracellular histamine correlates with wakefulness. *Hrh1*, which encodes the histamine H_1 receptor, is expressed in several neuronal populations in the POA with limited overlap with other POA thermoregulatory neurons. Acute activation of POA histamine H_1 receptor-expressing (POA^{Hrh1}) neurons increased body temperature and physical activity. Acute inhibition attenuated the dark phase increase in body temperature without affecting physical activity. There was no effect of inhibition on body temperature during the light phase, fever, cold exposure, or warm exposure. Assessing behavioral thermoregulation, we found that POA^{Hrh1} neurons stimulated nest building in both sexes, possibly contributing to cold-induced nesting behavior. POA^{Hrh1} neurons have projections to the arcuate, dorsomedial hypothalamic and tuberomammillary nuclei through which they can increase body temperature and physical activity. Overall, POA^{Hrh1} neurons participate in several thermoregulatory functions, including circadian body temperature regulation, physical activity, and nest building behavior.

Disclosures: R.A. Piñol: None. **A. Valeri:** None. **C. Xiao:** None. **S. Kulkarni:** None. **O. Gavrilova:** None. **A. Lutas:** None. **M.J. Krashes:** None. **M. Reitman:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP068.01/LBP154

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R01AG065830
NIH Grant R01GM133032

Title: Core clock timing properties in the PS19 mouse model of tauopathy

Authors: N. HALLOY, M. FORMANOWICZ, N. PHAM, *K. R. HOYT, K. H. OBRIETAN; Ohio State University, Columbus, OH

Abstract: Circadian disruptions are prevalent in neurodegenerative disorders, such as Alzheimer's disease and frontotemporal dementia, and the accumulation of hyperphosphorylated microtubule associated protein tau (MAPT) into neurofibrillary tangles - a pathological hallmark of these diseases - may be implicated in circadian dysfunction. The link between pathological tau aggregation and circadian dysfunction is not well understood, especially regarding the role of the suprachiasmatic nucleus (SCN), the principal circadian pacemaker. To investigate this

relationship, we conducted a histological and functional characterization of the SCN in the PS19 (Prnp-huMAPT*P301S) transgenic mouse model of tauopathy. Hyperphosphorylated tau was evident within the SCN of PS19 mice early in the disease process (starting at 2 months-of-age). Pathological tau was detected in both of the major SCN neuronal subpopulations, vasopressin-expressing neurons within the SCN shell region and vasoactive intestinal peptide-expressing cells within the SCN core region. To assess the functional output of the SCN, we profiled daily locomotor activity (a measure of SCN timing and phasing) in male PS19 (n=8) and wild-type (WT; n=8) mice from 3 to 11 months-of-age. and female PS19 (n=6) and WT (n=6) mice from 7 to 11 months-of-age. Analysis of the overall activity patterns, rate of re-entrainment to shifted light/dark cycles, or intrinsic circadian timing did not detect significant differences between WT mice and PS19 mice, indicating that both the clock timing and entrainment properties of the SCN clock are not affected by pathological tau. To further assess the effects of tau pathology on SCN timing properties, we turned to an in vitro fluorescence-imaging based profiling approach. To this end, a cross of the PS19 mouse line with a Per1-Venus fluorescent clock reporter mouse line was generated (PS19::Per1-Venus); This line was used in conjunction with a tau-fibril seeding approach to induce tau pathology. Despite robust levels of tau pathology in the seeded PS19 SCN tissue, no effects on clock periodicity were observed. These findings suggest that in the PS19 tauopathy model, tau aggregation within the SCN is not sufficient to disrupt its core clock timing properties. Collectively, these observations raise the possibility that circadian disruptions observed in tauopathy patients result from dysregulation of SCN-gated output pathways or downstream clock-gated circuits rather than from the disruption of the SCN core oscillator.

Disclosures: N. Halloy: None. **M. Formanowicz:** None. **N. Pham:** None. **K.R. Hoyt:** None. **K.H. Obrietan:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP068.02/LBP155

Topic: G.07. Biological Rhythms and Sleep

Support: DoD TSC2024002

Title: Leveraging a conditional knock-out interneuron mouse model to establish a potential link between circadian activity patterns and seizure propensity

Authors: *K. JURSCH[1], A. M. STAFFORD[2], A. M. YAW[3], D. VOGT[4], H. M. HOFFMANN[5]; [1]Michigan State University, Gladstone, MI; [2]Pediatrics and Human Development, MSU, Grand Rapids, MI; [3]Animal Science, Michigan State University, Lansing, MI; [4]Department of Pediatrics and Human Development, Michigan State University, Grand Rapids, MI; [5]Animal Science, Michigan State University, East Lansing, MI

Abstract: Sleep is a fundamental biological process that follows circadian (24h) patterns and plays a vital role in maintaining overall health and well-being. However, for individuals with seizures, neurological and sleep disturbance symptoms are common but remain largely overlooked. This is especially the case for rare monogenic syndromes that impact brain development and share these neurological symptoms. One such syndrome, neurofibromatosis 1, caused by mutations in the nf1 gene, results in both elevated seizures and sleep disruption. Deficits in inhibitory GABAergic neuron development are implicated in neurofibromatosis 1 related behaviors and may also underlie the elevated seizures and sleep disturbances, but this is still poorly understood. Understanding the intricate relationship between sleep and seizures is essential for optimizing patient care and improving quality of life. To further our understanding of the interaction between seizures and activity/inactivity cycles, we generated Nkx2.1-cre: Nf1-wild type, (Nkx2.1-cre: Nf1-flox/wt) referred to as cHET and (Nkx2.1-cre:Nf1-flox/flox) referred to as cKO. Nkx2.1-cre targets the majority of brain GABAeric progenitor cells, including interneurons of the telencephalon and most hypothalamic nuclei, with the exception of the circadian pacemaker, the suprachiasmatic nucleus. We found the cHET and cKO mice to be susceptible to chemically (PTZ) induced seizures. To further understand if the increase seizure susceptibility was associated with weakened activity/inactivity cycles, we placed the mice on running wheels during standard light12h:dark12h (LD) and constant darkness (DD). We found that the cHETs and cKOs were comparable to controls under LD. However, DD revealed reduced day/night differences in both cHETs and cKOs compared to controls (reduced activity profile amplitudes; $p<0.001$), suggesting a weaker circadian control over activity/inactivity behavior. This weakened circadian rhythmicity was more severe in the cKOs, as the cKO, but not cHETs, had reduced Chi2 periodogram amplitude compared to controls (Qp; $p<0.001$). Such lack of circadian behavior is typically linked to suprachiasmatic nucleus function, however, the Nkx2.1-cre does not target this structure, indication of the loss of circadian output is driven by the subparaventricular zone, a hypothalamic region which also plays important roles in rhythm regulation. Together this work shows an association between reduced rhythmic control of activity/inactivity patterns with increased seizure propensity, highlighting the need for targeted studies on how improved sleep-hygiene can reduce seizure risk.

Disclosures: K. Jursch: None. **A.M. Stafford:** None. **A.M. Yaw:** None. **D. Vogt:** None. **H.M. Hoffmann:** None.

Late-Breaking Poster

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Topic: G.07. Biological Rhythms and Sleep

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NIH grant EY027202 (H.Z. & R.L.B)

Title: ipRGC properties prevent light from shifting the SCN clock during the daytime

Authors: ***R. KOMAL**[1], C. BEIER[1], A. NATH[2], W. N. GRIMES[2], H. WANG[1], C. GAO[3], M. A. PENZO[1], J. S. DIAMOND[2], H. ZHAO[4], S. HATTAR[1];
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Abstract: The suprachiasmatic nucleus (SCN), the central circadian pacemaker, receives photic input exclusively from intrinsically photosensitive retinal ganglion cells (ipRGCs). Light, however, mainly shifts the SCN clock during nighttime. Here we induced phase shifts in the SCN clock during the daytime in mice by activating ipRGCs using chemogenetics or violet light. Our data reveals that light's failure to induce daytime shifts in most animals is not only attributed to the SCN, as has been proposed for decades, but also requires the limitation of ipRGC firing via depolarization block. Chemogenetic activation of ipRGCs induces large shifts during both the nighttime and daytime, but daytime shifts require brain circuits and neuropeptide transmitters that are dispensable for nighttime shifts. Thus, ipRGC propensity for depolarization block not only prevents daytime shifts in mice, but also limits the magnitude of nighttime shifts, suggesting the ipRGC-SCN acts as an integrated pacemaker across the circadian cycle.

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Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

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Topic: G.07. Biological Rhythms and Sleep

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NSF Grant 2047529

Title: Prior Neural Dynamics in Real-Time Detection of Slow Waves During Sleep

Authors: ***C. CHEN**, K. LEPAGE, S. VIJAYAN;
School of Neuroscience, Virginia Tech, Blacksburg, VA

Abstract: Slow-wave sleep (SWS) is a hallmark of non-rapid eye movement sleep and is critical for memory consolidation. Closed-loop auditory stimulation has been shown to enhance SWS by targeting the UP-state of slow waves; however, reliable real-time detection remains a challenge. Conventional approaches typically rely on fixed thresholds, which yield a large fraction of correct detections during N3 sleep (84.2%) but reduced performance during N2 (70.8%). In this study, we investigated the neural dynamics of data immediately preceding conventional slow

wave detector detections using linear models and assessed how variation in these neural dynamics can impact the performance of these models. Methods: We analyzed data from 26 healthy young adults in the ANPHY-Sleep open dataset (Wei et al., 2024). For each subject, a slow-wave detection algorithm (Ngo et al., 2013) was applied during N2 and N3 sleep to identify slow-wave events. Ground truth slow-wave events were annotated according to AASM criteria. Prior detected events were quantified and modeled using logistic regression, and detection precision was evaluated using leave-one-subject-out cross-validation. Results: Detection precision during N3 remained stable across prior time durations (Linear model: 0.821±0.024), with no significant improvements relative to baseline. In contrast, during N2, prior window length could influence performance: shorter time-window models (10-30 s) showed reduced or similar precision, while longer time-window models (50-60 s) yielded higher precision (0.720 ± 0.069). Statistical analysis revealed a trend at 50 s ($p = 0.055$) and a significant improvement at 60 s ($p = 0.045$), suggesting that longer time windows may benefit slow-wave detection during N2 sleep. Coefficient analysis indicated that past short-term events increased the chance of true slow waves, while long-term events decreased it. Conclusion: Our findings demonstrate that prior neural dynamics play an important role in slow-wave detection. Longer time window significantly enhanced detection precision during N2 sleep. Moreover, short-term and long-term detected events might shape the detection of subsequent slow waves. These results highlight the importance of prior neural dynamics in enhancing the performance of slow-wave detectors.

Disclosures: C. Chen: None. **K. Lepage:** None. **S. Vijayan:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

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Program #/Poster #: LBP068.05/LBP158

Topic: G.07. Biological Rhythms and Sleep

Support: Israel Science Foundation (ISF), Grant 1214/24
The German Israeli Foundation (GIF) Nexus, Grant no. G-1566-413.13/2023
Binational Science Foundation (BSF), Grant 2021177)

Title: Sleep and DNA breaks across evolution

Authors: *L. APPELBAUM;
The Faculty of Life Sciences and The Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan, Israel

Abstract: Sleep is a universal behavior essential for survival across the animal kingdom, ranging from jellyfish to fish and humans. Sleep benefits the brain, including memory and learning, however, even invertebrates with simple nervous system sleep, and the core cellular function of this enigmatic behavior is unclear. We combined imaging of DNA damage response proteins, cell-type specific conditional CRISPR/Cas system, real time imaging of neuronal activity, as

well as video tracking of behavior to show that sleep decreases neuronal DNA damage, which accumulated during wakefulness, in zebrafish. Extending this framework to basal metazoans, we examined a diurnal jellyfish and a crepuscular sea anemone and found that DNA damage contributes to sleep regulation in these evolutionarily distant cnidarians, despite their divergent chronotypes. Furthermore, we demonstrated the conservation and ecological relevance of this mechanism in tropical fish, showing that artificial light at night disrupts sleep and social behavior and elevates neuronal DNA damage in their natural reef habitat. These findings suggest that cellular stress and neuronal DNA damage are evolutionary drivers of sleep, which enables neuronal maintenance and recovery across diverse animal lineages.

Disclosures: L. Appelbaum: None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP068.06/Web Only

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R35GM142712

Title: Alpha-2 adrenergic agonist induced sedation and temperature changes are mediated by glutamatergic and adrenergic neurons outside of the rostral pons.

Authors: N. FRYOU[1], *A. R. MCKINSTRY-WU[2];
[1]Anesthesia, University of Pennsylvania, Philadelphia, PA; [2]Anesthesiology and Critical Care, University of Pennsylvania, Philadelphia, PA

Abstract: Intro: Agonism at adrenergic alpha-2a receptors produces sedation via activation of NREM sleep circuits. One of the highest densities of central alpha-2a receptors is in the rostral pons, surrounding the locus coeruleus (LC), medial parabrachial (PB) areas. It is contested whether this region is key to producing sedation. Using genomic and virally-mediated cell-specific knockouts, we sought to determine the type of neurons mediating alpha2-agonsits, and testing if that population is in the rostral pons.
Methods: Mice with floxed ADRA2A were crossed with cell-specific Cre-expressing lines to knock out ADRA2A pan-neuronally (Snap25-Cre), in glutamatergic cells (Vglut2-Cre), or adrenergic cells (Dbh-Cre). A separate cohort of floxed ADRA2A mice were injected with AAV9.mSlc17a6.Cre.P2A.mCherry.WPRE.SV40 in the LC (n = 7) AAV9.rTH.PI.Cre.SV40 in the PB (n = 8) or the control vector AAV9.DIO.mCherry.WPRE.SV40 at PB (n=8). Mice were given IP Dex at 0, 0.1, 0.3, and 1 mg/kg and placed on rotarod after 20 minutes for 3 trials and temperature checked at 1 hour. LC and PB transfection was confirmed by immunohistochemistry using anti-VGLUT2 and anti-Cre primary antibodies (abcam: ab79157, ab216262), or anti-Tyrosine Hydroxylase and anti-Cre (abcam: ab76442, ab216262). A 70% threshold for double-staining of target areas used to determine successful transfection. Fractional knockout was also

analyzed in a linear regression model to delta temperature and rotarod distance.
Results: Genomic vglut2 ADRA2A ko resulted in resistance to sedation and temperature change with dex administration compared to floxed controls, paralleling that of pan-neuronal adra2a knockout mice (n=8-12 per group, $p<0.001$). Dbh adra-2a knockout mice exhibited only minor resistance to alpha2 agonist induced sedation and temperature change ($p<0.01$). The 5 mice successfully transformed TH-Cre at the LC with TH-Cre, and the 4 with Vglut2-Cre at the PB showed non-significant resistance to the effects of dex compared to control animals.
Conclusion: While knockout of ADRA2A in all vglut2+ neurons confers profound resistance to alpha2-agonist sedation, and adrenergic ADRA2A knockout confers partial resistance, virally mediated knockout of ADRA2A in either PB vlgut2+ or LC adrenergic neurons does not produce resistance compared to control. This suggests alpha2a-Rs outside of the peri-fourth-ventricle rostral pons are responsible for alpha2-agonist-induced sedation and temperature change.

Disclosures: N. Fryou: None. **A.R. McKinstry-Wu:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP068.07/LBP159

Topic: G.07. Biological Rhythms and Sleep

Support: NS078410-01A1

Title: Sleep deprivation increases DNA double-strand breaks in the hippocampus

Authors: *A. RAJHANS[1], C. A. GHIANI[1,2], E. KYE[1], V. BALU[1], D. L. GLANZMAN[3,4], K. N. PAUL[3];
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Abstract: Double-strand DNA breaks (DSBs) are generated during normal neuronal activity and represent a form of genomic stress that, if unrepaired, can lead to cellular dysfunction and degeneration. The hippocampal trisynaptic circuit - comprising the dentate gyrus, CA3, and CA1 subfields - is a critical mechanism for encoding and retrieving episodic and spatial memories. Despite emerging evidence that sleep supports DSB repair, it remains unclear whether acute sleep deprivation (SD) heightens DNA damage, specifically within this essential circuitry. γ-H2AX is a phosphorylated histone variant that localizes at DSB sites. We sought to determine the influence of acute SD on DSBs by measuring γ-H2AX within the hippocampal CA1-3 regions. 12-16 week-old male C57BL/6J mice, underwent either 12 hours of SD on a rotating wheel or were allowed ad lib sleep in a wheel-locked apparatus (n=4/group; age-matched). Immediately after the experimental period, mice were transcardially perfused with 4%

paraformaldehyde (PFA), and brains were post-fixed, then sectioned at 50 μm thickness via free-floating cryostat sectioning to ensure optimal antigen preservation. We performed immunohistochemistry to detect γ-H2AX. Sections were blocked in 10% normal goat serum and 0.3% Triton X-100, then incubated for 2 hours at 37°C with a rabbit anti-γ-H2AX primary antibody. After washes, sections were incubated with a CY3 secondary antibody to visualize γ-H2AX foci. Nuclei were counterstained with DAPI to delineate cell layers. Confocal imaging of γ-H2AX fluorescence intensity was performed. SD mice exhibited higher γ-H2AX fluorescence intensity (59.05±4.49) in the trisynaptic circuit than controls (21.45±3.91; t=3.055; p=0.0224), demonstrating that sleep deprivation increased histone phosphorylation following SD. These findings suggest that acute SD elevates DNA damage within the hippocampal trisynaptic circuit. By establishing a link between sleep loss, hippocampal DNA damage, and potential vulnerability of hippocampal circuits to sleep loss, this exploratory investigation may reveal a mechanism through which sleep reinforces learning and memory.

Disclosures: A. Rajhans: None. **C.A. Ghiani:** None. **E. Kye:** None. **V. Balu:** None. **D.L. Glanzman:** None. **K.N. Paul:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP068.08/LBP160

Topic: G.07. Biological Rhythms and Sleep

Title: Neural circuit mechanisms of sleep homeostasis in the fly

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Abstract: Sleep is a highly conserved physiological and behavioral state that is essential for survival across animal species. Its regulation depends on circadian and homeostatic mechanisms, with the latter ensuring that sleep pressure accumulates during wakefulness and promotes recovery sleep when sufficient sleep need has accumulated. The fruit fly *Drosophila melanogaster* has emerged as a powerful model for studying sleep homeostasis, owing to its genetic tractability and established physiological approaches. In the fly brain, several brain regions have been implicated in the control of sleep homeostasis, most notably the dorsal fan-shaped body (dFB). Recent studies have revealed a pronounced molecular and anatomical heterogeneity of the dFB. This diversity suggests the existence of distinct neuronal subtypes within the dFB that may differentially contribute to sleep regulation. However, the specific cellular identities of sleep-control neurons and the functional role of this heterogeneity remain poorly understood. To address this lack of cellular resolution, we combine behavioral assays with in vivo whole-cell patch-clamp recordings and two-photon calcium imaging in behaving flies. Our results reveal pronounced functional heterogeneity within the dFB: whereas some neuronal subpopulations increase their activity with accumulating sleep need, others decrease,

and some remain unchanged, consistent with their respective effects on sleep behavior. These findings provide critical mechanistic insight into where and how sleep pressure is represented in the brain. More broadly, they advance our understanding of how internal states modulate behavior through defined neuronal circuits within the dFB, establishing the dFB as a key site for integrating physiological needs with behavioral output.

Disclosures: D. Shevchuk: None. **P. Dampenon:** None. **A. Kempf:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

Location: SDCC Hall B

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Program #/Poster #: LBP068.09/LBP161

Topic: G.07. Biological Rhythms and Sleep

Support: NIH grant R21HL170255 to PM

Title: A feature-driven classification method to identify space-time profiles of slow oscillations in low density EEG

Authors: J. GAITHER[1], S. MEDNICK[2], D. PLANTE[3], ***P. MALERBA**[4];
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Abstract: Introduction: Sleep slow oscillations (SOs, 0.5-1.5Hz) in the EEG reflect highly synchronous cortical large travelling waves, tied to cortical neurodevelopment, and thought to reflect sleep homeostasis, as well as support memory stabilization, in particular through their coordination with other sleep rhythms. Objective, data-driven description of the spatio-temporal organization of SOs on the EEG manifold is relevant to investigations on their functional role in cognition and health. Earlier work by our group has introduced a data-driven approach showing that SOs organize on the electrode manifold as Global, Frontal and Local SOs, based on their co-detection at multiple electrodes within a short delay. In a translational collaborative effort, this method was applied to sleep recordings from people with hypersomnolence (excessive sleepiness during the day), the most common sleep complaint, associated to emergence of depression and numerous comorbidities. We showed a specific excess in the amount of Frontal SOs in individuals related to hypersomnolence. However, our current approach requires at least 24 head electrodes, preventing its applicability in standard diagnostic polysomnography and at-home studies. We here introduce a deterministic method that identifies space-time profiles of SO types in low density EEG.
Methods: We use >200 waveform features spanning amplitude, phase, and signal complexity. We use a training set (22 individuals, 64 EEG channels) and validation set (34 individuals, 32 EEG channels). Timing of SO events was used to extract activity at 8 EEG channels: F3/4, C3/4, P3/4, O1/2. Machine learning classifiers (xgboost in python) were trained on progressively fewer

channels, in 4 conditions: FCPO, FCP, FC and F channels. A version of the model using restricted features was also tested. Model performance was quantified with accuracy and log-loss. Feature role in SO type prediction was studied with SHAP feature-importance.
Results: We introduce a portable SO classifier trained on data recorded from eight or less head EEG channels. Our model recovers an SO's class with accuracy around 75%, and log-loss below 0.6, with performance consistent across the three types. Loss of accuracy in validation was small for all cases except the F channels (only 2 electrodes). Feature importance showed that Global and Frontal SOs are characterized by central and frontal activity, respectively.
Conclusions: These portable simplified SO classification models expand the domain in which the space-time dynamics of sleep oscillations can be used to discover biomarkers and propose target for interventions in clinical populations.

Disclosures: J. Gaither: None. **S. Mednick:** None. **D. Plante:** Other; DT Plante has served as a consultant/advisory board member for Jazz Pharamceutical, Alkermes, Centessa, Harmony Biosciences, and Takeda, advisory board member for Apnimed, and a consultant for Aditum. **P. Malerba:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

Location: SDCC Hall B

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Program #/Poster #: LBP068.10/LBP162

Topic: G.07. Biological Rhythms and Sleep

Support: NIH Grant R01GM109086

Title: Assessing intrinsic neuronal properties of the hierarchical brain with human intracranial electroencephalography

Authors: *E. BUBLITZ[1], B. M. KRAUSE[2], H. KAWASAKI[3], K. V. NOURSKI[4], M. I. BANKS[5];
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Abstract: The hierarchical organization of the human brain supports efficient and flexible processing, with intrinsic neural and network properties varying across this hierarchy. However, defining the hierarchy can be challenging. Here, Human Connectome Project (HCP) resting-state fMRI functional connectivity (FC) data are used to measure hierarchy, and this measure is applied to human intracranial electroencephalography (iEEG) data to study differences in intrinsic neuronal properties across arousal states. iEEG data were collected from 24 adult neurosurgical patients with medically refractory epilepsy and implanted with intracranial electrodes for clinical monitoring prior to surgical resection. The study was approved by the

University of Iowa Institutional Review Board (ID #201804807). iEEG data were recorded during overnight sleep that was staged (wake, N1, N2, N3, REM) using polysomnography based on supplemental EEG and EMG recordings. Intrinsic timescale ($\tau_{intrinsic}$) was estimated as $1/2\pi f_{knee}$, where f_{knee} is the knee frequency of the power spectral density function (PSD) estimated from the data using the FOOOF algorithm. Delta power (1-4 Hz) at each recording site was estimated from the PSD. To define hierarchy, 1000 cortical (Schaefer-Yeo, 7 network) and 32 subcortical (Tian, S2) ROIs from HCP group-average FC data were mapped to a low-dimensional space using diffusion map embedding (DME). In DME, brain ROIs are mapped into a low dimensional space using eigendecomposition of the similarity matrix, derived from the FC matrix using cosine similarity and normalization by degree. In the resulting embedding space, ROI proximity indicates functional similarity. As reported previously, ROIs were organized in embedding space along a sensory-association axis, with unimodal sensory-motor ROIs at the lowest level of the hierarchy and default mode ROIs at the highest. The hierarchical position of each iEEG recording site (n=2478) was determined by assignment to one of the 1032 ROIs. In wake and N1, $\tau_{intrinsic}$ increased with ascending hierarchical position. In contrast, $\tau_{intrinsic}$ did not vary systematically across the hierarchy in N2, N3, and REM sleep. Overall, the shortest $\tau_{intrinsic}$ was seen in wake and the longest in N3, suggesting that wake has faster dynamics than sleep. Delta power varied across the hierarchy for all arousal states, increasing with ascending hierarchy, with wake having the steepest slope. As expected, overall delta power was highest in N3 and lowest in wake. This suggests that, while $\tau_{intrinsic}$ and delta power appear to be related, they likely have some differences in their underlying mechanisms.

Disclosures: E. Bublitz: None. **B.M. Krause:** None. **H. Kawasaki:** None. **K.V. Nourski:** None. **M.I. Banks:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

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Program #/Poster #: LBP068.11/LBP163

Topic: G.07. Biological Rhythms and Sleep

Support: R01 NS106032
WakeUp Narcolepsy

Title: Cataplexy triggered by social cues: a role for oxytocin in the amygdala

Authors: *C. E. MAHONEY, R. DE LUCA, E. ARRIGONI, T. E. SCAMMELL;
Beth Israel Deaconess Medical Center - Harvard Med, Boston, MA

Abstract: Introduction: Narcolepsy type 1 is characterized by chronic sleepiness, hypnagogic hallucinations and cataplexy. Cataplexy is sudden muscle paralysis which is usually triggered by by positive emotions and social experiences such as laughing with friends, yet the mechanisms through which social interaction promotes cataplexy are unknown. Amygdala neurons are active

during cataplexy, and cataplexy is reduced by lesions of the amygdala. We hypothesize that a subpopulation of central amygdala neurons that are sensitive to the prosocial neuropeptide, oxytocin (CeA-OTR), respond to rewarding stimuli and trigger cataplexy. Methods: We used pharmacology, in vivo calcium imaging, chemogenetic and optogenetic approaches to characterize the activity pattern of these neurons and to manipulate their activity state. Results: Cre-dependent anterograde tracing of the CeA-OTR neurons of the central amygdala indicate a moderate to dense projection to the REM sleep-regulatory region of the ventral lateral periaqueductal gray/lateral pontine tegmentum (vlPAG/LPT). Additionally, Channelrhodopsin Assisted Circuit Mapping (CRACM) experiments show that CeA-OTR neurons inhibit vlPAG neurons that innervate the REM atonia-promoting region, the sublaterodorsal nucleus. An oxytocin receptor agonist (Carbetocin) more than doubles cataplexy (26.9$\pm$4 bouts vs. saline 11.6$\pm$1.3 bouts, p=0.013). Targeted photostimulation of the CeA-OTR fibers in the vlPAG doubled the amount of cataplexy (21.5$\pm$2 bouts vs. 8.1$\pm$1.6 baseline, $p<0.01$), and co-administration of an oxytocin receptor antagonist (L-368-899) prevented this increase in cataplexy. In vivo GRAB-OT-v1.0 indicates oxytocin levels rise in the CeA prior to the onset of cataplexy (t=3.48, p=0.0038), and in vivo calcium imaging (GCAMP6s) indicates that the CeA-OTR neurons are active just prior to the onset of cataplexy (t=2.25, p=0.035). Chemogenetic activation of CeA-OTR neurons increased cataplexy (CNO 6.1$\pm$0.9% vs. saline 3.18$\pm$0.8%; p=0.01), whereas optogenetic inhibition of CeA-OTR terminals in the PAG reduces cataplexy in the presence of rewarding stimulus (29.5$\pm$9 vs. 58.8$\pm$12.2 bouts with no stimulation; t=4.09, p=0.0095 in the presence of chocolate). Photoinhibition also reduced cataplexy after treatment with carbetocin (7.7$\pm$2.6 vs. 28.5$\pm$4.9 bouts; t=8.17, p=0.0004)). Conclusion: The CeA-OTR subpopulation is necessary and sufficient to promote cataplexy and has a key role in socially-triggered cataplexy. Our future directions include determining the additional genetic markers of the oxytocin sensitive neurons and their role in cataplexy under different conditions of reward.

Disclosures: C.E. Mahoney: None. **R. De Luca:** None. **E. Arrigoni:** None. **T.E. Scammell:** None.

Late-Breaking Poster

LBP068: G.07. Biological Rhythms and Sleep

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Program #/Poster #: LBP068.12/LBP164

Topic: G.07. Biological Rhythms and Sleep

Support: P41-EB015896
R21-NS106706
R01-EB019437
P41- EB030006
R00-MH111748
R01-AG070135
S10-OD023637
S10-RR019371

Title: Spontaneous Hemodynamic Fluctuations Modulate Coordinated and Directional Cerebrospinal Fluid Flow in the Subarachnoid Space

Authors: *D. CHEN[1], F. WANG[2], H. YUN[1], A. STROM[1], J. R. POLIMENI[3], Z. DONG[2], L. D. LEWIS[1];
[1]MIT, Cambridge, MA; [2]MGH, Charlestown, MA; [3]Stanford, San Francisco, CA

Abstract: Cerebrospinal fluid (CSF) flow is a key component of maintaining healthy function in the central nervous system. Recent human studies have identified large-scale fluctuations in CSF flow in the fourth ventricle during sleep, suggesting a potential sleep-dependent brain clearance mechanism. However, how these flow dynamics unfold in the subarachnoid space (SAS), where CSF surrounds brain tissue, remains unclear. Here, we used MRI scanning with echo-planar-time-resolved-imaging (EPTI), an approach that combines whole-brain CSF flow mapping using a slow-flow-sensitized phase-contrast sequence and simultaneous multi-echo, distortion-free blood-oxygenation-level-dependent (BOLD) fMRI. We imaged fifteen subjects using 7-Tesla scanner at their habitual bedtime to test whether and how brain-wide CSF dynamics change during sleep. Each participant completed 1-4 resting runs of 45 minutes. We identified low-frequency spontaneous hemodynamic fluctuations by detecting large peaks in the cortical gray matter signal, and found that SAS flow dynamics were temporally coupled to these hemodynamic fluctuations. On average, 36.64% ± 4.69% (95% CI) of SAS voxels and 30.57% ± 4.58% of ventricular voxels showed significant flow changes. Importantly, these SAS flow changes formed spatially clustered patterns, with adjacent voxels exhibiting coherent velocity change in both direction and magnitude. Furthermore, we quantified this spatial distribution, and observed coordinated downward outflow in posterior spaces and upward inflow in anterior spaces, indicating a large-scale, brain-wide flow dynamic circulating from posterior to anterior. Accordingly, when locked to the 4th ventricle inflow signal, SAS flow patterns again showed significant temporal coupling, but its spatial organization was in the opposite direction to cortical hemodynamic fluctuations (i.e., posterior inflow and anterior outflow). This pattern reflects an established compensatory relationship between 4th ventricle inflow and cortical hemodynamic responses: as CSF enters the 4th ventricle, hemodynamic responses decrease, resulting in reversed SAS flow circulation. In summary, these results suggest a coordinated system in which brain hemodynamics drive spatially structured circular CSF flow patterns across the SAS during sleep, highlighting the important interaction between hemodynamic responses and CSF movement.

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Late-Breaking Poster

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VA CDA2 IK BX004905 (DSU)
NINDS R01 NS119277 (RB)

Title: The involvement of Thalamic Reticular Nucleus connexin36 in sleep-wakefulness and task-evoked EEG activity

Authors: S. CAREY[1], S. THANKACHAN[2], V. LOMBARDI[3], D. S. UYGUN[4], J. M. MCNALLY[5], *R. BASHEER[6];
[1]VA Boston Healthcare System, Boston, MA; [2]Psychiatry, VA Boston Healthcare Sys. & Harvard Medical School, West Roxbury, MA; [3]VA Boston Healthcare System, West Roxbury, MA; [4]VA Boston Healthcare System & Harvard Medical School, Marlborough, MA; [5]Psychiatry, VABHS, Harvard Medical School, West Roxbury, MA; [6]Psychiatry, VA Boston Healthcare System-Harvard Medical School, West Roxbury, MA

Abstract: Neuronal gap junction protein connexin36 (Cx36) forms electrical synapses. They are widely expressed in the mammalian forebrain and are suggested to play a significant role in state regulation and thalamocortical network activity. Cx36 is expressed in GABAergic neurons in the adult brain and is responsible for the electrical coupling between inhibitory neurons. Specifically, the intercellular communications between GABAergic neurons in the thalamic reticular nucleus (TRN) occur predominantly via Cx36-containing electrical synapses. We have examined the effect of a Cx36 global gene knockout (KO) and TRN-specific localized CRISPR-Cas-mediated Cx36 gene knockdown (KD) on sleep/wake-state and spontaneous and evoked EEG activity. We examined the sleep/wake state, spontaneous and task-evoked EEG activity during auditory steady-state response (ASSR), mismatch negativity (MMN), and social interaction behavioral test in Cx36KO mice and in PV-Cre-Cas9 mice before and after Cx36 gene KD in TRN. Cx36KO mice exhibited limited sleep/wake abnormalities. Power spectral density analysis of spontaneous EEG activity revealed significant impairment in gamma and beta band activity. The sigma band activity significantly decreased prior to NREM-REM transitions. While we observed no changes in sleep spindle density, the amplitude and duration of spindles showed statistically significant decreases in Cx36KO mice. Cx36KO mice exhibited a blunted gamma band response to acute ketamine (15 mg/kg; IP), impaired 40 Hz ASSR, an abnormal response in the mismatch negativity task (decreased ERP peak amplitude & evoked-power), and significant impairment in social investigation-induced low-frequency gamma band activity. Preliminary results from localized CRISPR KD of TRN-Cx36 KD (N=6 mice) showed a 19.7±12.3 % reduction in evoked cortical gamma power during ASSR when compared to pre-AAV-injection condition in the same mice. Similarly, in our sociability task, in the pre-AAV-injection condition, the cortical gamma power increased by 19.9% during 5 seconds of interaction with a novel mouse compared to the 1.5-second pre-interaction period. However, in the same mice, in post-injection Cx36KD condition, the gamma power was attenuated (-38.6%), suggesting a modulatory effect of TRN Cx36 KD on task-evoked cortical gamma activity. Our data suggest that Cx36 in TRN is involved in regulating oscillatory activity in the thalamocortical network. These observations are the first to suggest that impairments in Cx36KO mice are consistent with abnormalities observed in neuropsychiatric disorders, including schizophrenia, suggesting Cx36 as a novel therapeutic target.

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Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP069.01/LBP166

Topic: G.08. Food and Water Intake and Energy Balance

Title: The metabolic function of ERa neurons in the spinal cord

Authors: *X. WU, Y. XU;
University of South Florida, Tampa, FL

Abstract: Estrogen receptor alpha (ERα) in the brain is well-established to regulate metabolic homeostasis. Interestingly, ERα is also expressed abundantly in dorsal horn neurons throughout the spinal cord, yet the physiological roles of these neurons remain poorly understood. To address this, we injected an AAV-DIO-Kir2.1 virus into the thoracic and lumbar segments of the spinal cord in *Esr1*-Cre mice to selectively inhibit the ERα^{+} neuronal activity. We found that consistently silencing ERα neurons in the spinal cord led to an increase in body weight without any changes in food consumption, suggesting impaired energy expenditure. Additionally, the retrograde tracing by AAV2/9-Syn-Cre injected into the stomach in Ai9 mice shows high expression of tdTomato in the spinal cord, suggesting that visceral sensory neurons may regulate ERα neurons in the spinal cord. Taken together, our findings identify a previously unrecognized role for ERα neurons in the spinal cord in regulating energy metabolism and locomotion activity, and highlight a potential integrative pathway through which visceral inputs modulate systemic energy balance.

Disclosures: X. Wu: None. **Y. Xu:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP069.02/LBP167

Topic: G.08. Food and Water Intake and Energy Balance

Title: Brain-gut-brain endocannabinoid system control of food reward

Authors: *C. ALVAREZ[1], N. V. DIPATRIZIO[2];
[1]University of California, Riverside, Riverside, CA; [2]Division of Biomedical Sciences, University of California Riverside School of Medicine, Anaheim, CA

Abstract: Dysregulated neural and molecular pathways, including gut-brain endocannabinoid (eCB) signaling, contribute to obesity and overeating. It is unclear if gut-brain eCB signaling engages with brain dopamine (DA) reward pathways that control preferences for high-energy foods. We reported that mice rendered obese by chronic access to a high-fat/sugar "Western" style diet (WD) display increased activity of cholinergic neurons in the dorsal motor nucleus (DMV) of the vagus which increases eCB signaling at cannabinoid type-1 receptors (CB_1Rs) in the intestinal lining promoting overeating by a mechanism that includes suppressing release of the satiation peptide, cholecystokinin (CCK). In addition, mice strongly prefer WD over standard lab chow (SD) when given a choice. This preference is blocked in mice treated with a globally-acting CB_1R antagonist, AM251, and in mice that conditionally lack CB_1Rs selectively in the intestinal epithelium. We now investigated roles for (i) vagal efferent cholinergic signaling and (ii) vagal afferent satiation signaling in eCB-mediated preferences for WD. Dopamine activity in the nucleus accumbens was recorded for two hours during a WD versus SD preference test using a virally-mediated, genetically-encoded, fluorescent DA sensor (AAV-hSyn-GRAB_DA2m). Vehicle-treated mice displayed strong preferences for WD with sustained DA activity during the initial approach and consumption of WD. In contrast, both AM251, and the peripherally-restricted CB_1R antagonist, AM6545, reduced DA activity and preferences for WD. We next examined if efferent cholinergic neurotransmission participated in preferences for WD. Immunohistochemistry revealed higher expression of cFos/ChAT+ (cholinergic activity) in the DMV of mice engaging in WD versus SD preference test. Moreover, the peripherally-restricted general muscarinic acetylcholine receptor antagonist, methylhomatropine bromide, reduced preferences for WD. Finally, we determined if the inhibitory effects of AM6545 on preferences for WD were mediated through disinhibiting release of CCK from the gut. Mice received vehicle, AM6545, devazepide (CCKA receptor antagonist), or AM6545+devazepide prior to testing. AM6545 reliably reduced WD preference irrespective of co-administration with devazepide, which suggests that CCKA receptors may not be involved in eCB control of afferent signaling important for WD preferences. Collectively, these findings demonstrate that preferences for high-energy palatable foods are regulated by a mechanism that involves peripheral eCB and acetylcholine signaling, with both afferent and efferent vagal pathways likely playing key roles.

Disclosures: C. Alvarez: None. **N.V. DiPatrizio:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

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Topic: G.08. Food and Water Intake and Energy Balance

Support: Samsung Science and Technology Foundation SSTF-BA2001-09

Title: A pharynx-to-forebrain circuit for rapid thirst quenching

Authors: *M. KIM, D.-J. KOO, G. HAN, H. CHO, S.-Y. KIM;
Seoul National University, Seoul, Korea, Republic of

Abstract: Drinking fluids rapidly quenches thirst within seconds, well before fluids are absorbed in the gut and restore homeostatic balance. However, the sensory origin and neural mechanisms underlying this rapid satiation remain elusive. Here, in mice, we identify pharyngeal mucosal mechanosensation that occurs during swallowing reflex as the sensory origin for rapid thirst quenching. Using an integrated approach combining anatomical tracing, nerve transection, neural activity recording and manipulation, we delineate an ascending sensory pathway from the pharynx to the forebrain thirst center. Strikingly, this circuit functions as a high-pass filter, selectively transmitting signals from closely-paced swallows characteristic of fluid intake, while excluding those associated with solid food consumption. Disrupting this signaling prolongs ongoing drinking, establishing its causal role in thirst satiation. Our findings pinpoint the long-sought sensory origin of rapid thirst satiation and demonstrate the comprehensive characterization of the pharynx-to-forebrain circuit, which transforms pharyngeal mechanosensory signals into drinking-specific thirst-quenching signals.

Disclosures: M. Kim: None. **D. Koo:** None. **G. Han:** None. **H. Cho:** None. **S. Kim:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP069.04/LBP169

Topic: G.08. Food and Water Intake and Energy Balance

Support: CIHR PJT-175156

Title: Fructose-mediated neurotransmission at NPY/AgRP neurons

Authors: P. A. MILLER[1], M. A. PAYANT[1], ***M. J. CHEE**[2];
[1]Neuroscience, Carleton University, Ottawa, ON, Canada; [2]Carleton University, Ottawa, ON, Canada

Abstract: Fructose is added to processed foods and beverages in the form of added sugars or high fructose corn syrup. Dietary fructose is consumed together with glucose, but while glucose is an essential energy source for the body and brain, excessive fructose consumption can promote the development of obesity through neural actions. Recent work from our lab showed that when compared to chow- or glucose (dextrose)-fed mice, fructose-fed mice for up to eight weeks ate more calories, gained more body fat, and developed glucose intolerance. In *ex vivo* patch-clamp recordings from potent orexigenic Neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons

of male and female fructose-fed mice showed long-lasting synaptic excitation with sustained fructose exposure. Interestingly, this synaptic excitation also led to the excitability of NPY/AgRP neurons, albeit in a sex-dependent manner. Such fructose-mediated glutamatergic adaptations at NPY/AgRP neurons promoted a hunger state, but while hunger elicits a parallel reduction in inhibitory GABAergic input at NPY/AgRP neurons, it is not known whether fructose feeding would dampen inhibitory tone at NPY/AgRP neurons. We sampled spontaneous inhibitory postsynaptic current (sIPSC) events at NPY/AgRP neurons following one and eight weeks of fructose feeding in male and female mice. Unlike the acute effects of fructose feeding on glutamatergic input, the frequency and amplitude of sIPSC events at NPY/AgRP neurons were comparable between fructose- and chow- or dextrose-fed counterparts, and this inhibitory tone at NPY/AgRP neurons was also resilient to chronic fructose feeding. Taken together, our findings point to a glutamatergic neuronal network that is vulnerable to fructose feeding and that promotes fructose-mediated obesity.

Disclosures: P.A. Miller: None. **M.A. Payant:** None. **M.J. Chee:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP069.05/LBP170

Topic: G.08. Food and Water Intake and Energy Balance

Support: JP22KJ2330
JP22KJ2331
JP22K11827
JP19H03258
JP20K21760
JP22H00503

Title: Low-fat/medium-sucrose diet exacerbates obesogenic phenotypes of neurosecretory protein GL

Authors: *Y. NARIMATSU[1], M. KATO[1], E. IWAKOSHI[1], M. FURUMITSU[1], K. UKENA[2]; [1]Hiroshima University, Hiroshima, Japan; [2]Hiroshima Univ, Hiroshima, Japan

Abstract: <META NAME="author" CONTENT="成松 勇樹">Considerable reports have shown that hypothalamic neuropeptides significantly impact energy metabolism. Indeed, we found that a novel neuropeptide, neurosecretory protein GL (NPGL) markedly induced feeding behavior and fat deposition depending on dietary nutrients in rodents. Although high-fat diet (HFD) can attenuate fat accumulation by *Npgl* overexpression, sucrose-containing diet can exacerbate fat deposition. Hence, we speculated that low-fat/medium-sucrose diet (LFMSD) should have a crucial impact on NPGL-induced obesogenic phenotype. This study aimed to investigate the obesogenic effects of *Npgl* overexpression across murine strains under identical

LFMSD. Male ICR and C57BL/6 mice (7 weeks old, n = 7–9) were singly housed under standard conditions (25 ± 1°C under a 12-h light/12-h dark cycle) with ad libitum access to water and LFMSD. For *Npgl* overexpression, we generated adeno-associated virus (AAV)–based vectors, AAV-DJ/8-NPGL-IRES-GFP (AAV-NPGL) and AAV-DJ/8-IRES-GFP (AAV-CTL). Mice were bilaterally injected with AAV-CTL or AAV-NPGL into the mediobasal hypothalamus. *Npgl* overexpression was kept for 2 or 9 weeks in each strain. Food intake and body mass were measured during experiments. Body composition, area of pancreatic islets, and blood parameters were measured at the experimental endpoint of *Npgl* overexpression. Student's *t*-test and two-way repeated measures ANOVA were performed for statistical analyses. All results are presented as the mean ± standard error of the mean (SEM). Hypothalamic overexpression of *Npgl* significantly increased food intake, body mass, and white adipose tissue in both ICR and C57BL/6 fed with LFMSD. In ICR, the pancreatic islet area was expanded by *Npgl* overexpression for 2 weeks, corresponding to the hyperinsulinemia. Moreover, *Npgl* overexpression for 2 and 9 weeks promoted hepatic steatosis. In contrast to ICR, fatty liver was not observed in C57BL/6 overexpressed *Npgl* at 2 weeks. Nevertheless, prolonged *Npgl* overexpression in C57BL/6 induced hepatic steatosis and elevated circulating hepatic injury markers and lipids. Our present study suggests that NPGL elicited fat accumulation and metabolic disorders under LFMSD regardless of strain at least 9 weeks. This study could provide a time-efficient model for studying mechanisms of obesity and metabolic diseases

Disclosures: Y. Narimatsu: None. **M. Kato:** None. **E. Iwakoshi:** None. **M. Furumitsu:** None. **K. Ukena:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP069.06/LBP171

Topic: G.08. Food and Water Intake and Energy Balance

Title: Dietary, neural, and behavioral mechanisms underlying high-fat diet preference and obesity risk in mice

Authors: *T. A. MCCORKLE[1], S. HEGDE[2], A. K. SUTTON HICKEY[3];
[1]Temple University, Philadelphia, PA; [2]Department of Psychology & Neuroscience, Temple University, Philadelphia, PA; [3]Department of Psychology and Neuroscience, Temple University, Philadelphia, PA

Abstract: Energy-rich, high-fat foods are increasingly prevalent in diets worldwide, likely due to their induction of a sustained devaluation of more nutritionally balanced diets. This heightened preference for high-fat diets (HFD) following initial exposure is a critical component of overconsumption leading to obesity. Following chronic exposure to an animal-based HFD (aHFD), rodents demonstrate a robust preference for aHFD and a subsequent devaluation of their standard diet (SD), even in hunger states. However, it is unclear how acute versus chronic aHFD

exposure affects SD devaluation. Moreover, although vegetable-based fats are increasingly prevalent in human diets, vegetable HFDs (vHFD) are rarely used in preclinical studies, and it is unknown whether exposure to such dietary diversity alters SD devaluation and/or diet preference. Here, we conducted two 4-week behavioral paradigms in which mice were exposed to either a novel vHFD or the commonly used aHFD for (1) all four weeks or (2) 1-hour sessions each week. At various points in each experiment, mice were fasted overnight and presented with SD the following day to measure SD devaluation. To understand food preference during exposure to multiple diets, a final group of mice were provided with all three diets (SD, vHFD, and aHFD) for a week, with binge periods incorporated at the end of the paradigm. Following the completion of behavioral tests, immunohistochemistry was performed to examine neural activity associated with devaluation and food choice. Our results demonstrated that acute (1 day) and chronic (4 week) exposure to either aHFD or vHFD led to SD devaluation due to heightened HFD preference across either diet exposure. However, repeated 1-hour exposure was insufficient to drive lasting shifts in preference. The neural correlates of these findings primarily point to hypothalamic nuclei and other feeding-related regions, including the lateral septum and piriform cortex. Collectively, our findings offer insight into how diverse HFD exposure drives maladaptive feeding behaviors and food preferences, challenging perceptions of "healthy" fats and implicating mechanisms underlying addictive food behaviors exhibited in disordered eating.

Disclosures: T.A. McCorkle: None. **S. Hegde:** None. **A.K. Sutton Hickey:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

Location: SDCC Hall B

Time: Monday, November 17, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP069.07/LBP172

Topic: G.08. Food and Water Intake and Energy Balance

Support: NIH-DK130239
NIH - T32DK007314

Title: Central relaxin-3/RXFP3 signaling potently drives orexigenic behaviors and attenuates cisplatin-induced anorexia and body weight loss

Authors: *K. SUBRAMANIAN, C. GEISLER, B. C. DE JONGHE, M. R. HAYES; University of Pennsylvania, Philadelphia, PA

Abstract: The relaxin-3 system has been strongly implicated in having a role in regulating energy balance. Relaxin-3 producing neurons are found in the nucleus incertus (NI) of the brainstem and its receptor, relaxin family peptide receptor 3 (RXFP3), is widely distributed throughout the brain. Central administration of relaxin-3 potently increases food intake in rodents, while central Rxfp3 antagonism blocks this effect. Overall, these findings suggest that the relaxin-3 system regulates energy balance by modulating feeding behavior, although its underlying neurobiological and physiological mechanisms remain to be determined. To address

this, we aimed to characterize the mechanisms by which relaxin-3 promotes orexigenic behaviors. Intracerebroventricular (ICV) administration of relaxin-3 dose-dependently increased high-fat diet intake by augmenting meal size rather than meal frequency in rats. Additionally, RXFP3 expression in neurons was silenced by crossing synapsin-Cre (Syn-Cre) mice with floxed RXFP3 ($Rxfp3^{fl/fl}$) mice. While systemic relaxin-3 increased food intake in diet-induced obese (DIO) mice, its orexgenic effects were abolished in Syn-Cre/$RXFP3^{fl/fl}$ mice. Thus, neuronal RXFP3 signaling is required to mediate the orexigenic effects of relaxin-3. Furthermore, ICV relaxin-3 robustly increases food motivation to work for sucrose in a progressive-ratio task and intra-VTA relaxin-3 administration enhanced high-fat diet consumption in rats. These data suggest that central relaxin-3 acts through RXFP3 to strongly augment both food intake and motivation. We then sought to evaluate the therapeutic potential of the relaxin-3 system and test the hypothesis that central relaxin-3 can attenuate cisplatin-induced cachexia. Notably, ICV administration of relaxin-3 attenuated systemic cisplatin-induced anorexia and body-weight loss in rats without attenuating its nauseating effects (pica behavior). Interestingly, ICV relaxin-3 did not attenuate central GDF-15 induced anorexia, nausea and body weight reducing effects. These data suggest that potent orexigenic effects of central relaxin-3 can attenuate the anorectic and body weight reducing effects of systemic cisplatin, but not its nauseating effects, through potentially a GDF-15 independent pathway; offering a new therapeutic target to be combined with the polypharmacy approach of treating chemotherapy-induced side effects.

Disclosures: K. Subramanian: None. **C. Geisler:** None. **B.C. De Jonghe:** None. **M.R. Hayes:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

Location: SDCC Hall B

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Program #/Poster #: LBP069.08/LBP173

Topic: G.08. Food and Water Intake and Energy Balance

Support: VA Merit Review Award 5I01BX004102

Title: Detecting physiological as well as behavioral manifestations of visceral aversion induced by semaglutide

Authors: *J. E. BLEVINS[1,2], A. L. WILLIAMS[3], M. GOLDBERG[3], T. H. WOLDEN-HANSON[3], M. W. SCHWARTZ[2,4];
[1]Dept Veteran Affairs Med Ctr, Seattle, WA; [2]Division of Metabolism, Endocrinology and Nutrition, Department of Medicine, University of Washington School of Medicine, Seattle, WA; [3]Dept Veteran Affairs Med. Ctr., Seattle, WA; [4]UW Medicine Diabetes Institute, University of Washington School of Medicine, Seattle, WA

Abstract: In humans, gastrointestinal (GI) distress (diarrhea, nausea and vomiting) is a common side effect of glucagon-like peptide-1 receptor (GLP-1R) agonists. In rodent models, GLP-1R

agonists can also lower body temperature, a physiological manifestation of visceral aversion. In the current work, we investigated how this hypothermic response compares to standard behavioral measures of aversion following administration of the GLP-1R agonist semaglutide (Wegovy®). Adult male Long-Evans rats were implanted with temperature transponders (HTEC IPTT-300; Bio Medic Data Systems, Inc.) underneath interscapular brown adipose tissue (IBAT). Following a 4-h fast, animals (N=10/group) received one of 3 doses of semaglutide (1, 3, or 10 nmol/kg) or vehicle (TBS, pH 8.0) immediately prior to dark cycle onset. Each animal received each treatment over four sequential days in a dose escalation paradigm, so that each animal served as its own control. Animals remained fasted for an additional 4 h after drug administration (to prevent diet-induced thermogenesis), during which time IBAT temperature (T_{IBAT}; functional readout of BAT thermogenesis) was measured. In addition, daily food intake, body weight and kaolin intake (a behavioral assay of visceral illness) were measured. As expected, semaglutide (3 and 10 nmol/kg) reduced daily food intake and body weight ($P<0.05$), while kaolin intake increased ($P<0.05$). The same doses elicited sustained reductions of T_{IBAT} between 1.25- to 4-h post-injection ($P<0.05$), and postmortem analysis revealed that following the 10 nmol/kg dose, this hypothermic response was associated with significant (*UCP1*, *Cidea*, *Cox8b*; $P<0.05$) or near significant (*Prdm16*, *Gpr120*, *Rock2*; $0.05<P<0.1$) reductions of IBAT thermogenic gene expression ($P<0.05$; N=5/group). We conclude that physiological (reduced BAT thermogenesis) and behavioral (increased kaolin intake) manifestations of visceral aversion are induced in parallel by semaglutide. Studies to determine if a shared neurocircuitry underlies these distinct responses are underway.

Disclosures: J.E. Blevins: None. **A.L. Williams:** None. **M. Goldberg:** None. **T.H. Wolden-Hanson:** None. **M.W. Schwartz:** None.

Late-Breaking Poster

LBP069: G.08. Food and Water Intake and Energy Balance

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Topic: G.08. Food and Water Intake and Energy Balance

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NSF Grant CRCNS 1822550
NSF Grant CRCNS 2203119
Vannevar Bush Faculty Award ONR N000142012828

Title: A neural mechanism regulating water excretion in freshwater *Hydra vulgaris*

Authors: *W. YAMAMOTO, R. YUSTE;
Columbia University, New York, NY

Abstract: *Hydra* is a cnidarian with a simple, distributed nervous system of just a few hundred neurons and a gut-like gastric cavity. As one of the few cnidarians to successfully colonize

freshwater environments, its cells constantly accumulate water due to osmosis. Failure to remove excess water results in osmotic shock and cellular rupture.To prevent this, *Hydra* collects excess water in its gastric cavity and expels it through the mouth. The underlying neural and molecular mechanisms remain unknown. This adaptation could offer a simple model for investigating brain-body interactions and the evolution of interoceptive circuits at the cellular and molecular levels.We tested *Hydra*'s tolerance to salinity and osmolarity using seawater or sucrose solutions. *Hydra* showed a narrow tolerance range restricted to freshwater, with higher osmolarity leading to impaired survival and feeding, reflecting an evolutionary trade-off. Notably, blocking aquaporins, which are highly expressed in endodermal epithelial cells, significantly improved survival under high-salinity stress, suggesting these channels are key regulators of osmotic tolerance.Given the anatomical structure of the animal, where the endoderm lines the gastric cavity, we investigated the role of an endodermal ensemble of neurons known as rhythmic potential 2 (RP2) in water excretion. Using calcium imaging, we found that RP2 neuronal activity increased right before water excretion. Two-photon stimulation of RP2 neurons triggered water excretion. Pharmacological activation of Piezo mechanosensory channels also induced water excretion, indicating that stretch sensing may activate RP2 neurons. Furthermore, applying the RP2 neuropeptide GLWamide to the media triggered water excretion, suggesting that RP2 neurons regulate this behavior through GLWamide signaling.Our results reveal an interoceptive neural circuit in a simple system with a gut-like organ, linking internal state sensing to motor output. Future directions include tracing the evolutionary processes of interoception using a comparative approach, which may reveal how interoceptive circuits evolved to drive behavior, influence decisions, and adapt through plasticity.

Disclosures: W. Yamamoto: None. **R. Yuste:** None.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.01/LBP001

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIGMS R35 GM127338

Title: Impaired phagocytosis in draper mutants drives neuroinflammation and selective neuronal vulnerability in the aging brain

Authors: *G. LIU[1,2], J. SHIN[1], K. FARFAN[1], I. AMIN[1], C. SHI[1], K. MCCALL[2];
[1]Boston University, Boston, MA; [2]Department of Biology, Boston University, Boston, MA

Abstract: Neurodegenerative diseases exhibit selective neuronal loss, yet the mechanisms underlying this vulnerability remain elusive. In *Drosophila* mutants lacking Draper (the mammalian MEGF10 homolog), a glial phagocytic receptor essential for neuronal debris clearance, impaired phagocytosis causes age-dependent neurodegeneration marked by neuropil

vacuolization. These vacuoles lack nuclei, F-actin, or lipid, and display region-specific distribution in the aging brain. Using a computational pipeline to map vacuoles onto the Fly Brain Atlas, we found degeneration concentrated in the antennal lobe and antennal mechanosensory and motor center-regions critical for sensory processing-indicating selective neuronal susceptibility. Single-nucleus RNA sequencing of young and aged mutant heads revealed aging-dependent activation of Toll and Imd pathways, homologs of mammalian NF-κB signaling, consistent with chronic neuroinflammation. Aging also increased peripheral macrophages, hemocytes, migration toward the brain, where they closely associated with the surface of the brain and actively engulfed apoptotic glia. Although most hemocytes were excluded from entering the brain, their numbers and clearance activity were markedly elevated in *draper* mutants. To our knowledge, this provides the first evidence of hemocyte-driven glial clearance at the brain border during neuroinflammation in adult *Drosophila*. To test whether immune activation drives neurodegeneration, we performed a targeted genetic screen. Immune modulation revealed sex-specific effects: for example, knocking down the antimicrobial peptide *BomS4* in glia reduced neurodegenerative vacuoles in aged female *draper* mutants but not males. These findings suggest that loss of Draper impairs glial phagocytosis, triggering immune signaling and hemocyte recruitment that together drive neurodegeneration. Our work highlights how glial dysfunction, immune activation, and peripheral immune cell interactions converge to drive selective neuronal vulnerability in the aging brain.

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Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.02/LBP002

Topic: C.01. Brain Wellness and Aging

Support: Simons Foundation AWD023975C8
Glenn Foundation

Title: Integration of electrophysiological and proteomic signatures of resilience to age-related cognitive decline.

Authors: J. C. ALTHAUS[1], Y. CAO[1], R. CALLAGHAN[1], E. CAREY[1], Y. SONG[2], S. PARKER[2], K. KUCHINSKI[1], *S. J. MOORE[3], **C. C. KACZOROWSKI**[1];
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Abstract: Aging is generally associated with a decline in cognitive function, but some individuals are cognitively resilient, exhibiting little or no change in performance with age. Previous research has shown that appropriate modulation of neuronal excitability is associated

with successful learning and memory. It is likely that resilience to age-related cognitive decline is also mediated by neuronal excitability mechanisms involving protein-synthesis dependent modulation of ion channel function. We developed a single-neuron patch-proteomic pipeline to examine and integrate neurophysiological and proteomic signatures of cognitive resilience. Using contextual fear conditioning, we found that compared to adults (6-7mo), middle-aged (22-24mo) mice exhibit specific deficits in longer-term memory, assessed 7 days after training, while 24-hr memory is intact. This suggests that the earliest age-related deficits occur in extra-hippocampal regions, such as subiculum, which are involved in transferring memory out of the hippocampus for long-term storage in cortical and subcortical regions. However, as in humans, some middle-aged mice showed performance equivalent to adults, pointing to resilience-promoting neurophysiological and proteomic mechanisms in these areas. Electrophysiological recording from subicular pyramidal neurons revealed that better "transfer" of memory (7-day versus 24-hr performance) is associated with a *decrease* in neuronal excitability. Further, molecular analysis identified 35 age-specific novel candidate proteins correlated with good learning and memory exclusively in middle-aged animals, suggesting that there are unique pathways and mechanisms engaged with aging to confer cognitive resilience. These proteins include H3-5 and H2ax, which are both histone-encoding genes and are posited to have roles in transcriptional regulation, DNA repair, and chromosomal stability. Taken together, these molecular and cellular mechanisms associated with this resilience to age-related cognitive decline provide insight in potential novel therapeutic avenues for maintaining cognitive health across the lifespan.

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Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.03/LBP003

Topic: C.01. Brain Wellness and Aging

Support: Eli Lilly LRAP A141041
NIH K08NS121519

Title: A neuronal CRISPRi screen for lysosomal pH modifiers identifies PQLC2 as a novel regulator

Authors: *M. WELCH[1,2], S. SHU[3], Z. LIAU[1], T. ANTEE[4], P. J. SAMPOGNARO[5], M. KAMPMANN[6], A. W. KAO[7];
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of Neurology, San Francisco, CA; [5]University of California, San Francisco, Department of Neurology, San Francisco, CA; [6]Institute for Neurodegenerative Diseases, UCSF, San Francisco, CA; [7]University of California San Francisco, San Francisco, CA

Abstract: Lysosomes are key contributors to maintaining proteostasis in neurons and their age-related failure contributes to aging and the development of neurodegenerative diseases. One of the defining characteristic of lysosomes is their relative acidity compared to other subcellular compartments, a quality that enables the efficient breakdown of macromolecules and promotes cellular homeostasis. Evidence suggests that maintenance of neuronal lysosomal pH becomes dysregulated in both the aging process and neurodegenerative disease, yet the mechanisms by which lysosomal pH is maintained remain incompletely understood. To better understand neuronal lysosomal pH regulation, we conducted a genome-wide CRISPRi-based screen in iPSC-derived neurons for modifiers of lysosomal pH. The screen identified several previously known regulators of lysosomal pH and discovered novel pathways capable of modifying lysosomal pH including the protein UFMylation and mitochondrial integrity. We demonstrate that loss of lysosomal cationic amino acid exporter, PQLC2, strongly increases lysosomal pH, and we link this increase in lysosomal pH to an accumulation of amino acids within the lysosome. We also found that neuronal lysosomes have a unique pH optimum for degradation of the tangle-associated protein, tau, and that defects in lysosomal acidification due to loss of the *PQLC2* homologue, *Laat-1* impairs tau clearance in *C. elegans*. Our results highlight novel genes underpinning lysosomal pH homeostasis and advances understanding of direct and indirect effects on lysosomal pH setpoints.

Disclosures: M. Welch: None. **S. Shu:** None. **Z. Liau:** None. **T. Antee:** None. **P.J. Sampognaro:** None. **M. Kampmann:** None. **A.W. Kao:** 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.; Eli Lilly. F. Consulting Fees (e.g., advisory boards); Nine Square Therapeutics, Junevity.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

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Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

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Topic: C.01. Brain Wellness and Aging

Support: Susan A. Olde and Graham W. Hampson
Robert and Arlene Kogod Center on Aging
NIH UH3CA275669

Title: Exploring the impact of aged peripheral immune cells in driving brain inflammation and cognitive decline

Authors: *N. BHATNAGAR[1], A. LATHAM[2], E. LEITSCHUH[2], S. L. RODRIGUEZ[2], A. DOSCH[2], M. J. SCHAFER[2];
[1]Neuroscience, Furman University, Greenville, SC; [2]Department of Physiology and Biomedical Engineering, Mayo Clinic, Rochester, MN

Abstract: With rising life expectancy, the prevalence of age-associated cognitive decline and dementia continues to increase; approximately eight million individuals worldwide are diagnosed with dementia annually. Cognitive function relies on the integrity of the hippocampus (HP), cortex (CTX), and cortico-limbic white matter (WM) tracts. These anatomical regions are particularly vulnerable to age-related structural and functional decline, contributing to cognitive impairment. In the aging brain, T cells accumulate in the hippocampus-adjacent choroid plexus and infiltrate cortical and hippocampal gray matter regions and WM tracts, including the fimbria and corpus callosum. However, the extent to which the aging immune system contributes to maladaptive neuroinflammatory signaling in distinct brain microenvironments and cognitive decline remains poorly understood. Using a bone marrow chimera model, we lethally irradiated adult (4-8-month-old) JAXBoy mice ($CD45.1^+$ cells) followed by engraftment with bone marrow cells from either young (8-month-old) or old (25-month-old) C57BL/6N ($CD45.2^+$ cells) mouse donors. Successful engraftment was validated through flow cytometry, which showed that irradiated mice had greater than 94% donor $CD45.2^+$ splenocytes. At 11-13 weeks post-engraftment, adult mice with an aged immune system demonstrated heightened anxiety-like behavior in the open field test and increased latency to complete a spontaneous alternation in the Y maze spatial memory test compared to young immune controls. RT-PCR of microdissected HP, CTX, and WM from mice post-engraftment revealed modulated expression of genes associated with T cells and chemoattraction in in the CTX of adult females reconstituted with an old immune system. Additionally, through immunofluorescent staining we observed the accumulation of $CD3^+$ T cells in the choroid plexus and infiltration into the hippocampal gray matter. These findings suggest that aging of the peripheral immune system may contribute to neuroinflammation and cognitive impairment. Future work is necessary to understand the mechanism of immune-mediated cognitive changes.

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Late-Breaking Poster

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Topic: C.01. Brain Wellness and Aging

Support: NSF Grant 2233539

Title: Intestinal barrier dysfunction promotes aging brain and muscle phenotypes

Authors: *A. SALAZAR, S. LE;
Christopher Newport University, Newport News, VA

Abstract: A clearer understanding of the pathophysiological changes accompanying aging, and the discovery of novel therapeutics to assist in aging phenotypes, are absolutely essential. Recent advances have implicated perturbations in the gut as being closely linked to aging and mortality, with intestinal barrier dysfunction associated with age-related health decline in numerous organisms, including humans. Previous experiments have revealed that perturbed occluding junction expression in *Drosophila* intestines leads to various hallmarks of aging, with the loss of a specific occluding junction, Snakeskin (Ssk), leading to rapid and reversible intestinal barrier dysfunction, altered gut morphology, dysbiosis, elevations in immune activity, and a dramatically reduced lifespan. Remarkably, restoration of Ssk expression in flies showing intestinal barrier dysfunction reverses each of these phenotypes previously linked to aging. Intestinal up-regulation of Ssk protects against microbial translocation, improves intestinal barrier function during aging, limits dysbiosis, and extends lifespan. This study reveals that the genetic knockdown of Ssk leads to a highly significant increase in ubiquitinated protein aggregates and mitochondrial dysfunction in the *Drosophila* thorax muscles and brains of young flies, analogous to the aggregates mitochondrial elongation observed in aged flies. Both of these known hallmarks of aging are associated with diseases such as Alzheimer's and Parkinson's Disease, and reveal that perturbing the gut in a young organism is sufficient to induce aging phenotypes in tissue outside the gut, including aging in the brains and muscles. These elevations in protein aggregates and mitochondrial dysfunction observed in young flies accompanying induced intestinal permeability recapitulate protein aggregates and mitochondrial phenotypes observed in aged flies, revealing a tight connection between intestinal barrier dysfunction and brain and muscle aging.

Disclosures: A. Salazar: None. **S. Le:** None.

Late-Breaking Poster

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Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.06/LBP006

Topic: C.01. Brain Wellness and Aging

Title: Application of in vivo two-photon imaging of heterochronic myeloid cell replacement to investigate how age and brain environment shape microglia function

Authors: *C. GIZOWSKI[1], G. POPOVA[2], P. S. HOSFORD[3], O. HAHN[4];
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Abstract: Aging is the key risk factor for cognitive decline and impacts the brain in a region- and cell type-specific manner. Microglia in the white matter and cerebellum are considered among the fastest aging cell type; however, it remains unclear whether this phenomenon is mediated by intrinsic mechanisms or is primarily driven by age-related changes in neighbouring cells. Here, we describe a scalable and genetically modifiable system for heterochronic myeloid cell replacement, enabling the in vivo reconstitution of young and aged mouse brains with intrinsically young immune cells. Using confocal imaging, proteomics, and single-cell and spatial sequencing, we find that reconstituted myeloid cells in the brain adopt region-specific morphological and transcriptional profiles of microglia expression including a low-density, immune-vigilant state specific to the cerebellum. Strikingly, in aged brains, reconstituted cells rapidly acquired aging phenotypes, particularly in the cerebellum, indicating the local environment as a primary driver of microglia aging. To this end, we identified STAT1-mediated interferon signaling as one key axis controlling microglia aging in the cerebellum, whereas loss of STAT1 significantly prevented this aging trajectory in reconstituted cells. Spatial transcriptomics analysis combined with genetic cell ablation models identified rare and regionally restricted natural killer cells as the source of interferon signaling necessary for regulating microglia aging signatures in the cerebellum. Building on these findings, we are applying in vivo two-photon microscopy to study the impact of age and brain region on replacement-derived microglia.

Disclosures: C. Gizowski: A. Employment/Salary (full or part-time); calico life sciences. **G. Popova:** A. Employment/Salary (full or part-time); calico life sciences LLC. **P.S. Hosford:** A. Employment/Salary (full or part-time); calico life sciences. **O. Hahn:** A. Employment/Salary (full or part-time); calico life sciences LLC.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.07/LBP007

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant P01AG036695
American Federation for Aging Research

Title: Lipidomic profiling reveals age-dependent changes in complex plasma membrane lipids that regulate neural stem cell aging

Authors: *X. ZHAO[1], A. BRUNET[2];
[1]Yale University, New Haven, CT; [2]Genetics, Stanford University, Stanford, CA

Abstract: The aging brain exhibits a decline in the regenerative populations of neural stem cells (NSCs), which may underlie age-associated defects in sensory and cognitive functions. While mechanisms that restore old NSC function have started to be identified, the role of lipids -

especially complex lipids - in NSC aging remains largely unclear. Using lipidomic profiling by mass spectrometry, we identify age-related lipidomic signatures in young and old quiescent NSCs *in vitro* and *in vivo*. These analyses reveal drastic remodeling in several complex membrane lipid classes, notably phospholipids, in old NSCs. Moreover, several poly-unsaturated fatty acids (PUFAs) increase across complex lipid classes in quiescent NSCs during aging. Using spatial lipidomics, we validate that some of these changes are also observed *in situ* in intact tissues. Many age-related changes in complex lipid levels and side chain composition are occurring in plasma membrane lipids, as revealed by lipidomic profiling of isolated plasma membrane vesicles. Experimentally, we find that aging is accompanied by a decrease in plasma membrane order, a key membrane biophysical property, in old quiescent NSCs *in vitro* and *in vivo*. To determine the functional role of plasma membrane lipids in aging NSCs, we performed genetic and supplementation studies. Knockout of *Mboat2*, which encodes a phospholipid acyltransferase, exacerbates age-related lipidomic changes in old quiescent NSCs and impedes their ability to activate. Interestingly, *Mboat2* overexpression reverses age-related lipidomic changes in old quiescent NSCs and boosts their ability to activate *in vitro* and *in vivo*. Moreover, supplementation of plasma membrane lipids derived from young NSCs improves the ability of old quiescent NSCs to activate. Our work could lead to lipid-based strategies for restoring the regenerative potential of NSCs in old individuals, which has important implications for countering brain decline during aging.

Disclosures: X. Zhao: None. **A. Brunet:** None.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

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Program #/Poster #: LBP070.08/LBP008

Topic: C.01. Brain Wellness and Aging

Support: CHRI Alzheimer's Disease Research Startup

Title: Nipsnap1 deficiency induces neurodegeneration and cognitive deficit and alters gene expression and metabolic profile in mice

Authors: *M. SHAROAR[1], Z. ZAMAN[2], S. GRAHAM[3], N. SINGH[4], R. HOMAYOUNI[5]; [1]Internal Medicine, Corewell Health Research Institute, Oakland University William Beaumont School of Medicine, Royal Oak, MI; [2]Alzheimers' Disease Research, Corewell Health Research Institute, Royal Oak, MI; [3]Dept. of Obstetrics and Gynecology, Oakland University William Beaumont School of Medicine, Corewell Health Research Institute, Royal Oak, MI; [4]Dept. of Physiological Sciences, Oklahoma State University, Stillwater, OK; [5]Dept. of Foundational Medical Studies, Oakland University William Beaumont School of Medicine, Oakland University, Rochester, MI

Abstract: Neuronal homeostasis requires functional mitochondria, which is strictly regulated by mitophagy-mediated clearance of damaged mitochondria. Deregulated mitophagy is associated with multiple neurodegenerative diseases, including Alzheimer's and Parkinson diseases. Nipsnap1 (4-nitrophenylphosphatase domain and non-neuronal SNAP25-like protein homolog 1) is a mitochondrial protein involved in regulation of mitophagy. Nipsnap1 deficiency in Zabrafish impaired mitophagy and increased oxidative stress in the brain. However, the precise role of Nipsnap1 in axonal maintenance and neuronal survival is not yet known. To address this question, we created Nipsnap1 knockdown (Nip1KD) mouse and investigated gene expression, and metabolomic changes in the brain. We found significantly lower expression of genes involved neuritic development, axonogenesis, and neuronal differentiation in Nip1KD mouse brains. In contrast, genes involved in neuroinflamation were upregulated, specifically in female Nip1KD brains. Metabolomic analysis showed alteration in protein, lipid, and nucleotide metabolism with ~9-fold reduction of adenosine 5'-diphosphoribose in Nip1KD brains. Increased apoptosis and neurodegenration was observed in Nip1KD mouse brains, and neuronal survival was compromised in primary cultured Nip1KD compared to WT neurons. In addition, elevated microglia activation was observed in Nip1KD females. Behavioral test results demonstrated that Nip1KD mice are deficient in cognition. Our data implicate that Nipsnap1 plays critical role in axon maintenance, neuronal survival, and preserving memory in mice.

Disclosures: M. Sharoar: None. **Z. Zaman:** None. **S. Graham:** None. **N. Singh:** None. **R. Homayouni:** None.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP070.09/LBP009

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant R21NS133944

Title: SELENOI deficiency disrupts iron homeostasis in the brain

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Abstract: Selenoprotein I (SELENOI) is an essential enzyme for phospholipid synthesis that catalyzes the production of plasmenyl-phosphatidylethanolamine (plasmenyl-PE), a key component of myelin. Crucially, myelin-producing oligodendrocytes have the highest concentration of iron among cell types in the brain. Iron is a vital metal cofactor due to its aptitude for redox reactions, but this propensity also predisposes it to generating reactive oxygen

species via Fenton reactions. Additionally, an excess of redox-active iron promotes cell death via ferroptosis, an iron-dependent phospholipid peroxidation process. In the brain, iron dysregulation has been implicated in neurodegenerative disorders such as Alzheimer's Disease, Parkinson's Disease, and hereditary spastic paraplegia (HSP). In humans, loss-of-function mutations in multiple genes involved in plasmenyl-PE synthesis have been linked to HSP, including SELENOI. SELENOI has also been negatively associated with ferroptosis; mechanistically, plasmenyl-PE contains a vinyl ether bond that may be sacrificially oxidized to protect against lipid peroxidation. We recently developed a mouse model of nervous system-specific SELENOI deficiency that recapitulates motor deficits, hypomyelination, and microcephaly observed in humans with HSP. Given the critical role of iron in myelination and ferroptosis, we investigated the effects of SELENOI deficiency on iron homeostasis in the brain. SELENOI deficiency elevated brain iron levels at 12 weeks of age; this was corroborated histologically by Perls' staining for ferric iron at 12 and 30 weeks of age. In parallel, SELENOI deficient brains exhibited heightened levels of the transferrin receptor (Tfr1), a putative marker of ferroptosis, in white matter tracts such as the internal capsule and corpus callosum. Notably, Tfr1 immunostaining predominantly occurred in oligodendrocyte lineage cells (Olig2+), and this coincided with an increased density of Olig2+ cells. In white matter regions where ferroptosis was apparent, we also observed increased expression of ferritin heavy chain (FTH); this was primarily observed in active microglia, though deposits were also seen in neuron and Olig2+ populations. Differences in FTH levels were also confirmed by western blot analysis. Although sex differences were observed in immunohistochemical staining, SELENOI deficient brains showed differences within sex groups for all markers of study. Overall, SELENOI deficiency (and therefore diminished plasmenyl-PE) was associated with iron accumulation in the brain, which coincided with microglial activation, FTH upregulation, ferroptosis, and neurodegeneration.

Disclosures: K. Wurlitzer: None. **C. Ma:** None. **F.W. Hoffmann:** None. **M.W. Pitts:** None.

Late-Breaking Poster

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Program #/Poster #: LBP070.10/LBP010

Topic: C.01. Brain Wellness and Aging

Support: NIH Grant RF1 AG058218

Title: Treatment of age-related decreases in GTP levels restores endocytosis and autophagy, promoting the clearance of Aβ aggregates and oxidative nitration in isolated neurons from AD mouse models.

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Abstract: Age-related declines in neuronal bioenergetic levels may limit vesicular trafficking and autophagic clearance of damaged organelles and proteins. Age-related ATP depletion would impact cognition dependent on ionic homeostasis, but limits on proteostasis powered by GTP are less clear. We used neurons isolated from aged 3xTg-AD Alzheimer's model mice and a novel genetically encoded fluorescent GTP sensor (GEVAL) to evaluate live GTP levels in situ. We report an age-dependent reduction in ratiometric measurements of free/bound GTP levels in living hippocampal neurons. Free-GTP co-localized in the mitochondria decreased with age accompanied by the accumulation of free-GTP labeled vesicular structures. The energy dependence of autophagy was demonstrated by depletion of GTP with rapamycin stimulation, while bafilomycin inhibition of autophagy raised GTP levels. 24 hr. supplementation of aged neurons with the NAD precursor nicotinamide and the Nrf2 redox modulator EGCG restored GTP levels to youthful levels and mobilized endocytosis and lysosomal consumption for autophagy via the respective GTPases Rab7 and Arl8b. Furthermore, to support the use of this treatment, we used aged neurons isolated from mice in the Denali App^{SAA} Alzheimer's knock-in model to evaluate supplementation. The vesicular mobilization promoted the clearance of intraneuronal Aβ aggregates, improved viability, and lowered protein oxidative nitration in neurons from both AD models. Our results reveal age- and AD-related neuronal GTP energy deficits that impair autophagy and endocytosis. GTP deficits were remediated by an external NAD precursor together with a Nrf2 redox modulator which suggests a translational path.

Disclosures: R.A. Santana: None. **G.J. Brewer:** None.

Late-Breaking Poster

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U54GM133807
U54 MD007600 NIMHD
NIH Grant 2R25NS080687-11

Title: Metabolomic brain and blood profiling after glyphosate exposure in adult male rats

Authors: *E. A. RIVERA[1], L. L. MENDEZ-SANTACRUZ[2], A. VAZQUEZ[3], N. E. CHORNA[4], D. SIERRA-MERCADO[5];
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Abstract: The herbicide glyphosate may harm behaviors related to mental health. Preliminary work from our group suggests that safe levels of glyphosate (2.0 mg/kg/day, E.P.A.) increase anxiety-like behaviors in rats. Increased anxiety is detrimental and may affect other defensive behaviors such as avoidance. Our exploratory work is focusing on avoidance behaviors and determining the biological mechanisms by which glyphosate influences avoidance. Here, we focus on metabolites that participate in cellular homeostasis to regulate physiological processes, and metabolite levels associated with anxiety-like behaviors. There are two key brain regions implicated in avoidance: 1) medial prefrontal cortex and 2) amygdala. Thus, we hypothesized that exposure to glyphosate disrupts metabolites in both brain regions. We also compared systemic effects of glyphosate in the blood. We tested our hypothesis by assessing a subset of male rats (Sprague-Dawley, 3 months of age at commencement of experimetns) that were trained on platform mediated avoidance. Next, rats were exposed to glyphosate (2.0 mg/kg/day) or filtered water for controls for 12 weeks. Upon completion of the behavioral experiments, for brain samples (Glyph: n=6; Ctrl: n=6) and blood (Glyph: n=13 ; Ctrl: n=13) were collected. Brain tissue and blood samples underwent metabolomic analysis by researchers blinded to the experimental groups using gas chromatography-mass spectrometry. We observed that glyphosate exposure altered the concentrations of 27 metabolites in brain tissue and 10 metabolites in blood. Specifically, 4-hydroxybutanoic acid, a critical GABA metabolite essential for anxiety control, was decreased in blood ($p = 0.0004$), indicating compromised inhibitory neurotransmission. Additionally, L-serine showed decreased blood levels ($p = 0.0005$) but increased brain accumulation ($p = 0.014$), suggesting impaired neurotransmitter synthesis pathways. Concurrently, azelaic acid was elevated in brain tissue ($p = 0.033$), indicating active neuroinflammation and oxidative stress, while ethanolamine increased in brain ($p = 0.012$), reflecting membrane damage. These metabolic alterations demonstrate that glyphosate exposure disrupts GABAergic neurotransmission and induces neuroinflammation, providing molecular evidence for the observed anxiety-like behavioral phenotype.

Disclosures: E.A. Rivera: None. **L.L. Mendez-Santacruz:** None. **A. Vazquez:** None. **N.E. Chorna:** None. **D. Sierra-Mercado:** None.

Late-Breaking Poster

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Topic: C.01. Brain Wellness and Aging

Support: NIH Grant P30AI050409
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US Department of Education Grant P217A220077

Title: Modulating mitochondrial signaling as a potential therapeutic for HIV Associated Neurocognitive Disorders (HAND)

Authors: *M. L. HICKSON[1], J. DE VASTEY[1], R. COOK[2], K. WILLIAMS[3];
[1]Spelman College, Atlanta, GA; [2]Spelman College, Conyers, GA; [3]Environmental and Health Sciences, Spelman College, Atlanta, GA

Abstract: HIV Associated Neurocognitive Disorders (HAND) are a pervasive comorbidity for people living with HIV, consisting of infiltration of immune cells and release of neurotoxins. Despite the success ofcombined anti-retroviral treatments, these therapeutics are unable to enter the brain and mitigate HIV induced neuroinflammation. Therefore, novel adjunctive and targeted therapeutics are needed. Previous research suggests that the activation of estrogen's G protein coupled receptor (GPER) has a neuroprotective effect on neuroinflammation but still much is unknown about the non-classical estrogen receptor or its effects during HAND. In this research we sought to investigate the role of GPER and its interactions with mitochondrial integrity and downstream anti-oxidant responses during HIV. We hypothesized that activation of GPER via the G1 agonist will reduce mitochondrial dysfunction andpromote the expression of downstream antioxidants in cells exposed to HIV. To test this hypothesis,human monocyte derived macrophages were stimulated with HIV, G1, and/or the specific GPER antagonist G15 . The cells were then cultured on coverslips and stained using SIRT3 to visualize the mitochondria and measure changes in the morphology. Cells were also cultured on 12 well plates and their protein collected to evaluate key antioxidants via Western Blot. The results were analyzed using Image Lab and normalized to the untreated for each donor. Mitochondria of macrophages exposed to HIV may exhibit fragmented morphological changes associated with oxidative stress compared to untreatedmacrophages with healthy elongated tubular mitochondrial structures. We also saw that SIRT3 and SOD expression increased in cells treated with G1 and HIV in a GPER dependent manner. Antioxidants GCLC and HO-1 resulted in an increased trend in G1+HIV cells compared to HIV, though this was not GPER dependent. These results suggest that activation of HIV may reduce mitochondrial integrity and activationof the GPER may increase its functions and expression of antioxidants. Therefore, GPER may be a strong therapeutic target to reduce HIV induced neuroinflammation and oxidative stress.

Disclosures: M.L. Hickson: None. **J. de Vastey:** None. **R. Cook:** None. **K. Williams:** None.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

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Topic: C.01. Brain Wellness and Aging

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Title: Photosensitivity of an aging brain

Authors: S. THANKACHAN[1], D. N. ATOCHIN[2], K. KASTANENKA[3], ***D. GERASHCHENKO**[2];
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Abstract: Red light is considered less phototoxic than blue light and is widely used in both research and photobiomodulation therapy. However, the difference in the brain's response to light exposure between young and old mammals is currently unknown. In the present study, we investigated the effects of light irradiation on brain damage as a function of age and assessed the functional consequences of that damage on sleep and electroencephalogram (EEG) power. To that end, we exposed a large area of the brain to light by placing an LED on top of the mouse skull. Experiments were conducted on 52 mice of various ages (3-24 months), using both blue-light (475 nm) and red-light (629 nm) LEDs. Light was delivered in 10 ms pulses at a frequency of 10 Hz, with a power output of approximately 15 mW (red light) or 10 mW (blue light), during non-rapid eye movement sleep via a closed-loop stimulation system. We hypothesized that the effect of light exposure on the brain depends on both the light's wavelength and the animal's age. We found that brain exposure to blue light caused local damage in the cerebral cortex in both young and old mice. In contrast, red light exposure had no noticeable effect on young mice but caused a marked reduction in EEG power, damage to fiber bundles throughout the brain, and a coma-like state in old mice. We observed fiber loss and tissue lesions in the thalamus, located 2 mm or more beneath the brain surface. Although the light power density was expected to be up to 100 times higher in the cerebral cortex directly beneath the LED compared to deeper brain regions, no visible neuronal loss was observed in the cortex. While sleep duration was minimally affected, EEG power was significantly reduced. The effect of red light on EEG power was dose-dependent and particularly pronounced in the theta frequency range. The differences between effects on sleep and EEG power were especially evident in 7.5-month-old mice, in which EEG power exhibited substantial changes correlated with stimulation duration, while only minor alterations in sleep patterns were observed. When delivered at lower intensity over a longer period, red light caused a similar reduction in EEG power and brain damage as that seen with higher-intensity, shorter-duration irradiation. These results indicate that the impact of light on EEG activity and brain tissue is strongly influenced not only by the light's wavelength, duration, and intensity but also by the animal's age and the specific brain tissue exposed.

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Late-Breaking Poster

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Location: SDCC Hall B

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PNRR “ON Foods", European Union-Next Generation EU.- Research and innovation network on food and nutrition Sustainability, Safety and Security

Title: CB2 Receptor Reduces Microglial Lipid Droplet Formation and Restores Synaptic Homeostasis in High Fat-Induced Obesity

Authors: B. MARFELLA[1,2], A. NICOIS[3,2], N. FORTE[2], R. IMPERATORE[4], M. CRISPINO[5], L. PALOMBA[6], M. MOLLICA[5], V. DI MARZO[7], ***L. CRISTINO**[8];
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Abstract: In obesity, excessive saturated fat intake predisposes microglia to dysfunction, characterized by impaired phagocytosis, cholesteryl ester accumulation, lipid-droplet formation, and the onset of a pro-inflammatory phenotype named LDAM (Lipid Droples Accumulating Microglia). This study investigates the role of the cannabinoid type-2 receptor (CB2) in these processes, using both in vivo obese mouse models and in vitro neuron-microglia co-culture systems. Part of the endocannabinoid system, CB2 is primarily expressed in microglia and has been implicated in the regulation of neuroinflammation and immune responses. However, its role in obesity-induced neuroinflammation remains largely unexplored. Our results demonstrate that obesity-induced microglial alterations correlate with downregulation of CB2 expression and loss of neuroprotective functions, suggesting CB2 as a potential therapeutic target. Adult male C57BL/6 mice were fed a high-fat diet (HFD) for 8 weeks. Microglial LD accumulation was evaluated in the hippocampus, and CB2 protein levels were measured using immunohistochemistry and selective fluoroligand binding assay. In obese mice, microglia exhibited the typical foamy morphology associated with prominent LD formation. Reactive oxygen species overproduction was observed in the hippocampal area, accompanied by mitochondrial morpho-functional dysfunction in microglia and synaptosome, and release of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, and IFN-γ. A reduction in CB2 expression was demonstrated in microglia within hippocampus of obese mice, associated with altered microglial ramifications, as revealed by skeleton analysis, and reduced PSD95 labeling in the same brain area. In vivo electrophysiological recordings revealed that LTP in the dentate gyrus of HFD animals is impaired; however, LTP in hippocampal slices appears comparable to that of controls, likely because pro-inflammatory factors are removed during slice preparation. Notably, treatment with the CB2 agonist JWH-133 rescued LTP in hippocampal slices exposed to LPS, which was used to mimic the inflammatory state characteristic of HFD. In co-culture systems under saturated fatty acid challenge, pharmacological stimulation with JWH133 restored microglial phagocytic activity and neuronal synaptic efficiency, whereas CB2 antagonism with AM630 exacerbated neuronal injury. Our combined in vivo and in vitro evidence indicates that obesity compromises microglial lipid metabolism and CB2 activity is both essential and a therapeutic target for preserving synaptic homeostasis and preventing cognitive decline in neurodegenerative diseases.

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Late-Breaking Poster

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Program #/Poster #: LBP070.15/LBP015

Topic: C.01. Brain Wellness and Aging

Support: AG051459

Title: Age-related Disruption of Glial Interactions And Mitochondrial Metabolism In The Mouse Hippocampus

Authors: *Y. YASUMOTO, N. SESTAN, T. L. HORVATH;
Yale University, New Haven, CT

Abstract: Aging is a major risk factor for neurodegenerative diseases and cognitive decline. While glial cells are known to contribute substantially to brain aging, how glia-glia and glia-neuron interactions are altered remains incompletely understood. Here, we investigated how aging affects glial connectivity and mitochondrial function in the mouse hippocampus. Single-nucleus RNA sequencing revealed that glial and vascular-associated cells exhibited the highest number of differentially expressed genes (DEGs) with aging. Chromatin accessibility profiling further showed that non-neuronal cells displayed the most pronounced epigenomic remodeling. Immunostaining demonstrated increased physical attachments between oligodendrocyte precursor cells and blood vessels in aged brains, and cell-chat analysis identified age-dependent ligand-receptor interactions. Aging-associated metabolic stress is hypothesized to reshape cellular crosstalk as an adaptive mechanism to maintain homeostasis. To systematically define pathways driving these changes, we extracted gene sets enriched for aging-related transcriptional alterations in non-neuronal cells (NNCs) compared to neurons. Clustering analysis highlighted NNC-specific enrichment of pathways linked to mitochondrial electron transport chain dysfunction, reactive oxygen species (ROS) responses, chromosomal integrity, and lipid metabolism. Consistent with these signatures, dihydroethidium (DHE) staining revealed marked age-dependent increases in ROS production in blood vessels, microglia, and oligodendrocytes. Electron microscopy further showed less fragmented mitochondria in aged astrocytes and microglia. Together, these findings reveal that non-neuronal cells are uniquely vulnerable to redox imbalance during aging, reflected in both transcriptional and functional changes. This vulnerability likely disrupts glia-glia and glia-neuron interactions, contributing to age-related hippocampal dysfunction.

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Late-Breaking Poster

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Topic: C.01. Brain Wellness and Aging

Support: "One case, one policy" grant from Shandong Province (China) awarded to BH

Title: Metacontrol-related aperiodic and periodic neural activity in aging: evidence from anodal transcranial direct current stimulation

Authors: *Y. PI[1], B. HOMMEL[2], L. S. COLZATO[2];
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Abstract: Metacontrol, the ability to adapt cognitive control to task demands, declines with age and is thought to be reflected in aperiodic and periodic neural dynamics. Given that anodal transcranial direct current stimulation (atDCS) can modulate cortical excitability via membrane potential shifts, we tested whether atDCS alters the neurophysiological signatures of metacontrol in younger and older adults. In a mixed design, younger and older participants performed a Go/Nogo task under both atDCS and sham stimulation conditions; resting-state EEG data were also acquired. Aperiodic activity was analyzed using the FOOOF algorithm, and periodic activity was examined through time-frequency analysis. Behaviorally, younger adults showed higher accuracy and faster responses than older adults, but no significant stimulation effects emerged in either group. Results showed that compared to sham, aperiodic activity (FOOOF exponent) increased after atDCS, particularly in older adults, indicating reduced cortical noise in the aging process. However, resting-state aperiodic activity did not predict stimulation-induced effects within either group. In the periodic domain, atDCS increased theta-band power during Nogo trials in older adults, whereas theta-band power showed only a Go/NoGo task effect without stimulation-related effects in younger adults, and alpha power showed no significant effects in either group. Importantly, changes in aperiodic and theta band activity were not correlated, suggesting distinct mechanisms. These results indicate that atDCS may selectively enhance neural signal fidelity during metacontrol, supporting its potential as a neuromodulatory tool in aging.

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Late-Breaking Poster

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NIH R01ES031656

Title: Gulf War Illness: Targeting Myelin

Authors: *B. C. JONES;
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Abstract: In 1991, the United States and allies sent nearly 1,000,000 troops to the Middle East to counter actions by Saddam Hussein against Kuwait. Between 25 and 35% of combatants became ill with a multisymptomatic malaise, Gulf War illness or GWI, that included gastrointestinal and neurological symptoms. The neurological signs included general lethargy, memory problems, headaches and insomnia. Collectively, these symptoms resemble "sickness behavior," the underlying basis for which is neuroinflammation. A likely potential cause of GWI is likely exposure to organophosphate (OP) chemicals including sarin and chlorpyrifos, encountered by many troops in theater. O'Callaghan and Miller proposed that the sickness behavior-like symptoms were a result of neuroinflammation caused by exposure to the OPs and high circulating cortisol as might be expected during the physiological stress of combat. Thus, they developed an animal model of the exposure experienced by the combatants. This included exposure to corticosterone (as a stressor surrogate) followed by exposure to diisopropylfluorophosphate (DFP), a sarin surrogate. This protocol produces neuroinflammation in rodents and research into the genetics of differential susceptibility has revealed candidate genes underlying acute susceptibility. The major problem about GWI is its chronicity. Many of the GWI veterans are still ill, having suffered for 30+ years. The major issue is to understand the mechanisms of chronicity to identify therapeutic strategies. One salient chronic feature of GWI is diminished myelin with associated chronic peripheral pain Chronic GWI likely has epigenetic underpinnings, so our approach was to identify methylation of candidate genes and individual differences. Our experimental approach was to add corticosterone for 7 days to the drinking water of male and female mice from 11 BXD inbred strains. On the 8th day, we administered DFP to mimic the exposure to OPs of Gulf War troops. Our initial study identified several genes related to myelination, notably: ***Cnp* - 2'',3''-Cyclic Nucleotide 3'' Phosphodiesterase.** This gene codes for the third most abundant myelin-related proteins. ***Plp1* - Proteolipid Protein 1**, This gene encodes a transmembrane proteolipid protein that is the predominant component of myelin ***Mbp* -Myelin Basic Protein**. This gene is essential for the formation and stabilization of the myelin sheath. Our chronic, epigenetic study identified ***Eif2b5* - eukaryotic translation initiation factor 2B subunit epsilon.** This gene is critically important for the production of myelin, and we propose should be a target for therapeutics. Supported by grants DOD GWI160086 and USPHS R01ES031656

Disclosures: B.C. Jones: None.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.18/LBP018

Topic: C.01. Brain Wellness and Aging

Support: NIH NINDS R01 NS127284

Title: Cognitive stimulation rescues vascular cognitive impairment and exerts long-lasting protective effects on memory function

Authors: *A. THAQI, R. L. KALISH, B. DENG, A. SHEHRYAR, G. M. DEMARCO, E. J. BAUMOEL, A. C. CHAPMAN;
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Abstract: Chronic hypertension accelerates age-related cognitive decline and increases the risk for vascular cognitive impairment (VCI) by 60%. Older people with VCI are more likely to live alone and less likely to comply with prescribed medications, increasing the need for holistic interventions. Cognitive stimulation improves neurocognitive health through increased brain-derived neurotrophic factor (BDNF). Females have higher BDNF levels, however, the efficacy of cognitive exercise in improving VCI remains unclear. We hypothesized that cognitive stimulation would increase hippocampal BDNF levels and improve VCI to a greater extent in females than males. Using the spontaneously hypertensive rat model of VCI, males and females (n=6/group) were either housed in social isolation (naïve) or housed in groups with two months of stimulated learning tasks. Two and six months later, long-term memory was tested using a novel object recognition task, spatial working memory tested via continuous y maze task and recognition and alternation indices calculated, respectively. BDNF levels were measured via enzyme-linked immunosorbent assays. Data are mean ± SEM and comparisons made via two-way ANOVAs with post hoc Tukey tests. Naïve rats had impaired object memory, with recognition indices of ~ 0.50. There were main effects of sex ($F_{1,29} = 8.63$, $p = 0.006$) and cognitive stimulation ($F_{2,29} = 24.98$, $p < 0.001$) on object memory, with better memory performance in stimulated females and to a greater extent males compared to naïve rats (Fig 1). Spatial working memory was unaffected in either sex six months post-cognitive stimulation but was transiently improved at two months in males, as alternation index was 0.74 ± 0.04 compared to 0.58 ± 0.03 in naïve males, 0.50 ± 0.04 in naïve females and 0.50 ± 0.04 in stimulated females ($p < 0.05$). There were no differences between groups in brain or serum BDNF levels. These data suggest that brief cognitive stimulation can rescue VCI and persistently improve long-term memory function for at least six months, although efficacy as a therapeutic intervention may differ by sex.

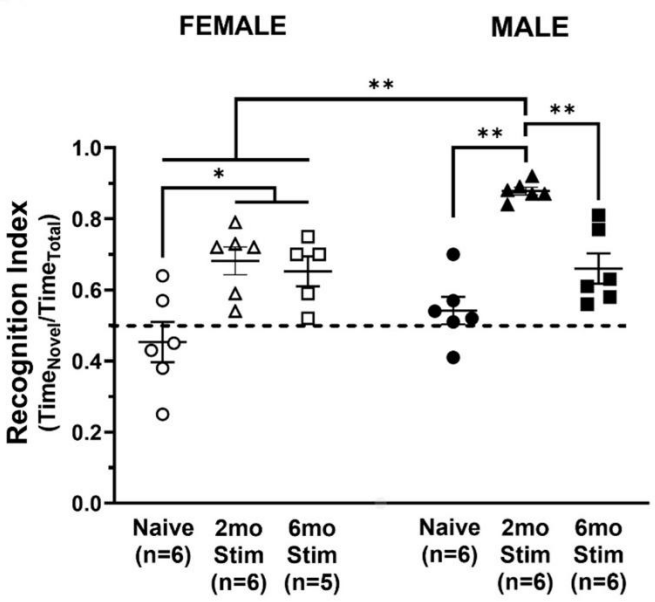

Fig 1. Long-term memory function was assessed in male and female rats with VCI that were living an isolated lifestyle (Naïve) or an enriched lifestyle that included two months of cognitive stimulation (Stim). Memory was tested two and six months after cognitive exercise ended.

Disclosures: A. Thaqi: None. **R.L. Kalish:** None. **B. Deng:** None. **A. Shehryar:** None. **G.M. DeMarco:** None. **E.J. Baumoel:** None. **A.C. Chapman:** None.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.19/LBP019

Topic: C.01. Brain Wellness and Aging

Support: K99AG070390
U19AG074879

Title: Pre-analytical Characterization of CNS-Derived Extracellular Vesicles from Human Saliva: Effect of Room Temperature and Cellular Origin

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Abstract: Saliva-derived extracellular vesicles (sEVs) are an attractive, non-invasive source for Alzheimer's disease (AD) biomarkers, but their use is limited by unstandardized methods for collection, storage, and the isolation of EVs from central nervous system (CNS) cells. This study aimed to optimize the enrichment of CNS-specific sEVs and evaluate the effects of cellular origin and storage temperature on AD and inflammatory biomarker levels. Using saliva from the UC San Diego Nathan Shock Healthy Aging Study, we isolated EVs from neuronal, astrocyte, microglial, and oligodendrocyte origins. Executive function and attention were measured in all

study participants using the Cognition Battery of the NIH Toolbox. Quantification via high-sensitivity immunoassays showed that Aβ40, Aβ42, and total tau were significantly enriched in astrocyte-derived EVs. In contrast, TDP-43 was most abundant in EV-depleted saliva, while inflammatory cytokines were broadly detected across all EV fractions and in EV-depleted saliva. Although storage temperature did not consistently impact biomarker levels, storage at -20°C was found to be optimal for biomarker quantification. Critically, lower levels of inflammatory cytokines (IFN-γ, IL-10, and IL-6) detected in native saliva were associated with enhanced working memory, suggesting sEVs can reflect a neuro-inflammatory state linked to cognitive performance. This is the first study to characterize and compare multiple CNS-sEV populations within the same individuals, establishing a robust methodology that lays the groundwork for using sEVs as prognostic and diagnostic biomarkers of AD.

Disclosures: L. Licatini: None. **L.M. Licatini:** None. **F. Haddadin:** None. **C.N. Winston:** None.

Late-Breaking Poster

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Title: Greater choroid plexus volume is linked to sleep disruption, neurodegeneration, and cognition in older adults: Evidence from the IGNITE Study

Authors: *M. G. CHAPPEL-FARLEY[1], K. R. SEWELL[2], A. M. COLLINS[2], C. MOLINA-HIDALGO[2], S. JAIN[2], H. HUANG[2], P. SOLIS-URRA[2], L. OBERLIN[2,3], G. A. GROVE[4], A. F. KRAMER[5,6], E. MCAULEY[7,6], J. M. BURNS[8], C. HILLMAN[5,9], E. D. VIDONI[8], B. SUTTON[10], A. MARSLAND[4], M. KAMBOH[11], C. KANG[1], L. WAN[2], K. I. ERICKSON[2], K. A. WILCKENS[1];
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KS; [9]Physical Therapy, Movement, & Rehabilitation Sciences, Northeastern University, Boston, MA; [10]Bioengineering Department, University of Illinois Urbana Champaign, Champaign, IL; [11]Human Genetics, University of Pittsburgh, Pittsburgh, PA

Abstract: Impaired clearance of neurotoxic waste via cerebrospinal fluid (CSF) transport may contribute to neurodegeneration. Notably, this clearance process is principally active during sleep, suggesting poor sleep may drive neurodegenerative cascades. The choroid plexus (ChP) produces CSF and ChP enlargement is associated with impaired waste clearance and cognitive decline. Prior studies have not directly linked sleep, ChP volume, neurodegeneration, and cognition within a single sample of older adults. We tested whether greater ChP volume was associated with poor sleep, neurodegeneration, and cognition in a sample of 556 cognitively unimpaired older adults (u_{age}=69.7±3.7, 70% Female) enrolled in the IGNITE study (NCT0287530). Neurodegeneration was determined by examining hippocampal and gray matter volumes adjusting for estimated total intracranial volume. Sleep was assessed with the Pittsburgh Sleep Quality Index (PSQI) and actigraphy. Confirmatory factor analysis generated composite scores of subjective cognitive decline, episodic memory, working memory, processing speed, executive function(EF)/attentional control, and visuospatial function from a comprehensive neuropsychological battery. A multiple regression approach tested hypotheses adjusting for age, sex, study site, and *APOE4* carriage; education was included as another covariate for models with cognition. Mediation models tested for mediation by ChP volume in sleep-neurodegeneration relationships adjusting for the same covariates. Consistent with predictions, lower PSQI-assessed sleep quality (β=0.13, p=0.001), sleep duration (β=-0.10, p=0.009), and sleep efficiency (SE; β=-0.12, p=0.004) were associated with greater ChP volume. Actigraphy-derived sleep measures were not associated with ChP volume. Greater ChP volume was associated with smaller hippocampal (β=-0.38, p<0.001) and gray matter volumes (β=-0.09, p=0.02). ChP volume mediated the relationship between PSQI-assessed sleep quality (standardized indirect effect (SIE)=-0.05, 95% CI [-0.076, -0.020]) and SE (SIE=0.04, 95% CI [0.014,0.077]) with hippocampal volume, and self-reported sleep duration with gray matter volume (SIE=0.009, 95% CI [1.85, 475.48]. Finally, greater ChP volume was associated with poorer processing speed (β=-0.10, p=0.02) and EF/attentional control (β=-0.10, p=0.02), but not other domains. Alterations to ChP morphology may underlie associations between poor sleep and neurodegeneration, contributing to downstream cognitive consequences in older adulthood. Disrupted sleep may contribute to cognitive decline by compromising brain regions critical for waste clearance.

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Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.21/LBP021

Topic: C.01. Brain Wellness and Aging

Title: Towards an objective electroencephalogram biomarker for tinnitus

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Abstract: Tinnitus is a symptom of a perceived ringing or buzzing sound that affects over 10% of adult populations in the US, severely affecting the quality of life of 0.5%. While progress has been made in associating various pathologies with the symptom, there is a lack of an objective marker to assess the severity of tinnitus or the effectiveness of interventions. Previous fMRI studies have shown functional connectivity differences in the thalamus and left inferior occipital gyrus as well as default mode network differences. In this study, we aim to identify an electroencephalogram (EEG) marker correlated with the tinnitus symptom. 8 subjects consisting of 1 female, 7 males, ages 20-36 were recruited for this study. 5 reported chronic tinnitus (tinnitus symptom >6 months) and 3 control. All subjects presented moderate to no hearing loss. The subjects were asked to relax with their eyes closed for a 10 minute period, followed by which their response to the Tinnitus Functionality Index (TFI) was recorded. Clustering the global field potentials into n different microstates, we found that n=4 resulted in greater than 60% global explained variance (GEV) for all subjects, with no significant differences in the microstates exhibited by the two groups. On further exploring the microstate durations and transition probabilities for the two groups, we found significant differences in the bidirectional transition probabilities between two of the states. Using these features in a linear classifier, we were able to classify held out subjects with a cross-validated accuracy of 73%. On expanding this analysis to 51 subjects selected from a larger public dataset (Ibarra Zarate et al., 2022), we saw a similar classification accuracy. We are currently exploring the markers of significantly different microstates, their transition probabilities and their relation to the neural correlates of tinnitus. In conclusion, this ability to classify tinnitus subjects from control suggests the presence of an objective marker present in the dynamical system analysis of resting state EEG data.

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Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.22/LBP022

Topic: C.01. Brain Wellness and Aging

Support: EU Horizon Europe research and innovation programme under grant agreement No 101087124

Title: Spiritual well-being as a predictor of cognitive trajectory in healthy aging and early AD. Data form Czech Brain Aging Study

Authors: *K. SHEARDOVA[1], P. ŠIMKO[2];
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Abstract: Objectives: Spiritual well-being has been proposed as a resilience factor in cognitive aging, yet its longitudinal neurocognitive correlates were unclear. The Czech Brain Aging Study (CBAS) provided a unique setting, combining fluid and imaging biomarkers, multimodal cognitive testing, and the validated SHALOM scale of spiritual well-being—defined as harmony/purpose in life across personal, communal, environmental, and transcendental domains.**Methods:** CBAS participants were followed annually with UDS-based neuropsychological assessments. We analyzed 142 participants with baseline SHALOM data (96 biomarker-confirmed stage 1-3 Alzheimer's disease [AD], 46 biomarker-negative controls [CTR]). AD was defined by positive amyloid PET/CSF; CTR by biomarker negativity and/or ≥3 consecutive normal neuropsychological exams. Of these, 60 AD and 37 CTR contributed ≥1 follow-up between 2-6 years (AD Ns: 43/40/29/18/13; CTR Ns: 25/20/19/14/12 at 2y-6y). Domain-specific composites (processing speed, memory, attention-working memory, executive function) were computed. Linear mixed-effects models tested 3-way interactions between time (2-6y bins), group (AD vs CTR), and baseline SHALOM, with covariates for baseline age, sex, and years of education.**Results:** Significant 3-way interactions were found for processing speed (binned model, FDR-corrected $p < 0.05$) and attention-working memory (trend-level, $p = 0.066$). Higher baseline SHALOM predicted more favorable 2-6y cognitive trajectories in both groups, especially in AD. Covariates showed the expected effects: older baseline age predicted faster decline in processing speed, higher education supported attention-working memory, and sex was non-significant. **Conclusions:** Higher spiritual well-being moderated long-term cognitive trajectories in both aging and early AD. Resilience effects were most pronounced for processing speed and attention-working memory, independent of demographic covariates. Findings highlighted the protective role of psychosocial and existential resources in both healthy and pathological cognitive aging.

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Late-Breaking Poster

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Program #/Poster #: LBP070.23/LBP023

Topic: C.01. Brain Wellness and Aging

Support: NIH/NIA Grant 1R01AG053961

Title: Medial Temporal Lobe-Cortical Functional Connectivity is Lower in Older Adults of African Ancestry with ABCA7-80 Risk Allele bu not in APOE-ε4 Carriers

Authors: *M. BUDAK[1], V. PARUZEL[1], S. MOALLEMIAN[1], P. A. WHITE[1], M. A. ISHAQ[1], B. A. FAUSTO[2], M. A. GLUCK[3];
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Abstract: APOE-ε4 and ABCA7-80 (rs115550680) are major genetic risk factors for Alzheimer's disease (AD). While APOE-ε4 is prevalent in European ancestry, ABCA7-80 confers disproportionately elevated risk in African ancestry. The medial temporal lobe (MTL), an early locus of AD-related pathology, supports top-down integration of learning, attention, and memory. Our prior work showed reduced MTL flexibility in ABCA7-80 risk carriers versus non-carriers and APOE-ε4 carriers, suggesting impaired neural adaptability. However, whether seed-based functional connectivity patterns differ across these genotypes remains unclear. Understanding genotype-specific alterations in MTL functional connectivity is essential for identifying early biomarkers of AD in African-ancestry populations.Participants (N=146; Mean Age=69.7±6.3; 110women; Table1) were drawn from the Aging & Health Alliance study at Rutgers-Newark. Saliva-based genotyping identified APOE-ε4 and ABCA7-80 status. Resting-state fMRI assessed seed-based functional connectivity among MTL subregions−Subiculum, Cornu Ammonis1 (CA1), Dentate Gyrus (DG)/CA3, Parahippocampal Cortex (PHC), Perirhinal Cortex (PRC), Anterolateral and Posteromedial Entorhinal Cortex (aLEC and pMEC)−and their cortical targets. Group differences were tested using age-adjusted t-statistics and Threshold-Free Cluster Enhancement (TFCE, $p<.05$).ABCA7-80 risk carriers exhibited significantly reduced subiculum-seeded connectivity with a temporoparietal cluster peaking in the left temporo-occipital middle temporal gyrus (TFCE $p<.05$; Figure 1), and reduced DG/CA3-seeded connectivity in the right superior parietal lobule (TFCE $p<.05$; Figure 2), compared to APOE-ε4 carriers. These regions support attention, visuospatial integration, and memory-guided behavior.ABCA7-80, but not APOE-ε4, is associated with disrupted MTL-parietal connectivity in cognitively unimpaired older adults of African ancestry, underscoring ABCA7-80 as an ancestry-informed biomarker and a promising target for precision interventions in preclinical AD.

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Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.24/LBP024

Topic: C.01. Brain Wellness and Aging

Support: Canada Research Chair (Tier 2) in Memory Modulation

Title: fMRI Co-Fluctuations Reveal Age-Related Declines in Network Segregation: A Role for Basal Forebrain

Authors: *T. YANG[1], A. Y. YOUM[2], R. WILFORD[2], J. PENG[2], M. COHN[2], K. D. DUNCAN[2];
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Abstract: At rest, brain regions have coordinated activity, forming well-organized networks that support specialized and segregated information processing. With age, this organization becomes less distinct, marked by reduced network segregation (decreased within-network connectivity and increased between-network connectivity), which particularly affects networks such as the default mode network (DMN; Spreng & Turner, 2019). This phenomenon has been associated with age-related cognitive decline (Koen et al., 2020), but its underlying mechanisms remain unclear. Given the basal forebrain's (BF) role in regulating large-scale brain activity via cholinergic projections (Taylor et al., 2024) and its vulnerability to age-related decline (Schmitz & Spreng, 2016), we hypothesized that BF BOLD activity would predict network segregation. In an exploratory study, we applied the edge time series method (Zamani Esfahlani et al., 2020) to resting-state fMRI data from older adults (N = 62; age range 57-90; M_{Age} = 74.49 years). This method captures moment-to-moment co-fluctuations in regional activity, dynamically tracking changes in functional connectivity. From these co-fluctuations, we derived a time-resolved measure of network segregation and tested its relation to the rolling average of preceding and concurrent BF BOLD responses. Replicating prior work, we observed significant age-related declines in segregation across the brain, and within the DMN, in particular. While individual differences in segregation did not correlate with performance on neuropsychological assessments, segregation positively correlated with performance on an experimental sustained attention task that aimed to assess the function of participants' BF cholinergic system. Contrary to our hypothesis, resting-state BF BOLD activity did not significantly predict segregation across the brain, nor within the DMN. Importantly, though, the degree to which the BF activity predicted DMN segregation was positively moderated by the functional integrity of participants' BF, indexed through responsivity on a separate monetary incentive task (p = 0.006, FDR-corrected p = 0.052); BFs that were less attuned to motivational tasks were also less likely to

predict DMN segregation. Together, these preliminary findings suggest that changes to BF function in aging may have consequences for cortical network organization, with potential implications for the cognitive health of older adults.

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Late-Breaking Poster

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Program #/Poster #: LBP070.25/LBP025

Topic: C.01. Brain Wellness and Aging

Support: NIH R01 AG068990

Title: Regional heterogeneity of brain white matter aging underlying age-group dependent cognitive associations

Authors: *R. E. CHIN, X. HU, J. RANIERI, J.-H. KIM, H. OH;
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Abstract: Brain white matter (WM) microstructure undergoes extensive changes with age yet how these alterations relate to cognition across the adult lifespan remain unclear. While traditional diffusion tensor imaging (DTI) has revealed broad age-related changes, advanced microstructural modelling, such as Neurite Orientation Dispersion and Density Imaging (NODDI), may offer greater precision in quantifying underlying tissue organization. This study leverages a multi-parameter diffusion MRI approach to characterize age-related alterations in white matter microstructure and to determine how these differences differentially relate to cognitive performance in younger and older adults. Eighty-six cognitively normal adults (Young: n=33; Older: n=53) underwent multi-shell diffusion MRI. WM microstructure was quantified using DTI (FA, MD) and NODDI (NDI, ODI, FWF) at global (mean WM skeleton), regional (50 atlas-defined tracts), and voxel-wise levels. Cognitive performance was summarized into six PCA-derived domains. Age group effects on WM microstructure and age group × WM interactions on cognition were tested using permutation-based GLMs, controlling for sex and education. Whole-brain voxel-wise analyses were also performed with tract-based spatial statistics (TBSS). Age-related WM alterations were widespread, with converging global, regional, and voxel-level evidence implicating commissural, association, and limbic pathways, with NODDI-derived indices, especially FWF and ODI, showing the strongest effects. Older adults exhibited reduced FA and NDI, and elevated MD, ODI, and FWF across global WM summary measures (FA, MD, ODI, FWF: F=11.4-68.4, all $p_{FDR}<0.01$; NDI: F=3.46, $p_{FDR}=0.076$), consistent with microstructural degradation and increased extracellular free water. Regional analyses revealed that twelve tracts, primarily commissural and limbic pathways, exhibited multimodal effects across all five WM microstructural metrics, with the fornix

showing the strongest effects (FWF; $\eta^2p = 0.51$). Critically, age moderated WM-cognition relationships in a tract- and domain-specific manner. Younger adults showed stronger links between NDI and ODI in commissural and association tracts with language and visual memory ($p_{FDR}<0.05$). In contrast, older adults showed stronger links between NDI of the limbic and projection tracts (e.g., fornix and corticospinal tract) for executive and language domains ($p_{FDR}<0.05$). These findings underscore the regional heterogeneity of brain WM aging and demonstrate the enhanced sensitivity of advanced diffusion models for capturing age-related WM and associated cognitive changes.

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Program #/Poster #: LBP070.26/LBP026

Topic: C.01. Brain Wellness and Aging

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Epstein Breakthrough Alzheimer's Research Fund

Title: LC-linked cortical structural changes and their associations with emotional changes in older adults

Authors: *C. LEE[1], H. YOO[1], M. DAHL[2,1,3], K. NASHIRO[1], C. CHO[1], N. MERCER[1], P. CHOI[1], H. LEE[1], J. THAYER[4], M. MATHER[1];
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Abstract: The locus coeruleus (LC) is a critical hub for arousal and emotion regulation in aging, yet little is known about how LC-related structural changes link to emotional functioning. Using voxelwise partial least squares correlation (PLSC), we identified cortical regions covarying with LC contrast change and examined their associations with emotions in older adults.We analyzed data from 53 participants who completed a 10-week biofeedback training program. These participants underwent MRI scanning at three time points (pre, mid, and post) to acquire LC contrast and cortical volume measures, and also completed a full set of emotion questionnaires at pre- and post-training. LC contrast was computed from high- and low-resolution LC scans, while T1- and T2-weighted structural images were processed with the HCP pipeline and FreeSurfer to obtain vertexwise cortical volumes. Whole-brain voxelwise PLSC between LC contrast change and cortical volume change yielded 17 cortical clusters after multiple-comparison correction using Monte Carlo z. Individual- and timepoint-specific cluster volumes were then extracted and entered into a second PLSC with emotion measures (PANAS, DASS-21, mood prediction, mood-dependent memory).The 17 LC-linked cortical cluster volume changes showed significant

latent variable associations with emotional changes. The strongest contributions emerged from depression and negative affect measures, indicating that structural variation in LC-coupled cortical regions covaried with higher depressive symptoms and negative mood states. Bootstrap ratios confirmed robust loadings in frontal, temporal, and parietal regions including postcentral, insula, and precuneus clusters. In contrast, positive affect and mood prediction variables showed weaker associations.These findings demonstrate that LC-related cortical structural changes are specifically linked to negative emotional processes in older adults. By integrating multimodal imaging and targeted emotion assessments, this study highlights associations between the LC and its distributed cortical partners and affective vulnerability.

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Late-Breaking Poster

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Title: Visualizing Microstructural Changes in Aging and Cognitive Decline through Soma and Neurite Density Imaging on Ultra-High Gradient Diffusion MRI

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Abstract: Structural MRI can provide insight into age-related cortical thinning and atrophy, but only at the macroscopic level when cellular damage is already evident [Rutherford, 2022]. Here, we studied age-related microstructure alterations in gray matter and their associations with cognition using Soma and Neurite Density Imaging (SANDI) [Palomobo, 2020] with state-of-the-art MRI hardware. Twenty-eight healthy adults (19-49 years, 15F/13M; “younger” cohort) and twelve healthy older adults (51-83 years, 9F/3M; “older”) were recruited under the approval of the Mass General Brigham IRB. All subjects underwent a multi-shell diffusion protocol on the

3T Connectome 2.0 MRI system (G_{max}=500 mT/m, $Slew_{max}$=600T/m/s; MAGNETOM Connectom.X, Siemens) [Ramos-Llorden, 2025]. T1-weighted images were acquired for region-of-interest (ROI) extraction. The SANDI model was fitted to obtain cell body (soma) signal fraction (f_{soma}). Older adults were administered the Montreal Cognitive Assessment (MoCA) to evaluate cognitive function [Nasreddine, 2005]. To investigate age-related effects, we examined associations between f_{soma} and age using partial Pearson' correlations, adjusting for age and sex. Compared to younger adults, the older cohorts showed reduce f_{soma} across cortical ROIs, with significant declines ($p<0.05$) particularly evident after age 50, across cortical ROIs. The frontal lobe and the anterior cingulate gyrus show weaker effects compared to other lobes, suggesting distinct development trajectories in these regions. To further examine observed reductions in the context of cognitive function in normal aging, we correlated MoCA scores and ROI-averaged f_{soma} values, controlling for age and sex. Significant associations ($p<0.05$) were observed in the global gray matter, frontal, parietal, anterior cingulate, and posterior cingulate regions, with the strongest effect found in the frontal cortex. Our previous work using a weaker gradient system (300mT/m) showed a similar association between f_{soma} and age in a larger cohort of 72 individuals [Lee, 2024]. The present findings suggest that the stronger gradients of the new system, providing greater sensitivity, may enable improved detection of microstructural changes within a smaller sample. Detecting gray matter microstructural changes in this manner can be beneficial to better understand subtle changes in normal aging, as well as the distribution of neurodegenerative changes in Alzheimer's disease.

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Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP070.28/LBP028

Topic: C.01. Brain Wellness and Aging

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Title: Increased inter-individual variability in functional network organization of older adults compared to younger adults

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Abstract: The brain is organized into distributed, functionally relevant large-scale systems. Recent methodological advances have allowed for the mapping of this organization at the individual level using noninvasive and highly reliable fMRI methods in humans. Research leveraging these "precision fMRI" methods have shown a large degree of inter-individual variability in the functional connectivity (FC) patterns and spatial organization of networks. However, most current research examines only younger adults, raising the question of how inter-individual variability may differ during aging in light of neurodegeneration and experience accumulation. Here, we use precision fMRI to investigate the degree of inter-individual variability in network organization in older adults compared to younger adults. We collected extended amounts of data (62-231 min. per person) from 19 older adults (OA; ages 60-75) and 76 younger adults (YA; ages 18-35) across 4-5 sessions to obtain reliable measures of FC. While FC matrices were consistent within participants across sessions, when compared across participants, the similarity of FC patterns was lower among older adult individuals (M_{OA}=0.46, SD_{OA}=0.05) than in younger adults (M_{YA}=0.55, SD_{YA}=0.03; $p<0.0001$). Indeed, older adults were more similar to younger adults than they were to other older adults ($M_{OA/YA}$=0.49, SD_{OA}=0.07/SD_{YA}=0.02; $p<0.0001$). These results suggest that inter-individual variability increases with aging. However, rather than following a uniform trajectory of network reorganization, these results may indicate that older adults vary in their trajectories in highly heterogeneous ways, such that their FC patterns are more similar to young adults than to other older adults. This may reflect the fact that aging is not a uniform process. Rather, differences in health, neurodegeneration, and lifestyle factors may lead to highly individualized trajectories of network reorganization. These results mirror recent findings suggesting that children show less inter-individual variability than young adults (Demeter et al., 2025), thus providing further evidence for a "starburst" model of network development and reorganization. In this model, networks reorganize across the lifespan, diverging from a central tendency in highly heterogeneous ways that give rise to age-related increases in inter-individual variability. This finding underscores the importance of accounting for heterogeneity in functional organization in studies aimed at understanding age-related differences in functional networks and their relationship to cognitive decline.

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Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

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Title: Age-Dependent Effects of Cholinergic Circuit Manipulation on Memory and Plasticity

Authors: *V. A. RIVERA;
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Abstract: Memory is essential for an organism's survival but is vulnerable to disruption during aging. Aging-related memory decline is hypothesized to be driven in part by changes in the brain's cholinergic system. As part of this system, the medial septum sends cholinergic projections to the hippocampus, which is essential for episodic and spatial memory processing. However, the impact of aging on this circuit, and how it relates to memory impairments associated with aging, remain unclear. Here, we used chemogenetics to manipulate the activity of medial septum cholinergic neurons during consolidation of object-location memory (OLM) and contextual fear memory (CFM) tasks, in male and female mice of varying ages. Following CFM recall, mice were sacrificed to characterize hippocampal network activity patterns associated with memory recall. We found that chemogenetic activation in young mice resulted in a greater OLM performance, while chemogenetic inhibition had no effect on OLM consolidation. In contrast, we found sex-specific effects in the OLM task in older mice. OLM consolidation in younger females, but not males, was improved with chemogenetic activation of medial septum cholinergic neurons. Chemogenetic manipulation did not affect CFM, in either sex or age-group. However, successful CFM recall in older mice was associated with increased activity in some hippocampal subregions, compared with young mice. These data suggest that the regulation of memory consolidation by cholinergic signaling might differ between sexes, and as a function of aging. Understanding these mechanisms may lead to a better understanding of aging-related memory loss in humans.

Disclosures: V.A. Rivera: None.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

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Program #/Poster #: LBP070.30/LBP030

Topic: C.01. Brain Wellness and Aging

Title: The relationship between estradiol and brain connectivity in females during midlife

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Abstract: Perimenopause is a significant neuroendocrine aging process that occurs during midlife in females and may have effects on brain connectivity that are relevant to both normal and pathological aging. Perimenopause may be accompanied neurological symptoms such as disruptions in sleep, anxiety and depression, and changes in cognitive performance that result from fluctuating levels of estradiol (E2); however, declines in cognitive performance during perimenopause are often transient and do not persist into menopause. It remains unclear what factors contribute to some people experiencing a persistent decline in cognitive processes, while others do not experience cognitive changes around menopause. One potential contributing factor to the individual differences in cognition and risk for pathological aging is the brain's response to decreased levels of E2. In the present study we assessed the level of task-modulated effective connectivity between brain regions during an episodic memory task in females during midlife. In our investigation we utilized data from the Human Connectome Project - Aging 2.0 release. Data acquired by HCP-A researchers included imaging, hormone, and demographic data. One hundred and fifty female HCP-A participants between 40 and 55 years of age were included in the present analysis. A total of 146 of the 150 participants utilized in the present study had out-of-scanner FaceName retrieval accuracy data available and the mean number of faces recalled was 7.49 (SD=2.467). We assessed connectivity during the FaceName task utilizing Conn Toolbox on a connection level. We identified changes in connectivity associated with E2. A total of nine connections reached significance during the recall portion of the FaceName task at a $p<.05$ FDR corrected level after controlling for age in years. Connections that reached significance included those among the superior frontal gyrus left and brain stem and the middle temporal gyrus anterior division right, among others. There was no significant relationship between E2 and FaceName task performance ($r(144)=-0.004$, $p=0.965$). E2 level was correlated with age in years ($r(148)=-0.346$, $p<0.001$. In conclusion, our results indicated that task-modulated effective connectivity between brain regions was related to E2 level during midlife in females.

Disclosures: A.A. Testo: None. **J.A. Dumas:** None.

Late-Breaking Poster

LBP070: C.01. Brain Wellness and Aging

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Topic: C.01. Brain Wellness and Aging

Support: NIH R01 AG068990

Title: Age-related differences in regional activation and functional connectivity patterns during visual perceptual categorization

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Abstract: Advanced age is commonly associated with decline in higher-order cognition such as memory and executive functions supported by frontoparietal control and medial temporal memory networks. Age-related changes in perceptual categorization and their underlying neural correlates, however, remain largely understudied. In this study, we examined whether and how regional activations and functional connectivity across brain regions underlying visual object categorization change with age. Twenty-four healthy young (15 females; mean age = 20.3) and 21 cognitively normal older adults (12 females; mean age = 67.5) performed visual categorization tasks with faces and scenes during an fMRI study in which intact and scrambled images for faces and scenes were presented in separate blocks. We applied general linear models to examine regional activations for categorizing faces and scenes presented as intact or scrambled images. To assess functional connectivity, we applied generalized psychophysiological interaction (gPPI) and Dynamic Causal Modeling (DCM) to evaluate age-related differences in connectivity strength and directionality between independently defined seed regions - face fusiform area (FFA) and place parahippocampal area (PPA) for faces and scenes, respectively - and other brain regions. Behaviorally, lower accuracy and slower response time were found for the scrambled compared to intact conditions and for the scene compared to face conditions ($ps < 0.001$). Older adults, compared to young adults, showed significantly longer response time to scrambled images ($ps < 0.001$). Collapsing visual categories, greater frontoparietal activation was found for scrambled than intact images, across age groups. Assessing brain-wide functional connectivity patterns with FFA and PPA revealed greater connectivity between the left FFA and the dorsomedial prefrontal cortex for scrambled than intact faces and increased connectivity between the left PPA and the left superior and right inferior parietal lobes for intact than scrambled scenes. Compared to young adults, older adults additionally showed increased left FFA connectivity with the right inferior frontal cortex for intact than scrambled faces. DCM results revealed directed connection from dorsomedial frontal cortex to FFA and PPA visual association cortices for both scrambled and intact images at different degrees. Our results indicate that neural substrates underlying simple visual perceptual

categorization changes with age at the brain-wide connectivity level and these age-related changes may affect higher-order cognition involving visual object information processing.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

Support: 1K99AG078557-01A1
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19PABH134610000

Title: Ribosubstitution in human neurons links aging and sporadic Alzheimer's disease

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Abstract: Chronological aging is the greatest risk factor for Alzheimer’s disease (AD) and related neurodegenerative disorders. Here, we uncover a novel molecular signature of neuronal aging and sporadic AD: ribonucleotide incorporation into genomic DNA, termed ribosubstitution events (RSEs). Using age-retaining induced neurons (iNs), single-nucleus RNA-seq, and a newly developed RSE-seq method, we demonstrate that impaired nucleotide homeostasis—driven by downregulation of ribonucleotide reductase subunit RRM1—leads to an increased rNTP/dNTP ratio and subsequent RSE accumulation. RSEs are enriched in open chromatin, particularly introns and promoters, and disrupt transcription. We identify hundreds of RSE-enriched genomic loci unique to aging or AD, suggesting RSEs distinguish healthy from pathological aging. Exogenous rNTP treatment phenocopies these effects and further implicates impaired ribonucleotide excision repair in AD. Our findings establish RSEs as a hallmark of neuronal aging, provide mechanistic insight into genomic instability in sporadic AD, and identify RRM1 and RSE-prone loci as potential therapeutic targets.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

Support: 5R01AG082127

Title: Integrated gene expression and chromatin accessibility profiling reveals molecular insights into tauopathies in the PS19 Mouse Model

Authors: *C. HE[1], N. R. ZEMKE[2], J. CHIU[3], W. BARTOSIK[4], E. VELAZQUEZ[5], Z. TAN[6], C. GLASS[7];
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Abstract: Tauopathies, pathologically defined by the deposition of neurofibrillary tangles, are implicated invarious neurodegenerative disorders, including Alzheimer's disease (AD). While transcriptomicstudies of AD-related tau pathology have revealed molecular characteristics, the mechanismsdriving these features remain poorly understood. In this study, we investigated gene expressionand chromatin accessibility in the entorhinal cortex, dorsal hippocampus, and prefrontal cortexof the P301S tau mouse model (PS19), which recapitulates key phenotypes of AD-related taupathology. We profiled PS19 transgenic mice (TG) and wild-type (WT) mice at the age of 4months and 10 months, representing the early stage and advanced stage of AD. Using 10xMultiome technology to simultaneously profile single nucleus gene expression (snRNA-seq) andchromatin accessibility (snATAC-seq), we characterized the gene expression and generegulatory landscape of AD-related tau pathology in this model. From the single nucleus geneexpression profiles, we recovered 934,211 high quality nuclei and identified 47 cell types acrossbrain regions. We Identified 816,287 candidate cis-regulatory elements across 3 brain regions inour snATAC-seq dataset. We also observed region-specific neuronal loss and microglia cellexpansion in TG mice. Tau pathology in our mouse model induces robust transcriptionalchanges in microglia, specifically, microglia in TG mice exhibit upregulated inflammatory geneexpression and downregulated homeostatic signature genes. These changes are accompaniedby coordinated chromatin accessibility changes. We identified distinct activated microglial statesthat emerge in response to tau pathology and are shaped by genotype, age, sex, and brainregion. We inferred trajectory dynamics using RNA velocity, revealing a unidirectional transitionfrom homeostatic to activated microglial states along the tauopathy progression axis. Wemapped transcription factor (TF) regulatory networks, highlighting state-specific TF motifaccessibility and expression for each microglial state. In conclusion, our study provides acomprehensive multiomic atlas of the PS19 mouse brain across genotype, age, sex, and region,revealing how tau pathology and aging differentially shape cellular identity and

regulatoryprograms in a region- and cell type–specific manner. We identify microglia as primaryresponders to disease, and characterize the TF networks and chromatin landscapes thatunderpin these transitions. The progressive microglial state shift reveals a trajectory that mayserve as a key biomarker of early tau pathology.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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Title: Interrogating conserved transcriptomic signatures of cognitive resilience in the frontal cortex

Authors: *L. A. FISH[1], T. LUQUEZ[2], S. CANCHI[1], Y. WU[4], V. A. JANVE[5], K. O'CONNELL[6], T. J. HOHMAN[4], V. MENON[3], C. C. KACZOROWSKI[7];
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Abstract: Development of effective drugs for Alzheimer’s Disease (AD) is challenging, likely due in part to poor recapitulation of AD in animal models. To address this challenge, we developed the genetically diverse AD-BXD model by crossing mice from the BXD genetic reference panel with the 5xFAD mouse model. These AD-BXD mice reflect the variation in age at onset and extent of cognitive decline in human AD and thus offer the flexibility to generate multi-modal data (genetic, transcriptomic, proteomic, imaging, and behavior) to identify features

of susceptibility and resilience to disease that overlap with what is seen in humans. To uncover novel gene expression signatures and cell types that are underlying or promoting cognitive resilience to AD mutations and are conserved across species, we integrated frontal cortex AD-BXD single-nuclei transcriptomic data (N=56) with a larger human dataset (N=465, ROSMAP) to generate translationally relevant mouse cell annotations (Telpoukhovskaia et al., 2023, *bioRxiv;* Green et al., 2024, *Nature*). We first confirmed conservation of cell type clusters between species. Then, using animals' memory performance on a fear conditioning task as a continuous cognitive resilience metric, we conducted differential gene expression (DE) analysis in 14-month (aged) AD-BXDs to identify genes associated with resilience. We identified 39 DE genes associated with cognitive resilience in AD-BXDs. Further, when we restricted the mouse query genes to those that are associated with resilience in humans (Luquez et. al, AAIC 2025), overlapping DE genes in mouse included those that were nominated in AMP-AD and TREAT-AD's Agora database as potential therapeutic targets for AD. One of these, malate dehydrogenase 1 (*MDH1*), is shown to be downregulated in AD in humans, but was upregulated in astrocytes in both resilient AD-BXDs and resilient humans. This conservation lends enthusiasm about the other genes including *PDE1A*, *NCAM2*, and *SOX2-OT* in somatostatin-expressing neurons (SST) neurons and *SCN1B* in astrocytes.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.04/LBP035

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

Support: MCHRI Fellowship
Deans Fellowship

Title: Multiplexed Cas13d Screen to Identify Genetic Modulators of Neuroimmune Interactions in Alzheimer's Disease Models

Authors: *E. LI[1], S. GUERRERO[2], X. CHEN[3], C. CHEN[3], V. TIEU[4], S. QI[3];
[1]Bioengineering, Stanford University, Stanford, CA; [2]Stanford University, Sammamish, WA; [3]Stanford University, Stanford, CA; [4]Stanford University, San Francisco, CA

Abstract: Alzheimer's disease is a complex neurological disorder that is influenced by both environmental factors (aging, poor cardiovascular health) and genetic disease risk factors (APOE4, PSEN1). Previous data has shown that as the blood brain barrier breaks down in aging, T cells can infiltrate into the brain. However, the molecular mechanisms that underlie T cell infiltration into the brain to trigger or exacerbate neuronal death are unclear. To investigate how genetic risk factors can interact with environmental risk factors such as aging to contribute to Alzheimer's disease phenotypes, we have developed a novel CRISPR-Cas13d screening platform (MEGA) in hiPSC-derived neurons and glial cells that allows for systematic perturbation of two or more genes at the same time. MEGA leverages the self-processing capability of Cas13d-guide arrays, enabling robust and scalable genetic interaction screening without the need for complex multi-vector delivery systems. Our initial screens identified genes that decreased microglia sensitivity to inflammatory stimuli, leading to lower phagocytosis. For example, preliminary screens targeting T cell exhaustion factors have revealed that knockdown of *NR4A1*, a known AD risk factor, synergized with knockdown of the gene *TOX2*, which though expressed in brain cells, has been sparsely studied in microglia. These results demonstrate the power of the MEGA platform to dissect complex genetic interactions and identy novel pathways and potential therapeutic targets for mitigating T cell-mediated pathology in Alzheimer's disease.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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Program #/Poster #: LBP071.05/LBP036

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

Title: Immune Dysregulation in Cerebrospinal Fluid Reveals Chronic Inflammation and Cytotoxic Signaturesin Alzheimer's Disease

Authors: *Q. WANG;
iLab research Institute, Mountain View, CA

Abstract: Immune Dysregulation in Cerebrospinal Fluid Reveals Chronic Inflammation and Cytotoxic Signatures in Alzheimer's Disease Claire Tian, Qian WangiLab Research Institute, Mountain View, CA94043Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the leading cause of dementia, affecting an estimated 6.9 million Americans. Cerebrospinal fluid (CSF) provides a window into AD pathology, as immune alterations within CSF reflect neuroinflammation in the central nervous system.**Methods:**This

study reanalyzed the single-cell RNA-seq dataset GSE200164, comprising CSF from 45 healthy individuals and 14 AD patients with mild cognitive impairment or dementia. After quality control, 70,388 cells were retained, including 16,124 from AD patients and 54,262 from controls. Major immune lineages included monocytes, T cells, and natural killer (NK) cells.**Results:**Monocyte lineage cells were expanded in AD CSF (22.5% vs. 14.7%), with enrichment of nonclassical, resting classical/intermediate subsets, and conventional dendritic cells (cDCs)expressing APOE and TREM2, characterized by upregulation of APOE and TREM2. Healthy controls instead showed higher proportions of mature cDCs, activated monocytes, and monocyte-derived macrophages expressing IL1B, TNF, and CCL4. T cells were reduced in AD CSF (69.5% vs. 79.6%). Subcluster analysis revealed expansion of $CD4^+$ central memory T cells (T_CM), including activated T_CM with helper potential, lymphoid-homing/survival T_CM, and cytotoxic $CXCR6^+$ effector-memory $CD4^+$ T cells expressing GZMA, GZMH, CCL5, and other cytotoxic/effector modules. Regulatory T cells with activation/suppressive signatures were also elevated. By contrast, healthy CSF contained more early-activation $CD4^+$ T_CM expressing IL7R, S1PR1 and other genes. $CD8^+$ T cell subsets in AD, including $CXCR4^+$ and $CD7^+$ NK-like $CD8^+$ T cells, showed upregulation of cytotoxic mediators and chemokines (GNLY, GZMB, NKG7, CCL5, and others). NK cells were more frequent in AD CSF (5.4% vs. 2.8%) and upregulated cytotoxic granule machinery, inflammatory chemokines (CCL5), and antigen presentation/interferon-response genes.**Conclusions:**AD CSF is characterized by expansion of monocytes with chronic inflammatory profiles, enrichment of activated and cytotoxic $CD4^+$ T cell subsets, and hyperactive NK-like $CD8^+$ and NK cells. Together, these findings indicate a dysregulated immune landscape that likely promotes neurodegeneration in AD.

Disclosures: Q. Wang: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

Support: NIH Grant R01AG073230

Title: The neurovascular transcriptome during Alzheimer's Disease: a central view from the inward-rectifying K^+ (K_{IR}) channels

Authors: *Z. SHIH[1], F. MIOT[1], N. IWAKOSHI[1], S. SALLOUM[1], P. CHUM[1], M. BISHARA[2], E. J. BEHRINGER[1];
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Abstract: Over 55 million people worldwide live with Alzheimer's disease (AD), a major cognitive disorder due to insufficient blood flow regulation throughout the brain. Inward

rectifying K^+ (K_{IR}) channels, particularly $K_{IR}2$ and $K_{IR}6$, are abundant in cerebral vessels and fine-tune cerebral blood flow in response to metabolic demand, a process suppressed with dyslipidemia during AD. We sought to: 1) resolve neurovascular pathogenesis underlying AD; 2) identify whether lipid disruption with cannabidiol (CBD) alters the molecular profile of AD onset; 3) determine if activating calcium-activated potassium channels (K_{Ca}) impacts $K_{IR}2$ and $K_{IR}6$ channels during AD pathogenesis. We explore the hypothesis that **AD represents uncoupling of neurovascular $K_{IR}2$ and $K_{IR}6$ channels, prominent stewards of cerebral perfusion**.
We extracted RNA from pial arteries, cortex, and hippocampus of male and female 3xTg-AD mice (n=3-6; 2 & 18 mo[CW1]) for RNA sequencing (Zymo Research). We treated one cohort of male mice (6.5 mo, initial AD onset) with dietary CBD treatment (80-100 mg/kg/day; 2 mo duration). In another cohort of male and female animals (n = 2-15; 4-7 mo, 21-26mo), we used dietary SKA-31 treatment (10mg/kg/day; 2 mo duration). Differentially expressed genes (DEGs) and Ingenuity Pathway Analysis (IPA) resolved molecular pathogenesis of AD. We assessed participation in activities of daily living with nest building.
Comparing 18 mo to 2 mo (no AD pathology) mice, inflammation-related pathway changes were prevalent. Further, diminished neurovascular coupling and K^+ channel signaling was seen in extracerebral pial arteries, with atherosclerosis and phospholipase C signaling indicated in the cortex and hippocampus. Relative to vehicle controls, CBD modulated networks among K_{IR} and lipid regulators with highlighted roles for markers of neuroinflammation and AD perhaps sequelae of dysfunctional blood flow regulation (e.g., CXCL10, HLA-A, IGKV12-46). Statistically significant improvements in nesting behavior were not consistently observed among AD and wild-type groups in response to drug interventions (CBD or SKA-31). Yet, age, sex, and AD status all affected nest building performance. Altogether, interactive molecular signaling among neurovascular inflammation, lipid, and K+ channel signaling pathways define conditions of AD pathology with CBD treatment as a potential preventive therapeutic option.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.07/LBP038

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

Title: CAMKK2 Dysregulation and Loss of Iron Transport Proteins in the Hippocampus: A Retrospective Postmortem Study Linking to Tau Pathology in Alzheimer’s Disease

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Abstract: Background: Dysregulation of iron homeostasis is a hallmark of Alzheimer's disease (**AD**), yet the molecular mechanisms remain poorly understood. Previous work from our group demonstrated that calcium/calmodulin-dependent protein kinase kinase 2 (**CAMKK2**) regulates receptor-mediated transferrin (**TF**) trafficking, a key pathway for cellular iron uptake. We also reported significant loss of CAMKK2, TF, and transferrin receptor (**TFRC**) in the postmortem temporal cortex tissues of AD patients, associated with abnormal iron homeostasis and poor survival. Given the hippocampus's critical role in learning and memory, its early vulnerability in AD, and single-cell RNA-seq evidence showing CAMKK2, TF, and TFRC expression across multiple hippocampal cell types, this study investigated whether CAMKK2-TF-TFRC signaling is disrupted in the hippocampus during AD progression. **Objective:** To quantify hippocampal CAMKK2, TF, and TFRC proteins across neurodegenerative conditions and assess their relationship with microtubule associated protein tau (**MAPT**) pathology, age, and sex. **Methods:** Hippocampal tissues from cognitively normal (CN, n=29), AD (EOAD n=42; LOAD n=31), frontotemporal dementia (FTD, n=7), and Parkinson's disease (PD, n=9) were analyzed by immunoblotting. MAPT aggregation was assessed as an AD marker. Correlation analyses evaluated associations among CAMKK2, TF, TFRC, and MAPT. Logistic regression tested the predictive value of these proteins for disease status. **Results:** CAMKK2 and TF were significantly reduced in EOAD, LOAD, FTD, and PD compared to CN ($p<0.05$), whereas TFRC reduction was specific to LOAD ($p=0.018$). MAPT abundance was markedly elevated in AD relative to CN, FTD, and PD ($p<0.001$). CAMKK2 declined with age in both CN and AD, but the rate of decline did not differ by group. CAMKK2 and MAPT were positively correlated in CN ($r=0.512$, $p=0.0045$) but not in AD ($p=0.981$), indicating loss of CAMKK2-MAPT coupling in disease. TF and CAMKK2 were strongly correlated in CN ($r=0.541$, $p=0.0025$) but weakly in AD ($r=0.173$, $p=0.144$). No significant associations were observed between TFRC and MAPT or CAMKK2. **Conclusions:** CAMKK2 downregulation and iron-transport protein loss are common hippocampal features of neurodegeneration, with TFRC reduction emerging as a late AD event. Disruption of CAMKK2-MAPT coupling highlights a potential mechanistic link between calcium signaling and tau pathology. Restoring CAMKK2-mediated signaling may offer a novel therapeutic strategy to preserve iron homeostasis and reduce tau-associated neurotoxicity.

Disclosures: M.G. Sabbir: None. **S. Raju:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.08/LBP039

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

Support: R01 MH116046
P30 AG066468

Title: Proteomic analysis reveals separate molecular signatures for core AD pathology and postsynaptic density disruption

Authors: *S.-H. KU[1], S. J. MULLETT[2], Z. SUI[3], Y. DING[3], A. K. YOCUM[4], M. L. MACDONALD[1], S. L. GELHAUS[2], J. K. KOFLER[5], R. A. SWEET[1];
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Abstract: Alzheimer's disease with psychosis (AD+P) is a subgroup of AD patients with more rapid cognitive deterioration and greater loss of postsynaptic density (PSD) proteins. Prior study showed that AD burden and comorbid pathologies only partially explained the risk for AD+P phenotype. While GWAS and transcriptomic analyses have provided insights into additional molecular risks for AD+P, the specific proteomic landscape and its relationship to PSD integrity remains poorly understood. Identifying proteins in the broader cellular environment that influence PSD loss address a critical knowledge gap about synaptic dysfunction mechanisms in early disease stages.We conducted quantitative proteomic analysis using mass spectrometry on dorsolateral prefrontal cortex gray matter homogenate samples from 127 individuals (48 AD-P; 61 AD+P; 18 normal controls). Following quality control and normalization, we analyzed 4,705 proteins. Statistical analysis included multivariate linear regression and weighted correlation network analysis (WGCNA). Over-representation analysis (ORA) was performed to identify enriched Gene Ontology terms associated with differentially expressed proteins. All analyses corrected for multiple comparisons.AD+P versus control showed the most pronounced alterations in protein abundance (n = 178 proteins, $q<0.05$), while 53 proteins ($q<0.05$) were identified comparing AD-P with control. However, correlation analysis demonstrated that AD-P and AD+P show highly similar changes relative to controls ($R^2=0.965$, $p<0.001$). WGCNA identified four modules significantly associated with disease status ($q < 0.05$) comparing all AD subjects to control, but none differed significantly between AD+P and AD-P. Because these analyses suggest AD+P largely represent a continuum of severity rather than a dichotomous state, we evaluated the relationship of homogenate protein abundances with PSD yield. This identified 15 proteins significantly correlated with PSD yield ($q < 0.05$), including ENPP6, a gene linked to AD+P by GWAS. Additionally, PSD yield-associated proteins showed minimal overlap with broadly altered AD proteins (1 of 137 proteins). Module-level PSD analysis revealed one module significantly correlated with PSD yield across all samples ($q<0.05$), enriched for inflammatory terms.This study demonstrates that AD+P and AD-P share core protein alterations and protein co-expression module disruptions. In contrast, PSD disruption involves distinct molecular mechanisms separate from the broader AD proteomic signature, including further implicating ENPP6 in the molecular mechanisms underlying the greater PSD disruption in AD+P.

Disclosures: S. Ku: None. **S.J. Mullett:** None. **Z. Sui:** None. **Y. Ding:** None. **A.K. Yocum:** None. **M.L. MacDonald:** None. **S.L. Gelhaus:** None. **J.K. Kofler:** None. **R.A. Sweet:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.09/LBP040

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

Support: R56AG084128
RF1AG055549

Title: A Unified Hypothesis of Alzheimer's Disease Rooted in Glial Cholesterol Flux and ANLS Collapse

Authors: *C. C. FUNK[1], L. E. HOOD[2], R. KADDURAH-DAOUK[3], M. MAPSTONE[4], A. I. LEVEY[5], T. J. HOHMAN[6], L. B. MCINTIRE[7], T. PATERSON[8];
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Abstract: We propose that Alzheimer's disease (AD) begins with a failure of glial cholesterol clearance, which disrupts the astrocyte-neuron lactate shuttle (ANLS) and establishes a feed-forward loop of neuronal loss and degeneration. To capture molecular transitions across disease stages, we organized ADNI participants into quartiles based on ADAS13 cognitive scores, independent of clinical diagnosis, enabling detection of pathophysiological changes across a continuous spectrum. Multiomic analysis of plasma lipidomics, CSF proteomics, and genetic data identified CER.D19, an odd-chain sphingolipid produced during cholesterol side-chain β-oxidation, as a sentinel marker of flux strain. In cognitively intact individuals in quartile 2 (Q2), CER.D19 levels correlated with expression of LDHB and two Lands' cycle enzymes, PLA2G7 and LPCAT2, which liberate and reacylate fatty acids required for phospholipid synthesis. We interpret this pattern as consistent with impaired lipoprotein particle production needed to offload excess cholesterol from neuronal debris. In quartile 3 (Q3), which was enriched for individuals with mild cognitive impairment (MCI), molecular divergence intensified. Participants with elevated CER.D19 in Q3 showed increased CSF tau and hippocampal atrophy, along with reductions in omega-3 plasmalogens and CNS-derived XL-HDL particles, consistent with astrocytic lipid overload and disrupted flux. CER.D19 levels were associated with variants near four AD GWAS loci—PICALM (clathrin-mediated trafficking), INPP5D (lipid phosphatase), TSPOAP1 (lipid droplet-mitochondria tethering), and TNIP1 (NF-κB signaling)—and were linked to functional variation in NR1H3 (LXRA), a key transcriptional regulator of cholesterol efflux. Together with the observed omega-3 deficits, these findings suggest that glial flux capacity reflects both genetic constraint and environmentally modifiable factors. These results support a model in which genetically constrained glial flux capacity impairs cholesterol recycling, disrupts ANLS signaling, and initiates metabolic collapse upstream of amyloid and tau pathology.

Disclosures: **C.C. Funk:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fulcrum Neuroscience. F. Consulting Fees (e.g., advisory boards); Fulcrum Neuroscience. **L.E. Hood:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fulcrum Neuroscience. **R. Kaddurah-Daouk:** None. **M. Mapstone:** None. **A.I. Levey:** None. **T.J. Hohman:** None. **L.B. McIntire:** None. **T. Paterson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Fulcrum Neuroscience. F. Consulting Fees (e.g., advisory boards); Fulcrum Neuroscience.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.10/LBP041

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

Support: 5R01 AG072643-04

Title: Multiomics analysis of human cortex reveals candidate genes and pathways linked to NPTX2 expression in Alzheimer’s disease

Authors: ***Y. LAO**[1], M. XIAO[2], S. JI[1], I. S. PIRAS[3], A. BONFITTO[3], S. SONG[4], A. ALDABERGENOVA[3], J. SLOAN[4], A. TREJO[5], C. GEULA[6], E. J. ROGALSKI[7], C. H. KAWAS[8], M. CORRADA[8], G. E. SERRANO[9], T. G. BEACH[9], J. C. TRONCOSO[10], M. HUENTELMAN[3], C. A. BARNES[11], P. WORLEY[2], C. COLANTUONI[2];
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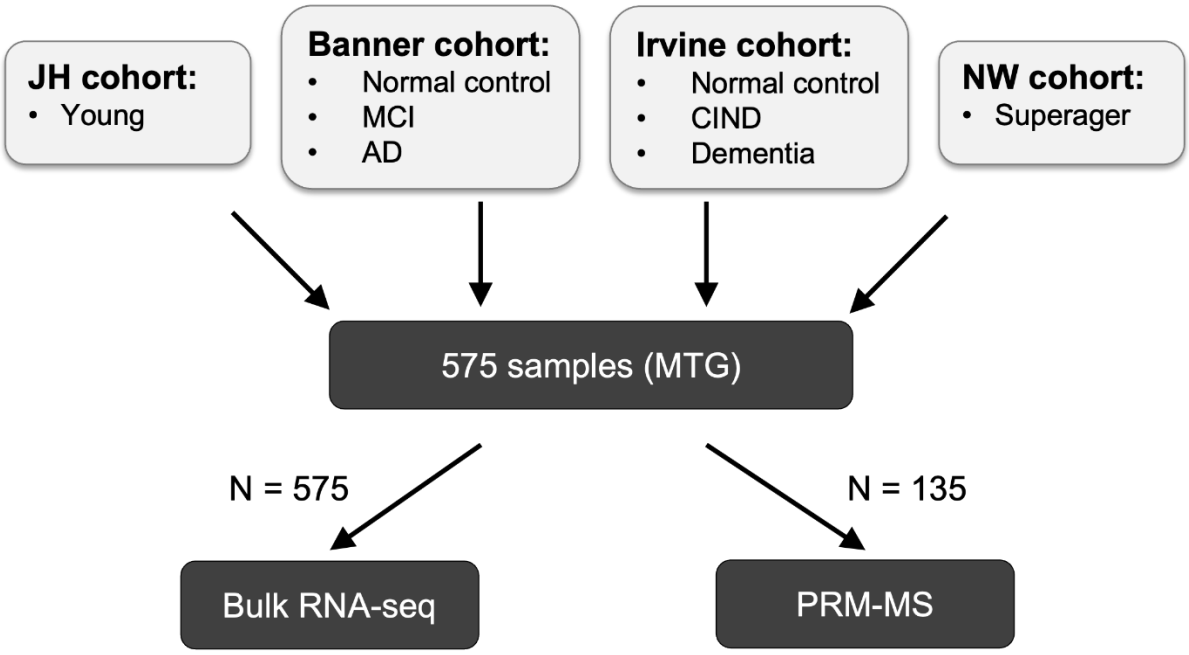
Abstract: The expression of NPTX2, a neuronal immediate early gene (IEG) essential for excitatory-inhibitory balance, is altered in the earliest stages of cognitive decline that anticipate Alzheimer’s disease (AD). Here, we use NPTX2 as a point of reference for Omics studies to identify genes and pathways linked to its position in AD onset and progression. We integrated bulk RNA sequencing from 575 frontotemporal cortical samples across four cohorts together with targeted proteomics in the same samples using parallel reaction monitoring-mass spectrometry in 135 representative cases, focusing on 20 curated proteins spanning synaptic, trafficking, lysosomal, and regulatory categories. NPTX2 RNA and protein were significantly reduced in AD, and to a lesser extent in “cognitive impaired, not-dementia” (CIND) or mild cognitive impairment (MCI). BDNF, VGF, SST, and SCG2 correlated with both NPTX2 mRNA

and protein. We identified NPTX2 correlated synaptic and mitochondrial programs that were negatively correlated with lysosomal and chromatin/stress modules. Notably, different HDACs were present in the opposing modules. Gene set enrichment analysis (GSEA) of NPTX2 correlations across all samples confirmed positive associations with synaptic and mitochondrial pathways, which were less correlated within the AD samples. In contrast, in the proteomic data that showed a negative association with transcription regulator activity, correlations were more negative within the AD samples, with unexpected transcriptional regulators—FOXJ1, ZHX3, JDP2, and ZIC4—that have not been previously implicated in AD, highlighting novel candidates for investigation in NPTX2-mediated AD pathophysiology.



Disclosures: Y. Lao: None. **M. Xiao:** None. **S. Ji:** None. **I.S. Piras:** None. **A. Bonfitto:** None. **S. Song:** None. **A. Aldabergenova:** None. **J. Sloan:** None. **A. Trejo:** None. **C. Geula:** None. **E.J. Rogalski:** None. **C.H. Kawas:** None. **M. Corrada:** None. **G.E. Serrano:** None. **T.G. Beach:** None. **J.C. Troncoso:** None. **M. Huentelman:** None. **C.A. Barnes:** None. **P. Worley:** None. **C. Colantuoni:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.11/LBP042

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

Support: CIRM DISC4-16292 ReMIND-L Award

Title: Air Pollution (PM2.5) Drives Pathological Protein S-Nitrosylation in the Brain to Contribute to Alzheimer's disease and Autism Spectrum Disorder.

Authors: *A. SHARMA[1,2], W. BAZBAZ[3], Y. WANG[2], C. K RASPUR[2], P. PATEL[2], Q. ZHAO[2], T. NAKAMURA[2], H. AMAL[3], S. A. LIPTON[2];
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Abstract: Air pollution has long been associated with cardiopulmonary diseases but growing epidemiological evidence links fine particulate matter <2.5 microns and NO-related species ($PM2.5/NO_x$) found in air pollution to neurological disorders, including Alzheimer's disease (AD), Parkinson's disease (PD), and Autism Spectrum Disorder (ASD). Experimental models support these observations and show that PM2.5 can accumulate in the brain. Prior work has identified aberrant protein S-nitrosylation (SNO-proteins) as a causal pathogenic mechanism for neurodegenerative and neurodevelopmental disorders. Here, we tested whether $PM2.5/NO_x$ induces nitrosative stress and pathological S-nitrosylation in the rodent brain. Using *SNO*TRAP/mass spectrometry technology to characterize the S-nitrosoproteome, we found that $PM2.5/NO_x$ delivered transnasally to the brain causes ~1,000 proteins to be aberrantly S-nitrosylated. Many of these SNO-proteins have already been implicated in the pathogenesis of ASD and AD. These findings, together with recent human epidemiological reports, suggest that air pollution-induced nitrosative stress may contribute causally to neurodevelopmental and neurodegenerative diseases. Our ongoing work is aimed at further proving this premise, identifying novel therapeutic targets, and developing new drugs to combat this insult.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.12/Web Only

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

Title: Mitochondrial protein aggregation trajectories differ between normal aging and Amyloid beta or Tau expression in C. elegans AD models

Authors: *S. PAHAL[1], S. AYYADEVARA[2];
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Abstract: Mitochondrial protein aggregation is a hallmark of aging and is further altered in Alzheimer's disease (AD). We asked how insoluble proteomes differ between normal aging and

the expression of AD seed proteins. Using C. elegans models expressing human Aβ (CL2355) or Tau^{WT} (VH255) at 20 °C, we profiled mitochondrial insoluble aggregates across adulthood. Mass spectrometry revealed that Aβ broadly expanded and accelerated aggregation, driving early sequestration of metabolic enzymes, translation factors, and replication machinery. In contrast, Tau^{WT} produced a smaller, core-weighted set that peaked earlier, enriched for vesicle trafficking, cytoskeletal components, and nuclear pore proteins. Cross-species mapping to human AD brain and serum proteomes, combined with interactome analysis, defined a conserved subset of early-aggregating proteins with functions spanning glycolysis, the TCA cycle, oxidative phosphorylation, ATPases, translation, chaperones, and trafficking systems. Functional assays confirmed their significance. Paralysis (n = 80-130 animals per group, three independent repeats) was exacerbated by RNAi knockdown of most candidates (paired one-tailed t-tests, $p < 0.05$; strongest $p < 0.005$), with chi-square tests on raw counts confirming significance in the majority. Chemotaxis to butanol was likewise impaired, especially for candidates in metabolic and trafficking categories. These results show that mitochondrial insoluble proteomes follow distinct aggregation trajectories under normal aging, Aβ, or Tau^{WT} influence. Rather than knockdown targets, the conserved early-aggregating proteins represent a functional signature linking aging biology to AD progression and offering translational value for pre-symptomatic detection.

Disclosures: S. Pahal: None. **S. Ayyadevara:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.13/LBP043

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

Support: Merakris Therapeutics, Inc.,

Title: In vitro model of microglia-activated tauopathy using human iPSC derived neurons in compartmentalized microfluidic devices

Authors: *T. NAGENDRAN[1], J. T. GAMBLE[2], R. ILAGAN[2], A. M. TAYLOR[1];
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Abstract: Neuroinflammation exhibited by microglia activation occurs frequently in tauopathies, including Alzheimer's Disease, Frontotemporal Dementia, and ALS. The purpose of this study was to develop a reliable in vitro model for microglia-activated tauopathy using human iPSC-derived neurons. Because human neurons respond differently to other animal models, there remains a need to develop in vitro models using human neurons. Recent guidance from the FDA articulates a desire to phase out animal testing by replacing testing "with more effective, human-relevant models." Here we use compartmentalized microfluidic chips to create an in vitro co-culture assay allowing us to activate human iPSC-derived microglia in an isolated compartment

that receives axons from human iPSC-derived cortical glutamatergic neurons. The resulting changes in tau localization within neurons are quantified. Importantly, activation of microglia using LPS led to a significant increase in the number of tau1 puncta in proximal axons ($p<0.05$, one way ANOVA) compared to vehicle control. In contrast, with the absence of microglia in the axonal compartment, LPS treatment had no effect. We then tested the effect of amniotic fluid (AF) on tau1 mislocalization during LPS-induced microglia activation. AF, enriched in growth factors and anti-inflammatory molecules, may provide protection in various neurological conditions marked by harmful neuroinflammation. Interestingly, the presence of AF rescued microglia-activated tau1 mislocalization, restoring levels comparable to both the vehicle control and AF treatment without LPS activation. In summary, we demonstrate the use of a neuroinflammation co-culture assay to investigate tauopathy in a simplified and reproducible format using human iPSC neurons and microglia. Further, these results suggest components in AF may provide a level neuroprotection against tauopathy.

Disclosures: T. Nagendran: A. Employment/Salary (full or part-time); Xona Microfluidics, Inc. **J.T. Gamble:** A. Employment/Salary (full or part-time); Merakris Therapeutics, Inc. **R. Ilagan:** A. Employment/Salary (full or part-time); Merakris Therapeutics, Inc. **A.M. Taylor:** A. Employment/Salary (full or part-time); Xona Microfluidics, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Inventor, Patent no. US2024/0034993A1, Xona Microfluidics, Inc..

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.14/LBP044

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

Support: the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. RS-2024-00409403)

Title: Microglial IRE1α/NOD/RIPK2 axis Drives Neuroinflammation and Neurotoxic Reactive Astrocytes in Alzheimer's Disease

Authors: *C. CHAU[1], S.-H. KWON[2], H. KO[3], B. SEO[4];
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Abstract: Accumulating evidence indicates that neuroinflammation and neurotoxic reactive astrocytes, driven by microglial activation, pro-inflammatory cytokine release, and innate immune signaling, are key contributors to Alzheimer’s disease (AD) pathogenesis. However, the

definitive mechanisms that can effectively suppress both neuroinflammation and the formation of neurotoxic reactive astrocytes remain unclear in AD. In this study, we performed high-sensitivity mass spectrometry on primary microglia treated with amyloid-β oligomers (AβO) and on 5xFAD mice, and identified a variety of upregulated pathways, among which the endoplasmic reticulum (ER) stress pathway was notably activated. We found that pharmacological inhibition of IRE1α in AβO-treated primary microglia significantly suppressed the expression of pro-inflammatory cytokines and neurotoxic reactive astrocytes, indicating that IRE1α functions as a critical mediator linking AβO to neuroinflammation. Furthermore, our proteomics results showed that AβO upregulates the NOD-RIPK2 (Nucleotide-binding oligomerization domain-containing protein-Receptor Interacting Serine/Threonine Kinase 2) signaling pathway, which can be activated by IRE1α and leads to NF-κB/MAPK downstream activation. Finally, we observed that pharmacological inhibition of IRE1α or genetic depletion of NOD2/RIPK2 in 5xFAD mice prevented neuroinflammation, the formation of neurotoxic reactive astrocytes, Aβ pathology, and cognitive impairment. Collectively, our findings reveal that AβO-triggered activation of the microglial IRE1α/NOD/RIPK2 signaling pathway orchestrates neuroinflammation and neurotoxic reactive astrocyte formation, highlighting this pathway as a potential therapeutic target in AD.

Disclosures: C. Chau: None. **S. Kwon:** None. **H. Ko:** None. **B. Seo:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.15/LBP045

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

Support: NIH R01-AG078859

Title: Targeting double-stranded RNA to reduce inflammation in astrocytes

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Colorado State University, Fort Collins, CO

Abstract: Department of Health & Exercise Science, Colorado State University, Fort Collins, CO 80523
Astrocyte-related inflammation is a key contributor to neuroinflammation with brain aging and Alzheimer’s Disease (AD). However, the exact causes of pro-inflammatory astrocyte activation and processes that may prevent it are incompletely understood. One potential cause of pro-inflammatory signaling in astrocytes may be endogenous double-stranded RNA (dsRNA). These “self” dsRNAs likely originate from non-coding regions of the genome and can accumulate intracellularly due to dysregulated dsRNA degradation processes. These events may be particularly important in aging and neurodegeneration, in which cellular quality control systems are impaired. To determine if inhibiting such dsRNA and the signaling events it causes might

reduce inflammation, we are inducing dsRNA accumulation in primary human astrocytes and treating them with small molecules that inhibit dsRNA signaling and/or break down dsRNA. In initial experiments, we have found that in astrocytes with increased dsRNA levels, treatment results in a modest decrease in MDA5, TNF and ICAM-1, markers of dsRNA- and astrocyte-related inflammation, respectively. To follow up on this experiment, we are profiling additional markers of pro-inflammatory signaling, performing similar experiments in senescent astrocytes (relevant to aging and AD), and identifying potential sources of dsRNA. Together, our data suggest that endogenous dsRNAs may in fact contribute to astrocyte inflammation, and that targeting these dsRNAs may be a viable therapeutic strategy.

Disclosures: A. Pacheco: None. **C. McEntee:** None. **T. LaRocca:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.16/LBP046

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

Support: This project was conducted with financial support from Allan and Company and the Stein Family Fund.

Title: Progesterone Improves Altered Mitochondrial Functions in Alzheimer’s Disease:*In Vitro*Evidence

Authors: *S. YOUSUF[1], F. ATIF[2], D. G. STEIN[3];
[1]Emory University, Atlanta, GA; [2]Emergency Medicine, Emory University, Atlanta, GA; [3]Emergercy Medicine, Emory University, Atlanta, GA

Abstract: Mitochondrial dysfunction is increasingly recognized as a significant contributor to the pathogenesis of Alzheimer's disease (AD). In AD, mitochondrial abnormalities can lead to energy deficits, oxidative stress, and neuroinflammation which contribute to neuronal cell death, synaptic dysfunction, exacerbating cognitive decline. Impaired mitochondrial functions are also associated with the accumulation of amyloid-β (Aβ) plaques and hyperphosphorylated tau tangles, the hallmark pathological features of AD. Therefore, targeting mitochondrial health is being explored as a potential therapeutic strategy in managing Alzheimer's disease. Mitochondria are sexually dimorphic; female mitochondria show more resilience against stressors compared to male mitochondria suggesting a regulatory effect of sex hormones. Progesterone (P4), a pleiotropic neurosteroid, plays an important role in maintaining mitochondrial functions in the brain. In this study, utilizing two different *in vitro* models of AD, we examined the beneficial effects of P4 against amyloid beta (Aβ) and streptozotocin (STZ)-induced mitochondrial dysfunctions in a mouse hippocampal neuronal cell line (HT-22). HT-22 cells were exposed to Aβ and STZ and then treated with different concentrations of P4. Cell death assays and mitochondrial stress test, a Seahorse analyzer, were performed. Both Aβ and STZ caused

significant ($p<0.05$) cell death and mitochondrial dysfunctions in HT-22 cells. P4 treatment significantly ($p<0.05$) inhibited the cell death and improved mitochondrial functions. These findings suggest a potential therapeutic role of P4 in the treatment of AD; however, further studies are warranted in animal models of AD.
Keywords: Progesterone, Alzheimer's disease, Mitochondria, HT-22, Seahorse Assay, Streptozotocin, MTT Assay, Lactate Dehydrogenase Assay.

Disclosures: S. Yousuf: None. **F. Atif:** None. **D.G. Stein:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.17/LBP047

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

Support: R01 AG085545
R01 AG061872
RF1 AG061729
William and Ella Owens Medical Research Foundation

Title: Loss of the myelin lipid sulfatide modulates amyloid-β deposition and distribution in alzheimer's disease mice

Authors: *X. LI[1], S. SONG[1], S. HE[1], X. HAN[1,2];
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Abstract: Amyloid-β (Aβ) accumulation is a central feature of Alzheimer's disease (AD), but the influence of myelin-derived lipids on plaque development is not fully understood. Sulfatide (ST), a galactolipid enriched in myelin and synthesized by cerebroside sulfotransferase (CST), shows profound depletion in AD brains. To evaluate whether sulfatide deficiency alters amyloid pathology in vivo, we generated CST-deficient 5xFAD mice. At three months of age, these animals displayed a striking reduction in parenchymal plagues. Such changes may reflect a direct impact of sulfatide loss on Aβ deposition, even though APP C-terminal fragment analysis indicated enhanced amyloidogenic processing. At two months, Sequential extraction revealed elevated TBS-soluble Aβ40 and Aβ42, pointing to altered distribution between soluble and deposited pools rather than diminished production. To investigate underlying mechanisms, we purified microglia and astrocytes by magnetic sorting. Microglia from knockout brains contained substantially less intracellular Aβ. Complementary BV2 cell assays showed that adding exogenous sulfatide increased uptake of fluorescent Aβ42, supporting a role for this lipid in regulating phagocytosis. Together, these findings indicate that sulfatide depletion reduces microglial uptake and compaction of Aβ, leading to fewer plaques but a larger soluble pool. This pattern resembles effects of CSF1R inhibition, which demonstrates that microglia contribute not

only to clearance but also to plaque formation. By influencing how microglia manage Aβ, our data help explain the paradox of reduced deposition despite elevated soluble Aβ, and link sulfatide loss to synaptic vulnerability. These results identify sulfatide as a key lipid determinant of Aβ distribution and a potential therapeutic target in AD.

Disclosures: X. Li: None. **S. Song:** None. **S. He:** None. **X. Han:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.18/LBP048

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

Support: NIA Grant RF1AG074566

Title: PLCG2 genetic variant P522R reduces amyloid pathology and enhances microglia-plaque engagement compared to risk variant M28L in a humanized amyloid mouse model

Authors: *C. FERGUSON[1], E. MESSENGER[1], J. KIM[2], B. T. LAMB[3], S. J. BISSEL[4]; [1]Indiana University School of Medicine, Indianapolis, IN; [2]Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, IN; [3]Stark Neurosciences Research Institute, Indianapolis, IN; [4]Stark Neurosciences Research Institute, Indiana University School of Medicine, Indianapolis, IN

Abstract: Alzheimer’s disease (AD) is a complex neurodegenerative disorder characterized by progressive memory loss and cognitive decline. Pathologically, AD is defined by the abnormal accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular tau that takes the form of neurofibrillary tangles. Recent genetic studies have highlighted variants of phospholipase C gamma 2 (PLCG2) as modulators of AD risk. In the brain, PLCG2 is predominantly expressed in microglia where it plays a central role in immune signaling pathways. Notably, two PLCG2 variants exert opposing influences on AD pathology. The M28L variant is associated with elevated AD risk and exacerbates pathology in murine models of AD. Conversely, the protective P522R variant of PLCG2 has mild hypermorphic activity and attenuates disease pathology in AD murine models. Previously, we observed that microglia in 5xFAD mice carrying the P522R variant exhibit enhanced engagement with Aβ plaques, whereas the M28L variant impaired microglia responsiveness to Aβ pathology. To further elucidate the impact of these PLCG2 variants using a cutting-edge model devoid of transgenic-related overexpression artifacts, we crossed mice bearing the PLCG2 variants to mice with humanized amyloid precursor protein harboring Swedish, Artic, and Austrian pathological mutations (SAA) to create SAA^{P522R} and SAA^{M28L} mice. We have assessed the effects of PLCG2 variants on disease progression in SAA mice using immunoblotting, immunofluorescence, and RT-qPCR. We discovered that cortical and hippocampal Aβ plaque burden is reduced in SAA^{P522R} mice compared to SAA^{M28L} and wild-type mice across 4-, 12-, and 18-month timepoints. Microglia plaque engagement is

increased in the cortex of SAA^{P522R} mice compared to SAA^{M28L} mice. Surprisingly, Iba1 percent area coverage of the somatosensory cortex is reduced in SAA^{P522R} mice when compared to SAA^{M28L} and wild-type mice, while disease-associated microglia gene markers were downregulated in both SAA^{P522R} and SAA^{M28L} mice. We are currently utilizing this model to dissect the molecular mechanisms underlying the divergent effects of PLCG2 variants. Our findings underscore the pivotal and contrasting roles of PLCG2 variants in modulating neuroinflammation and AD progression.

Disclosures: C. Ferguson: None. **E. Messenger:** None. **J. Kim:** None. **B.T. Lamb:** None. **S.J. Bissel:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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

Support: FAPESP 2023/05075-0
UCSB

Title: BAG2 phase separation coordinates protein quality control with immune surveillance under inflammatory stress

Authors: M. ALMEIDA[1], C. MACIEL CAMARGO[2], M. A. GOMES[1], E. BERALDO-NETO[3], A. P. LONGHINI[2], K. S. KOSIK[2], ***D. C. CARRETTIERO**[1];
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Abstract: Protein aggregation, prion-like propagation, and chronic neuroinflammation are defining features of many neurodegenerative disorders. Growing evidence implicates pro-inflammatory cytokines, particularly interferon-gamma (IFN-γ), as critical mediators linking persistent inflammation to proteostatic disruption and neuronal vulnerability. IFN-γ activates the immunoproteasome, enhancing the generation of antigenic peptides and their presentation via major histocompatibility complex class I (MHC-I) molecules. While this mechanism increases immune recognition, it also imposes a substantial proteostatic burden, forcing neurons to balance the competing demands of protein quality control and immune visibility. Here, using H4 cells in culture, we identify the co-chaperone BAG2 as a key coordinator of this balance. Immunofluorescence, qPCR, and Western blotting and proteomics were employed. In response to IFN-γ, *BAG2* mRNA levels increase, and the protein undergoes liquid-liquid phase separation (LLPS), forming condensates that act as dynamic scaffolds. These condensates selectively recruit immunoproteasome components, including the catalytic subunit PSMB8, thereby enhancing the processing of intracellular proteins for antigen presentation. In parallel, IFN-γ upregulates the expression of *MHC-I* and *PSMB8*, further amplifying antigen presentation capacity. Proteomic

analysis of CRISPRi-BAG2 knockdown cells stimulated with IFN-γ revealed distinct expression profiles. GO Biological process analysis showed that immune activation pathways were detected only in BAG2-positive cells, but not in BAG2 knockdown cells. Moreover, IFN-γ increases the expression of *HSP70*, a BAG2 partner, reinforcing protein quality control under inflammatory and proteotoxic stress. Our findings reveal a previously unrecognized function of BAG2 condensates: coupling protein homeostasis mechanisms with adaptive immune signaling. This dual role positions BAG2 as a central node at the intersection of proteostasis and neuroimmune responses. By integrating aggregate management with immune surveillance, BAG2 emerges as a key factor in neuronal adaptation to inflammatory environments, offering new perspectives on the mechanisms linking chronic inflammation to neurodegenerative disease progression.

Disclosures: M. Almeida: None. **C. Maciel Camargo:** None. **M.A. Gomes:** None. **E. Beraldo-Neto:** None. **A.P. Longhini:** None. **K.S. Kosik:** None. **D.C. Carrettiero:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.20/LBP050

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

Title: Digital Phenotyping of Young and Old Female 5xFAD Mice in Ventilated Cages

Authors: *P. PEREZ-BONILLA[1], H. YOON[2], A. MUELLER[2], D. HIRENALLUR SHANTHAPPA[3], C.-N. LIU[4];
[1]Animal Models and Imaging, Pfizer, Cambridge, MA; [2]Inflammation & Remodeling, Pfizer, Cambridge, MA; [3]Comparative Medicine, Pfizer, Cambridge, MA; [4]Animal Models and Imaging, Pfizer, Groton, CT

Abstract: The 5xFAD transgenic mouse model is widely used in Alzheimer's disease (AD) research due to its ability to mimic numerous AD-related characteristics, with a notably early onset and rapid disease progression. The amyloid peptide deposits and neuroinflammation induced as early as 2 months of age result in a wide range of behavioral deficits, including increased anxiety and exploratory behaviors. Traditionally, behavioral testing is conducted under variable housing and testing conditions, but this approach hinders reproducibility in preclinical studies. Capacitive-based ventilated cages, in contrast, enable unbiased behavioral monitoring in the home environment while avoiding stress-inducing experimental conditions that may confound phenotypes. Here, we pair-housed ninety 10-13 month-old (45 5xFAD, 45 WT littermates, Old) and thirty-six 2-5-month-old (18 5xFAD, 18 WT littermates, Young) female mice in digital ventilated cages (DVC) with standardized enrichment to 1) compare spontaneous behavioral profiles and circadian patterns between groups, 2) assess age impact on behavioral phenotypes within each genotype, and 3) identify behavioral markers in the digital home environment that may correlate with AD-related pathophysiology. Old 5xFAD mice exhibit significantly increased locomotor activity (LA) compared with WT littermates of same age. This

hyperactivity is evident both in overall cage movement and in peripheral locomotor activity, suggesting altered exploratory or anxiety-related behavior. While Old 5xFAD mice have increased overall LA, their activity pattern shows an unusual dip after nighttime peak, and they demonstrate increased regularity disruption index (RDI), suggesting more irregular and fragmented activity patterns. Moreover, Old 5xFAD mice display higher levels of stereotypic and fighting-like behaviors, indicating abnormal social interactions and exploratory activity. Young 5xFAD mice, in contrast, do not display abnormal LA levels, or deviations in normal activity patterns. However, they do show increased stereotypic and fighting-like behaviors. Overall, this study highlights the utility of digital home-cages in capturing nuanced behavioral changes across age that may be missed by conventional testing paradigms in an AD model. These behavioral signatures have translational value, and in the future, they could facilitate the evaluation and identification of treatments for AD. Disclosure: All procedures performed on animals were in accordance with regulations and established guidelines and were reviewed and approved by an Institutional Animal Care and Use Committee or through an ethical review process.

Disclosures: P. Perez-Bonilla: A. Employment/Salary (full or part-time); Pfizer Inc. **H. Yoon:** A. Employment/Salary (full or part-time); Pfizer Inc. **A. Mueller:** A. Employment/Salary (full or part-time); Pfizer Inc. **D. Hirenallur Shanthappa:** A. Employment/Salary (full or part-time); Pfizer Inc. **C. Liu:** A. Employment/Salary (full or part-time); Pfizer Inc..

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.21/LBP051

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

Support: NIH IRP NIEHS (1ZIAES103359-05)

Title: Immune receptor Lag3 deletion alleviates neurodegeneration phenotypes in a mouse model of Alzheimer's disease

Authors: *E. GJONESKA;
Neurobiology Laboratory, Neuroepigenomics Group, NIH/NIEHS, Durham, NC

Abstract: Immune receptor Lag3 deletion alleviates neurodegeneration phenotypes in an Alzheimer's disease model
Andrew T. Perl[1,2], Juan Wu[1], John D. Dong[1], Ashley M. Brooks[1], Andrew R. Yoblinski[1,3], Tia T. Vierling[1], Jian-Liang Li[1], Dana R. Ruby[1], Daniel Radzicki[1], Serena M. Dudek[1], Jesse D. Cushman[1], and Elizabeta Gjoneska[11]Neuroepigenomics Group, Neurobiology Laboratory, National Institute of Environmental Health Sciences, NIH, DHHS; Research Triangle Park, NC 27709. [2]University of Virginia, Charlottesville, VA 22903. [3]University of Pittsburgh, Pittsburgh, PA 15260

Alzheimer's disease (AD) remains one of the world's most prevalent neurodegenerative diseases, yet no effective interventions exist to slow disease progression. The hallmark pathological features of AD include extracellular amyloid-beta (Aβ) plaques, intracellular tau neurofibrillary tangles, and chronic neuroinflammation. Our previous work demonstrated that immune-associated master transcription factors, such as PU.1, regulate transcriptomic changes during neurodegeneration in a mouse model of AD, highlighting the immune system in disease etiology. One of the downstream target genes of PU.1, is the immune checkpoint receptor Lymphocyte-activation gene 3 (*Lag3),* which in the murine brain is exclusively expressed in microglia, the resident immune cells of the brain. Interestingly, *Lag3* shows increased expression and PU.1 binding in a mouse model of AD suggesting its involvement in AD pathology. Here, we report that deletion of *Lag3* ameliorates neurodegenerative phenotypes, including amyloidosis and microgliosis in the hippocampus of a familial AD mouse model, 5xFAD^{+}, at 9-month of age. Moreover, we show that *Lag3* deletion attenuated behavioral deficits, rescues aberrant gene expression, and reduces T cell infiltration in the hippocampus of 5xFAD^{+} mice. Specifically, transcriptional profiling reveals that *Lag3* deletion reverses aberrant expression of disease associated microglia (DAM) genes, which are typically upregulated in the 5xFAD^{+} mice, suggesting that *Lag3* deletion can restore microglia homeostasis. Our results demonstrate that *Lag3* plays a protective role in mouse AD pathogenesis by modulating neuroimmune interactions and cognitive processes, positioning *Lag3* as a promising therapeutic target for AD intervention.
* *This research was supported by the Intramural Research Program of the NIH, National Institute of Environmental Health Sciences.*

Disclosures: E. Gjoneska: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.22/LBP052

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

Support: National Natural Science Foundation of China, Grant No. 32371211 (to Yu Zhou)

Title: GHS-R1a: a new target for AD treatment

Authors: *F. HAN[1,2], Y. ZHOU[1,2];
[1]Qingdao University, Qingdao, China; [2]University of Health and Rehabilitation Sciences, Qingdao, China

Abstract: Memory loss is a key indicator of brain function decline in the early stages of Alzheimer's disease (AD), for which effective treatments remain unavailable. Recent studies indicate that GHS-R1a, a central receptor for the appetite-stimulating hormone ghrelin, is significantly upregulated in both AD patients and AD mouse models. However, the specific role of GHS-R1a in AD pathogenesis remains unclear. Here, we show that hippocampal GHS-R1a

expression increases well before memory deficits emerge in AD mice, driven by neuronal hyperactivity and metabolic stress. Genetic knockout or RNA interference targeting GHS-R1a reduced amyloid-beta (Aβ) plaques, alleviated neuropathology, and improved memory in AD mice. Conversely, selective overexpression of GHS-R1a in hippocampal excitatory neurons of wild-type mice rapidly induced AD-like pathology, including cognitive impairment, neuronal loss, and increased microglia-mediated synaptic pruning. Mechanistically, GHS-R1a deficiency reprogrammed microglia via elevated Trem2 expression, promoting microglial Aβ clearance and reducing excessive synaptic pruning. Single-cell RNA sequencing further identified significant downregulation of APOE and complement C1q, supporting restoration of a more homeostatic microglial state. Notably, these beneficial effects were reversed by Trem2 knockdown, while pharmacological blockade of GHS-R1a using the endogenous antagonist LEAP2 similarly improved memory in AD mice. These findings suggest a causal relationship between increased GHS-R1a expression and amyloid pathology in AD and highlight the potential of targeting GHS-R1a as a therapeutic strategy for AD treatment.

Disclosures: F. Han: None. **Y. Zhou:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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Program #/Poster #: LBP071.23/LBP053

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

Support: T32 NS121727
R35 NS116835
R01 FD00747

Title: Spatial transcriptomic imaging reveals an attenuated myeloid response to amyloid plaque pathology following viral encephalitis in 5XFAD mice

Authors: *D. I. JAVONILLO;
University of California, Irvine, Irvine, CA

Abstract: Alzheimer’s Disease (AD) is a progressive neurodegenerative disease characterized by the aggregation of extracellular amyloid-beta (Aβ) plaques, neurofibrillary tangles containing hyperphosphorylated tau protein, and chronic neuroinflammation. Recent studies revealed key immunological mechanisms within the central nervous system (CNS) that contribute to AD pathology. Additionally, analyses of human AD datasets have also associated viral encephalitis exposure (i.e., viral-induced neuroinflammation) with the development of AD and dementia, highlighting the need to better understand how viral encephalitis and neuroimmune mechanisms within the brain may impact AD pathologies such as Aβ plaque deposition. Using the neurotropic JHM strain of murine coronavirus, we previously reported the robust inflammatory responses to infection orchestrating sustained infiltration of peripheral immune cells (i.e.

monocyte/macrophages and T cells) within the CNS. To determine how coronavirus-induced encephalitis may impact established Aβ plaque deposition, we intracranially infected 5xFAD mice with the neurotropic JHM coronavirus. Histological staining of Aβ plaques revealed compacted dense-core plaques of JHMV-infected 5xFAD mice at 12 days post-infection, despite minimal changes in overall Aβ plaque load within the brain. Furthermore, we observed robust peripheral monocyte/macrophage infiltration into the brains of JHMV-infected 5xFAD mice, in addition to $CD4^+$ and $CD8^+$ T cell infiltration in brain regions correlating with compact dense-core Aβ plaques. To determine the transcriptional impact of acute viral encephalitis on cells within the 5xFAD mouse brain, we investigated gene expression within myeloid cells and other CNS cell types using spatial transcriptomic imaging. Utilizing differential gene expression and pathway analysis, we found that myeloid cells exhibited an increased proportion of myeloid cells demonstrating down-regulated disease-associated (DAM) pathways involving Aβ clearance, response to lipids, and macrophage activation within the post-encephalitis 5xFAD brains. Together, these findings suggest an attenuated myeloid cell response to Aβ plaque burden in 5xFAD mice following acute viral encephalitis. Future experiments aim to further dissect inflammatory mechanisms between infiltrating myeloid cells, T cells, and the progression of Aβ and tau pathology. Data derived from these experiments will further elucidate the viral-induced neuroimmune mechanisms that affect AD pathology and offer an opportunity to determine how these neuropathologic changes, such as subsequent neuronal damage, occur.

Disclosures: D.I. Javonillo: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.24/LBP054

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

Title: Inflammation Drives Nociceptive Alterations in Early Alzheimer’s Disease: Insights From Transcriptomics

Authors: Z. SHENG, B. DOU, F. XU, H. LI, ***Y. XU**;
Rutgers University, Newark, NJ

Abstract: Background & Aims: Alzheimer’s disease (AD) is characterized by progressive cognitive decline and neuropsychiatric symptoms, including chronic pain. However, the molecular mechanisms linking pain sensitivity and early AD pathology remain poorly understood.**Methods**: 4.5-month-old APP/PS1 mice were used to assess memory and cognitive performance in the novel object recognition (NOR) and Y-maze tests. Nociceptive sensitivity was subsequently assessed using the Von Frey test for mechanical stimuli, the Hargreaves test for thermal stimuli, and the cold plate test for cold sensitivity. Pathological, molecular and bioinformatic analyses were performed to further determine changes in gene and protein expression and the associated signaling pathways.**Results**: These results suggested that APP/PS1

mice did not exhibit memory impairment at 4~5 months of age, despite a significant increase in Aβ plaque burden in the brain, but not in the spinal cord or dorsal root ganglia (DRG). However, these mice showed reduced pain sensitivity, as indicated by an increased percentage of paw withdrawal threshold (PWT) in the Von Frey test and decreased paw withdrawal latency (PWL) in the thermal and cold-plate tests. RNA sequencing analysis revealed that dysregulated mRNA levels of two genes, PLIN4 and Prnp, in both central and peripheral pain-related regions, are closely involved in oxidative damage and inflammation related pathways. These findings were confirmed by immunoblot and ELISA analyses, which showed that the levels of ROS, TNF-α, and IL-1β in the pain-related regions of these AD mice were significantly increased. **Conclusions**: Early oxidative stress and inflammation in AD mice may be responsible for abnormal pain sensitivity before the onset of memory deficits and substantial β-amyloid deposition. These findings demonstrate that altered nociceptive perception could serve as an early clinical marker of AD progression.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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Program #/Poster #: LBP071.25/LBP055

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

Support: R01MH131219

Title: The ceramide response to inflammatory insult is exaggerated in the aging female mouse brain

Authors: S.-W. YOO[1], P. DEME[2], ***N. J. HAUGHEY**[2];
[1]Neurology, Johns Hopkins University School of Medicine, Baltimore, MD; [2]Tulane University School of Medicine, New Orleans, LA

Abstract: The ceramide response to inflammatory insult is exaggerated in the aging female mouse brain Women have a greater risk for Alzheimer's Disease (AD) and frequently exhibit accelerated disease progression compared with men. While sex-related differences in immune function and hormonal changes associated with menopause have been implicated in this increased risk for AD, these factors are insufficient to fully explain sex differences in AD risk. We have previously shown sex differences in circulating sphingolipids that become more pronounced with age. In particular, aging females show increases of circulating ceramides (Cer) compared with aging males. Here we provide evidence that brain expression of the sphingomyelin hydrolase neutral sphingomyelinase-2 (nSMase2; converts sphingomyelin to Cer) increases with age in female mice and is associated with a more robust Cer response to inflammatory challenge. Young (4-6 months, n=5) and old (12-16 months, n=5) C57BL/6J mice received a single intraperitoneal dose of saline or lipopolysaccharide (LPS; 5mg/kg) and

sacrificed 24h later. Cortical expression of cytokines, sphingolipids, key enzymes in Cer metabolism, and long-term potentiation (LTP) were measured in cortex. There were no sex differences in basal levels of cytokines in young or old mice. LPS increased IL-1β, TNF-α, IL-6 and KC/GRO in young and old mice to a similar extent, with no sex differences. No changes in Cer following LPS were observed in young female or male mice. However, LPS increased Cer in aging female mice but decreased Cer in aging male mice. Cortical expression of nSMase2 was selectively increased in aging female mice and was unchanged in aging male mice. LPS in aging females was associated with reduced PSD95 and LTP that was more pronounced in aging females compared with aging males. These findings suggest that the aging female brain may be more susceptible to synaptic damage by mechanisms that involve age-related changes in nSMase2 expression and the Cer response to an inflammatory challenge.

Disclosures: S. Yoo: None. **P. Deme:** None. **N.J. Haughey:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.26/LBP056

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

Support: NINDS Grant 2041009 1R01AG086443
UCSD Epstein Family Foundation Grant 2022148

Title: WILD-TYPE HEMATOPOIETIC STEM AND PROGENITOR CELLS PROMOTE DURABLE AND POST-ONSET COGNITIVE RESCUE IN 5XFAD ALZHEIMER'S MICE

Authors: *J. SCHENCK, R. PLAWAT, R. BADELL-GRAU, S. CHERQUI;
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Abstract: Alzheimer's disease (AD) is the leading cause of dementia, yet there are no effective disease-modifying treatments. We previously demonstrated that a single systemic infusion of wild-type (WT) hematopoietic stem and progenitor cells (HSPCs) into pre-symptomatic 5xFAD mice rescued memory function and reduced neuroinflammation at 4 months post-transplantation. Here, we investigated whether these benefits are durable and whether HSPC therapy retains efficacy when delivered after disease onset, a critical consideration for clinical translation. Male and female 5xFAD mice were myeloablated and transplanted with $Sca1^+$ HSPCs from WT (AD/WT^{HSPC}) or 5xFAD (AD/AD^{HSPC}) donors. In the durability paradigm, 2-month-old recipients were assessed 8 months post-transplantation. In the post-onset paradigm, 6-month-old recipients (with established amyloid deposition and emerging cognitive deficits) were analyzed 4 months later. Behavioral outcomes included the elevated plus maze, open field, and novel object recognition. Neuropathological analyses included $IBA1^+$ immunostaining and Sholl analysis of cortical and hippocampal microglia. In the durability cohort, AD/WT^{HSPC} mice showed significant improvements in cognitive and anxiety-related behaviors compared with untreated

littermates, whereas AD/AD^{HSPC} mice did not. Sholl analysis revealed increased microglial process complexity in AD/WT^{HSPC} hippocampus, consistent with reduced activation. In the post-onset cohort, AD/WT^{HSPC} mice again outperformed untreated and AD/AD^{HSPC} controls across behavioral measures, while cortical and hippocampal tissue showed decreased IBA1^{+} density and increased microglial process complexity, indicating a shift toward a less activated state. These findings demonstrate that WT HSPC transplantation produces long-lasting behavioral and neuropathological benefits and retains efficacy even when initiated after disease onset, despite significant amyloid burden. This work highlights the therapeutic potential of HSPCs in AD and motivates further mechanistic studies into how HSPC-derived cells modulate microglial states and neural circuit function.

Disclosures: J. Schenck: None. **R. Plawat:** None. **R. Badell-Grau:** None. **S. Cherqui:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I am cofounder, shareholder, and a member of both the scientific board and board of directors of Papillon Therapeutics Inc.. F. Consulting Fees (e.g., advisory boards); I am the Chair of the Cystinosis Research Foundation Scientific Review Board and member of the Board of Trustees.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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

Support: NIH grant R24AG073198
NIH grant T32 GM145427

Title: Single cell profiling of Octodon degus reveals gene regulatory programs associated with Alzheimer’s disease-like phenotypes

Authors: *J. H. CHIU[1], N. R. ZEMKE[2], B. YANG[3], W. BARTOSIK[4], B. M. GARDUÑO[5], Z. TAN[6], C. HE[7], E. VELAZQUEZ[8], K. VU[9], P. LAU[3], C. URRA[10], N. C. BERCHTOLD[11], P. COGRAM[12], B. REN[13], X. XU[14];
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California Irvine, Irvine, CA; [12]University of Chile, Santiago, Chile; [13]New York Genome Center, New York City, NY; [14]Anatomy and Neurobiology, Univ California, Irvine, Irvine, CA

Abstract: Alzheimer's disease (AD) poses one of the most daunting challenges of this century for our increasingly aging global society. The genetics of AD patients have revealed two forms: a heritable form known as familial AD (FAD), caused by defined mutations, and a much more common (>95%) spontaneous form known as late-onset AD (LOAD). While the molecular basis of LOAD is not fully understood, it is known to be influenced by certain environmental and genetic risk factors. In the past few decades, scientists have successfully developed dozens of transgenic mouse models to study AD by incorporating human FAD mutations into the mouse genome. However, these FAD-derived transgenic models fail to recapitulate the temporal pathological progression of LOAD. To this end, prior research has found O. degus (degu), a Chilean rodent, to exhibit known AD protein aggregates, such as Amyloid Beta plaques, hyperphosphorylated tau, and neurofibrillary tangle-like structures specifically in the brains of behaviorally deficient animals. These striking histological similarities with LOAD patients suggests degu as a promising unconventional model organism for AD. Thus, there is a basic scientific question of teasing out the gene regulatory program that leads to these pathological deposits in degu brains, as well as a translational need to examine whether programs mirror those found in human AD pathology. To define the gene regulatory programs related to cognitive impairment and AD-like pathology, we generated single-nucleus profiles of gene expression, chromatin accessibility, DNA methylation, and 3D genome organization from the dorsal hippocampus and prefrontal cortex tissues from 14 young and 26 aged outbred degus that were cognitively and pathologically phenotyped. From our single-cell profiling, we identified transcriptional and epigenetic changes associated with behavioral impairment and AD-like pathology across each cell type. Our analysis revealed an increase in expression for genes related to innate immunity, including Complement Receptor 1 in multiple neuronal cell types. For these genes, we identified putative enhancers with accessibility and DNA methylation dynamics associated with cognitive impairment. In the aged degus, we observed a major DNA methylome change in several cell types. Interestingly, behaviorally impaired animals in young had DNA methylomes more similar to aged animals. Our study reveals transcriptomic and epigenomic features associated with AD-like phenotypes in degus reflective of human AD, highlighting the potential for degu as a powerful unconventional model organism for AD research.

Disclosures: J.H. Chiu: None. **N.R. Zemke:** None. **B. Yang:** None. **W. Bartosik:** None. **B.M. Garduño:** None. **Z. Tan:** None. **C. He:** None. **E. Velazquez:** None. **K. Vu:** None. **P. Lau:** None. **C. Urra:** None. **N.C. Berchtold:** None. **P. Cogram:** None. **B. Ren:** None. **X. Xu:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.28/LBP058

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

Support: K99AG070390

Title: Neuropathological and Functional Impact of Astrocyte-Derived Extracellular Vesicles in an Aged Model of Alzheimer's Disease

Authors: B. G. QUACH[1], S. SALEHI[2], J. B. FLORIO[3], R. RISSMAN[4], *C. N. WINSTON[5]; [1]Neuroscience and Physiology, USC's Alzheimer's Therapeutic Research Institute, San Diego, CA; [2]Physiology and Neuroscience, Keck School of Medicine at USC, San Diego, CA; [3]USC's Alzheimer's Therapeutic Research Institute, San Diego, CA; [4]Physiology and Neuroscience, Alzheimer's Therapeutic Research Institute, University of Southern California, San Diego, CA; [5]Keck School of Medicine at USC, San Diego, CA

Abstract: Extracellular vesicles (EVs) are cell-derived vesicles bound by a lipid bilayer that carry various cargoes including proteins, lipids, miRNAs, and nucleic acids. Under pathological conditions, EVs can contribute to neurodegeneration. Plasma neuronal-derived EVs (NEVs) from patients with mild cognitive impairment (MCI) and Alzheimer's disease (AD) have been shown to induce tau accumulation and neurodegeneration in healthy mice, suggesting high pathogenic potential. Astrocytes, typically thought to be neuroprotective, may also release EVs that influence disease progression. We isolated plasma EVs from control, MCI, and AD patients and enriched astrocyte-derived EVs (AEVs) via anti-human GLAST immunocapture. Purity was confirmed with flow cytometry, nanoparticle tracking analysis (80-100 nm), and super-resolution microscopy for canonical EV tetraspanins (CD63, CD81, and CD9). We hypothesized that AEVs derived from control patients would attenuate neuropathology while AEVs from MCI and AD patients would exacerbate AD-like neuropathology in aged PSAPP mice. AEVs samples were pooled by cohort and unilaterally injected into the right hippocampus of 6-month-old female PSAPP mice, when amyloid plaques begin to accumulate. Six months post-injection, behavioral, biochemical, and neuropathological analyses were performed. Rotarod assessment revealed a statistically significant impairment in motor coordination in mice receiving AD- and MCI-AEVs compared with those receiving control-AEVs. Cognitive impairments as measured by the Morris water maze were observed in AD and MCI-AEV injected mice as compared to control AEV-injected mice however, no overt changes in amyloid plaque burden and neuroinflammation as measured by 6E10 and GFAP staining, respectively, was observed across all three AEV-injected cohorts. Moreover, immunoblotting using 82E1 and 22C11 antibodies confirmed that levels of Aβ and AAP remained unaltered in all AEV-injected mice. Notably, analysis of cerebellar synaptic activity via SY-38 staining, a correlate for motor function, also showed no reduction in the MCI and AD-AEV injected cohorts. Collectively, these results suggest that while plasma AEVs from healthy individuals may possess neuroprotective properties that preserve motor and cognitive function, they do not appear to mitigate established amyloid brain pathology in vivo. Future investigations will involve the proteomic profiling of these AEVs to elucidate the molecular mechanisms underlying these divergent effects.

Disclosures: B.G. Quach: None. **S. Salehi:** None. **J.B. Florio:** None. **R. Rissman:** None. **C.N. Winston:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.29/LBP059

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

Title: Neuroprotective function of astrocyte p75NTR in Alzheimer Disease through regulation of cholesterolmetabolism

Authors: *X. HAN;
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Abstract: Reactive astrogliosis in Alzheimer's Disease (AD) involves profound changes in the morphology, metabolism and secretion profile of astrocytes, but whether astrogliosis is beneficial or harmful, and under which conditions, remain open questions. Here we report an unexpected neuroprotective function of death receptor $p75^{NTR}$ in astrocytes through its ability to regulate cholesterol metabolism. AD knock-in mice expressing signaling-deficient $p75^{NTR}$ variants in astrocytes showed enhanced Aβ burden, brain histopathology and cognitive impairment, even when variants were introduced late in the disease process. Astrocytes expressing dysfunctional $p75^{NTR}$ variants showed impaired uptake of Aβ oligomers, and their conditioned medium enhanced Aβ production in AD neurons. $p75^{NTR}$ signaling negatively regulated astrocyte cholesterol biosynthesis and secretion, while cholesterol depletion restored Aβ uptake in mutant astrocytes and reduced Aβ production in AD neurons. In agreement with the role of astrocyte-derived cholesterol, statin treatment reverted the effects of astrocyte $p75^{NTR}$ mutants on AD neuropathology. Thus, although neuronal $p75^{NTR}$ has been widely recognized to amplify AD, astrocyte $p75^{NTR}$ plays a neuroprotective role

Disclosures: X. han: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.30/LBP060

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

Title: Computational neuroscience and machine learning analysis for understanding sex-specific differences in microglial morphology and cognitive function in Alzheimer's disease

Authors: *A. SRIRAM[1], S. M. ATTILI[2], P. SESHAIYER[3];
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Abstract: Alzheimer's disease (AD) disproportionately affects women, with females accounting for approximately two-thirds of all dementia cases (Rajan et al., 2021). Despite this striking disparity, the influence of biological sex on AD pathology and behavioral outcomes remains underexplored (Kolahchi et al., 2024). Microglia—the brain's resident immune cells—are critical for synaptic regulation, and their morphology reflects shifts in functional state. Therefore, detailed morphological analysis offers critical insight into how microglia influence AD pathology. In this study, we performed a computational investigation quantitatively comparing hippocampal microglial morphology and cognitive performance in female and male 5xFAD mice, a transgenic AD model, and their wild-type controls. Leveraging digitally reconstructed cells from NeuroMorpho.org, we analyzed >6,000 cells (AD n=4,834; Control n=1,176) using ten morphometrics; we further integrated 5-Choice Serial Reaction Time Task (5CSRTT) data from MouseBytes, an open-access rodent touchscreen database (Female: AD n=394, Control n=1289; Male: AD n=598, Control n=1028) to examine behavioral and morphological changes in 5xFAD mice during gender stratification. Except for the number of neurites, all morphometrics differed significantly between AD and Control groups (Welch's t-test, $p < 0.0001$). Principal component analysis (PCA) identified soma size and branching-based metrics as top contributors to PCA axes. Supervised models (random forest, gradient boosting; 5-fold CV) classified cells with 96% accuracy, while SHapley Additive exPlanations (SHAP) identified segments, soma radius, and segment length as key features in classification. Gender stratification revealed stronger AD-related effects in females (e.g. ~44% decrease in bifurcations and sections from control to AD), while males showed smaller changes across the same features. Analysis of 5CRSTT data revealed that males had larger differences in average threshold accuracy and average threshold condition, while females showed significantly larger differences in total perseverative correct responses (~34% decrease). ANOVA revealed that group (AD vs. Control) accounted for most variance in both morphology and behavioral metrics. Together, these results indicate that AD alters microglial morphology and cognitive performance in a sex-dependent manner, with females showing greater structural differences and both males and females exhibiting distinct behavioral deficits. These findings highlight the importance of considering sex in AD research and may inform the development of targeted, sex-specific interventions.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.31/LBP061

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

Support: IBS-R001-D2
HU23C0018
RS-2023-KH137130
RS-2023-00261784
2022R1A2C3013138

Title: Hemoglobin as a pseudoperoxidase and drug target for oxidative stress-related diseases

Authors: *W. WON[1], H. CHUN[2], S.-J. OH[3], H. RYU[4], A. PAE[5], C. LEE[6];
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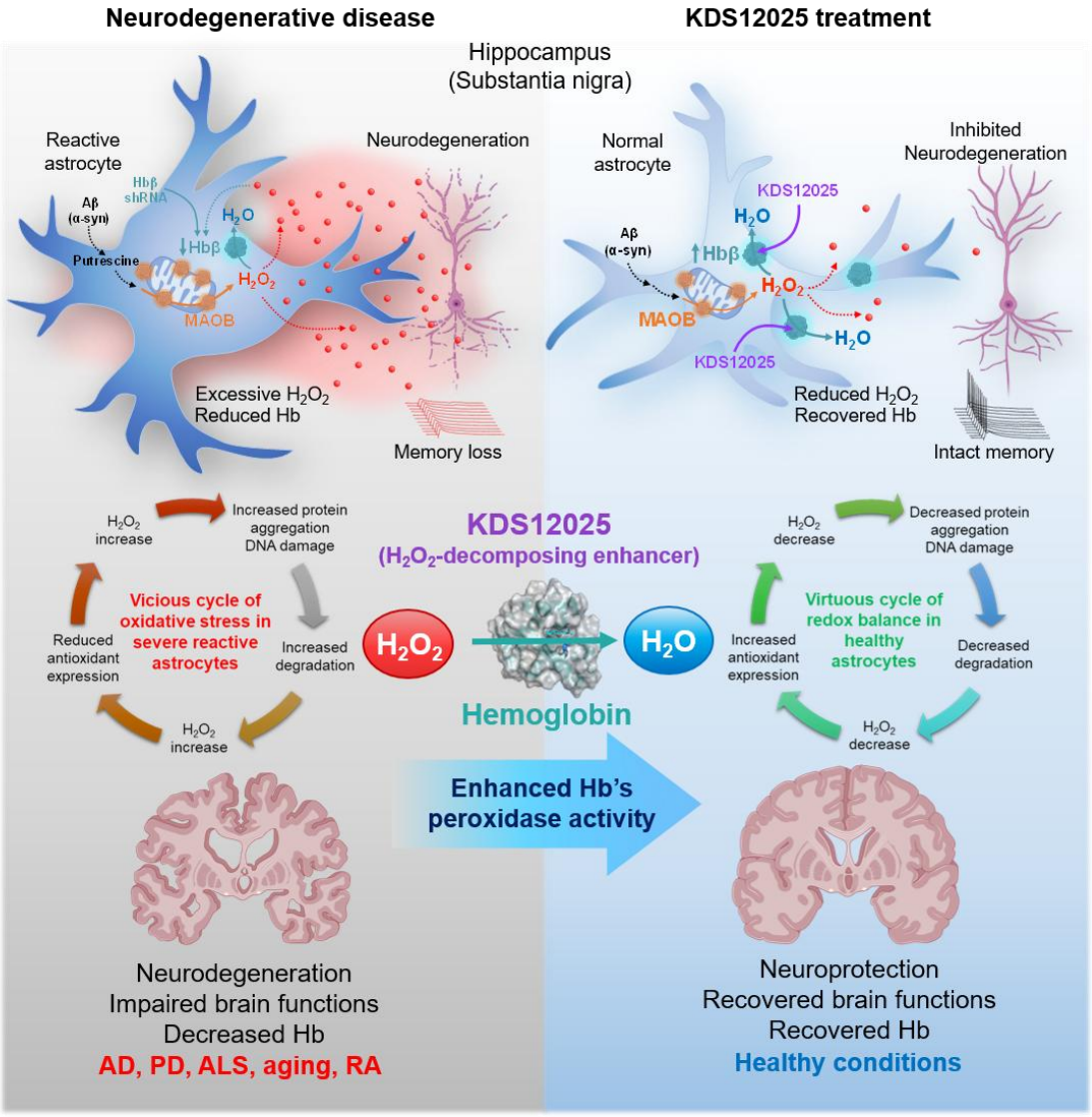
Abstract: Hemoglobin (Hb) is well known for transporting oxygen in the blood, but its role in the brain remains poorly understood. Here, we identified Hb in the cytosol, mitochondria, and nuclei of hippocampal and substantia nigra astrocytes and dopaminergic neurons. As a pseudoperoxidase, Hb decomposes hydrogen peroxide (H_2O_2) and mitigates H_2O_2-induced oxidative damage. However, in Alzheimer's disease, Parkinson's disease, and aging, excessive H_2O_2 diminishes astrocytic Hb, perpetuating a vicious cycle of oxidative stress and neurodegeneration. To counter the harmful effects of aberrant H_2O_2 production in diseases, we developed KDS12025, a BBB-permeable small molecule that enhances Hb pseudoperoxidase activity 100-fold, even at a low level of Hb. KDS12025 and its analogs achieve this enhancement through its electron-donating amine group, possibly stabilizing the complex between Hb, H_2O_2, and KDS12025. KDS12025 reduces astrocytic H_2O_2, alleviates astrogliosis, normalizes Hb, and reverts to a virtuous cycle of redox balance, preventing neurodegeneration without altering the oxygen-transport function of Hb. Gene silencing of Hb abrogates the impact of KDS12025 in both culture and animal models, confirming the necessity of Hb for the effects of KDS12025. KDS12025 extends survival and improves motor function even in severe amyotrophic lateral sclerosis and aging. Furthermore, the enrichment of astrocytic Hb in the nucleolus highlights a novel antioxidative mechanism potentially protecting against nuclear oxidative damage. Our findings suggest that Hb is a new therapeutic target for neurodegenerative diseases, with KDS12025 emerging as a first-in-class approach that enhances Hb pseudoperoxidase activity to reduce H_2O_2. Increasing Hb pseudoperoxidase activity with KDS12025 mitigates oxidative stress and alleviates neurodegeneration in AD, PD, and ALS patients and increases the degree of aging, with broad applicability for numerous oxidative-stress-driven diseases.



Disclosures: **W. Won:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); University of Washington. **H. Chun:** None. **S. Oh:** None. **H. Ryu:** None. **A. Pae:** None. **C. Lee:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.32/LBP062

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

Support: NIH Grant PAR22220

Title: Severe COVID-19/Acute Lung Injury (ALI) influences Neurodegeneration and Neurodegenerative Disease Pathology

Authors: *J. OGU[1], W. CHIANG[2], H. A. GELBARD[3];
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Abstract: Despite moving on from the SARS-CoV-2 pandemic as an unprecedented public health crisis, morbidity (i.e., Long-COVID) continues to present major challenges to healthcare. Specifically, it remains unclear how respiratory illness from SARS-CoV-2 and neuroinflammation (i.e., NeuroPASC) are associated with neurodegenerative disorders, such as Alzheimer's or Parkinson's Disease. SARS-CoV-2 induces a strong peripheral immune response in multiple organ systems, but peripheral factors that lead to neuroinflammation with neurodegenerative disorders, particularly in the elderly, still need to be elucidated. Thus, I hypothesize that fibrinogen, a precursor to fibrin that is crucial for hemostasis, when bound to SARS-CoV-2 spike protein, promotes immune cell recruitment to prime the premorbid brain for the pathogenesis of neurodegenerative disease. I explored this hypothesis using a transwell co-culture system to simulate the dynamic interactions between primary rat hippocampal neurons maintained with intact endothelial cell monolayers as part of the blood-brain barrier (BBB). Additionally, using a previously published structural and functional quantum dot biomimetic for SARS-CoV-2 (COVID-QDs), I investigated both independent and combinational roles for COVID-QDs and fibrinogen in driving BBB-hippocampal neuroimmune crosstalk *in vivo* and *in vitro*. These experiments model how SARS-CoV-2 spike protein and fibrinogen, together, traverse the blood-brain barrier to induce vascular damage in the healthy brain, increasing one's risk for neurodegenerative diseases like Alzheimer's and Parkinson's Disease.

Disclosures: J. Ogu: None. **W. Chiang:** None. **H.A. Gelbard:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.33/LBP063

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

Support: Coins for Alzheimer's Research Trust (CART) 8880-1041-00

Title: Investigating the role of caldesmon in pericyte-mediated Alzheimer's disease pathology

Authors: *Y. RODRIGUEZ[1], A. J. BAUMAN[2], A. ROBERTS[2], J. KIM[2], A. KNOTT[2], B. BAEZ-FORTUNATO[2], S. CHANEY[1], C. CHURCH[3], A. HINIKER[3], A. R. NELSON[1];
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Abstract: Alzheimer's disease (AD) is among the top ten causes of death worldwide. Emerging evidence implicates blood-brain barrier (BBB) dysfunction as an early contributor to many neurodegenerative disorders, including AD. Pericytes, contractile cells that envelop capillaries, play a critical role in maintaining BBB integrity by regulating cerebral blood flow and facilitating the clearance of neurotoxic proteins. Pericyte loss and dysfunction have been linked to increased BBB permeability, impaired amyloid-β clearance, and elevated neuroinflammation, all of which are key features of AD pathogenesis. To investigate molecular signatures of pericyte dysfunction in AD, we analyzed a publicly available RNA-seq dataset from human cortex and hippocampus, comprising vascular and perivascular cells from control and AD samples. Caldesmon emerged as a differentially expressed gene in pericytes, prompting further investigation into its role in pericyte physiology. We employed pericyte experiments *in vitro* with caldesmon silencing to determine the functional consequence of decreased caldesmon levels in pericytes. We also performed human post-mortem fluorescence brain tissue staining and imaging to assess how levels of caldesmon are altered with AD pathogenesis. Knockdown of caldesmon *in vitro* caused increased KCl-induced contractility but did not affect pericyte viability. Our preliminary studies revealed a decrease in caldesmon levels in pericytes in mild-cognitive impairment and AD compared to cognitively normal controls in the cortex and hippocampus. When evaluating post-mortem tissue from AD-diagnosed subjects of low, medium, or high levels of AD pathology (Braak & Braak staging), we found that increasing AD pathology does not alter caldesmon levels in the frontal cortex. Our findings suggest that caldesmon modulates pericyte contractility, and its reduction enhances pericyte contraction. While caldesmon expression does not appear to be altered by AD pathogenesis, the limited number of samples from cognitively normal individuals in our study limits definitive conclusions. These results support additional research with a larger cohort to explore caldesmon and related pathways in the earlier stages of dementia (e.g., mild cognitive impairment) compared to cognitively normal controls. Also, exploration of caldesmon's role in other neurodegenerative disorders characterized by impaired cerebral blood flow and/or neurovascular dysfunction may offer more mechanistic insights.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.34/LBP064

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

Title: APOE4 accelerates glycolytic metabolism and lipid accumulation in human iPSC-derived vascular endothelial cells

Authors: *M. BAMKOLE[1], Y. INOUE[1], T. KANEKIYO[2];
[1]Neuroscience, Mayo Clinic, Jacksonville, FL; [2]Neuroscience, Mayo Clinic Jacksonville, Jacksonville, FL

Abstract: *APOE* genotype is a major determinant of Alzheimer's disease (AD) risk, but the impact of *APOE4* on the metabolism in vascular endothelial cells remains poorly defined. Cerebrovascular endothelial cells forming blood-brain barrier (BBB) are uniquely vulnerable to metabolic stress compared to peripheral endothelium, suggesting that *APOE* genotype may differently influence barrier physiology. To test this, we differentiated isogenic human induced pluripotent stem cells (iPSCs) carrying homozygous *APOE3* or *APOE4*, and *APOE* knockout (KO) iPSCs into vascular endothelial cells.When mitochondrial respiration was assessed using Seahorse stress tests, the oxygen consumption rate (OCR) showed no significant differences between *APOE* genotypes. In contrast, extracellular acidification rate (ECAR) revealed increased glycolytic activity in vascular endothelial cells derived from *APOE4* and *APOE* KO iPSCs compared to those with *APOE3*. We also found the exacerbated lipid droplet accumulation in the vascular endothelial cells by *APOE4*.In addition, no significant differences were detected between *APOE* genotypes in the barrier integrity evaluated using transendothelial electrical resistance (TEER) and tight junction protein expression levels, indicating that metabolic alterations did not translate into overt structural disruption under baseline conditions.These findings demonstrate that *APOE* genotypes selectively influence vascular endothelial glycolysis and lipid storage without affecting oxidative metabolism or baseline barrier integrity. Increased glycolytic flux and lipid droplet accumulation in APOE4 vascular endothelial cells may represent early metabolic adaptations that predispose brain endothelium to cerebrovascular vulnerability in AD.

Disclosures: M. Bamkole: None. **Y. Inoue:** None. **T. Kanekiyo:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.35/LBP065

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

Support: NIA Grant AG067049

Title: Knockdown of ABHD17a, a neuronal depalmitoylating enzyme, as a potential new treatment for Alzheimer's disease

Authors: *H. KARTHIKEYAN[1], C. XU[2], S. DE LA ROSA[3], A. SNYDER[4], Y. DU[5], K. B. DORE[6];
[1]University of California, San Diego, La Jolla, CA; [2]Harker School, Cupertino, CA; [3]University of California, San Diego, San Diego, CA; [4]Neurosciences, University of California San Diego,

San Diego, CA; [5]Department of Neurosciences, University of California San Diego, La Jolla, CA; [6]Neurosciences, UCSD Dept. of Neurosciences, La Jolla, CA

Abstract: Synaptic loss is the earliest and primary biomarker of Alzheimer's Disease (AD). This synaptic loss is closely associated with PSD-95, a key synaptic scaffolding protein. PSD-95 is regulated by palmitoylation, a post-translational lipid modification. We previously demonstrated that inhibiting depalmitoylating enzymes using Palmostatin B rescues memory-related behaviors and synaptic deficits in APP/PS1 AD model mice. Since Palmostatin B is an inhibitor of several depalmitoylating enzymes, we decided to knockdown ABHD17a, the depalmitoylating enzyme most efficient towards PSD-95 and test if this approach could enhance PSD-95 palmitoylation and rescue AD deficits. Cell culture experiments were performed to validate the efficiency of 6 shRNA sequences against ABHD17a through image analysis and Western Blotting. AAV viruses using a forebrain specific promoter and the PHB.eb capsid were produced. Mice were then retro-orbitally injected with AAV-shRNA against ABHD17a (or scrambled control virus) to compare effects of ADHD17a knockdown in female and male WT and APP/PS1 mice. After one month of expression, memory-related behavioral tests, including object location memory (OLM), novel object recognition (NOR), and Morris water maze (MWM) were conducted. Furthermore, to assess the relevance of ABHD17a to human AD, we conducted sex-specific gene expression analysis in both excitatory and inhibitory neurons across various neuronal layers using the Chan Zuckerberg CELLxGENE AD dataset and our AI pipeline. We constructed cell-type specific gene co-expression graphs from human brain RNA-sequencing data and used a graph neural network reinforced using domain knowledge to reward networks with known early AD genes and AD neuronal pathology. Preliminary results from two cohorts of 20 mice will be presented. Trends suggested that APP/PS1 mice injected with AAV-shRNA had a rescue of memory-related behavior compared to their AAV-scrambled injected counterparts, suggesting that ABHD17a knockdown rescues spatial memory in AD model mice. We observed that expression of the *ABHD17A* gene increased from Braak 0 to II, which closely mirrors early synaptic changes observed in AD. Interestingly, effects were seen earlier in females than males, both in excitatory and inhibitory neurons. While current therapies focus on late-stage symptom relief, our study aims to target early molecular events and stop disease progression before clinical onset. This integrative framework bridges computational biology with experimental neuroscience, pinpointing biomarkers like ABHD17a. Ultimately, this study is important to validate the potential of targeting ABHD17a for AD.

Disclosures: H. Karthikeyan: None. **C. Xu:** None. **S. de la Rosa:** None. **A. Snyder:** None. **Y. Du:** None. **K.B. Dore:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.36/LBP066

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

Support: NIH NIA R01 AG062655
Alzheimer's Association SAGA23-1142437
NIH 5P01AG036675-13

Title: INCREASED RISK OF MEMORY DEFICIT IN FEMALES OF A HUMANIZED MOUSE MODEL OF LATE-ONSET ALZHEIMER'S DISEASE

Authors: *F. DEAK[1,2], A. M. RAFIQ[2], J. B. MILLER[2,3], A. SETH[2];
[1]Augusta University, Augusta, GA; [2]Department of Neuroscience and Regenerative Medicine, Augusta University, Augusta, GA; [3]Neuroscience Graduate Program, Augusta University, Augusta, GA

Abstract: Objectives: It is not well understood, why women have higher risk of late-onset Alzheimer's disease (LOAD). To assess the sex difference in susceptibility to LOAD, we designed studies in a novel humanized mouse model of LOAD, which allowed us to compare physiological and pathological effects of beta-amyloid from mouse amyloid precursor protein (APP) and humanized APP. We focused on changes in learning and memory and synaptic plasticity. Methods: We used wild-type and homozygous APP KI mice with normal expression levels of humanized Abeta sequence (generated in Dr. LaFerla's lab). We compared they behavior in open field, novel object, social interaction and marble burying tests at adult and old ages to WT mice. We also tested their learning and working memory by analyzing their performance in Y maze and radial arm water maze tests. We measured synaptic plasticity from hippocampal LTP using multi-electrode arrays. We also imaged synaptic neurotransmitter release using FM fluorescence dyes to estimate the size of vesicular pools. Results: We detected age and sex specific differences in behavior of APP KI mice. Adult APP KI mice were not cognitively impaired. At one-year of age, the most striking phenotype was their decreased social interactions. At 2-year of age, only female APP KI mice performed worse in RAWM, indicating impaired memory. Female APP KI showed marked impairment of LTP in hippocampal CA1 region. We found synaptic dysfunction and altered vesicular release also in cortical neurons of APP KI mice. No sex specific change in synaptic connections were detected at this age, and no senile plaques were present in the brain of APP KI mice. Conclusions: Exchanging mouse to human sequence of beta-amyloid in APP had subtle behavioral changes in young and adult age of homozygous APP KI mice and altered their synaptic function, which led to impaired synaptic plasticity at 18 months of age as well as learning and memory underperformance in female APP KI mice. Thus, this novel humanized AD model recaptures the higher risk of LOAD in females.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.37/LBP067

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

Title: The catechol structure of catecholamines rescues memory and synaptic function by reducing amyloid burden in an Alzheimer's disease mouse model.

Authors: *E. H. ORTIZ[1], D. GÁLVEZ-MÁRQUEZ[2], L. LANDA NAVARRO[3], M. TAPIA-RODRIGUEZ[4], F. BERMUDEZ-RATTONI[5], P. MORENO-CASTILLA[6];
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Abstract: Recent advancements in immunotherapies Alzheimer's disease (AD) have successfully reduced amyloid-beta (Aβ) deposits in the brain. However, these therapies often show limited cognitive improvement, highlighting the need for complementary therapeutic approaches that address amyloid pathology and synaptic function. Targeting endogenous molecules that naturally modulate Aβ aggregation is a promising yet underexplored approach. Catecholamines, known for regulating cognition, motivation, and synaptic plasticity, also contain a catechol moiety—a chemical structure that modulates protein-protein interactions. In vitro studies suggest that catechol molecules interfere with Aβ aggregation. However, whether these properties translate into effective Aβ reduction and cognitive improvement in AD mouse models remains unclear. In this study, we aim to fill this gap by evaluating the effects of systemic treatment with catechol on Aβ burden and memory performance in the triple transgenic AD mouse (3xTgAD) model. We developed a systemic treatment of catechol over 20 days, and we observed decreased hippocampal Aβ levels, improved spatial memory, and restored synaptic plasticity in the Schaffer collateral-CA1 pathway dose-dependent. Moreover, we observed an increase in basal extracellular dopamine levels within the CA1 dorsal hippocampus after the systemic treatment. Our results emphasize the dual role of catecholamines, decreasing amyloid pathology and restoring catecholaminergic activity to support cognitive processes. These results highlight a novel therapeutic avenue bridging the gap between amyloid clearance and cognitive recovery.

Disclosures: E.H. Ortiz: None. **D. Gálvez-Márquez:** None. **L. Landa Navarro:** None. **M. Tapia-Rodriguez:** None. **F. Bermudez-Rattoni:** None. **P. Moreno-Castilla:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.38/LBP068

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

Support: NIH/NIA R01AG063857
AHA SURF

Title: Frontal Connectivity Asymmetry During Task Switching for Cognitively Healthy Individuals with Low and High plasma pTau-217 levels

Authors: M. DEVER[1], A. AL-EZZI[1], I. MAN[2], D. BUENNAGEL[3], X. WU[4], N. ASTRAEA[4], R. KLONER[5], ***X. ARAKAKI**[6,7];
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Abstract: Introduction: We previously reported increased frontal alpha connectivity during task switching in those with early Alzheimer's disease (AD) pathology (CSF amyloid/tau ratios). Recently, plasma p-tau217 has been established as a reliable biomarker for early AD pathology. As AD pathology has shown asymmetrical burden in frontal regions, we explored left frontal and right frontal alpha functional connectivity with elevated plasma p-tau217. **Methods:** Seventy-five cognitively healthy (CH) individuals over age 60 were recruited under an IRB-approved protocol and plasma pTau-217 was measured by electrochemiluminescence. Electroencephalogram (EEG) was recorded during resting state (eyes closed (EC) and eyes open (EO)), and a task-switching paradigm (repeat = low load; switch = high load) using a 21-sensor dry electrode headset. Based on tertiles, participants with low (2.57 ± 0.50 pg/mL) and high (10.77 ± 4.94 pg/mL) pTau-217 were compared for functional connectivity (FC) analysis using Partial Directed Coherence (PDC) from EEG. Group comparisons were performed by effect size, calculated by Cohen's *d* (>0.5: Medium size). **Results**: Demographic comparisons revealed no significant differences in age, sex, or education between low- and high-pTau-217 groups. Behavioral performance—accuracy and response times—also did not significantly differ across groups during repeat or switch trials. With FC analysis, the high pTau-217 group showed increased connectivity with medium to large effect size from the left frontal region during eyes open compared to the low tertile group (0.156 ± 0.014 vs. 0.145 ± 0.021, Cohen's $d = 0.63$). Conversely, the high tertile group exhibited greater connectivity with medium to large effect size from the right frontal region during low-load task switching test (0.192 ± 0.052 vs. 0.164 ± 0.041, Cohen's $d = 0.58$). No other significant group differences were observed across regions or

conditions. **Conclusions:** These exploratory results suggest that the alpha functional connectivity in CH individuals with early AD pathology was greater in left frontal region during rest and was increased in right frontal region during cognitive challenge. Although confirmation with larger sample size is required, pilot analysis suggested dynamic asymmetrical changes in frontal brain with early AD pathology in CH older adults.

Disclosures: M. Dever: None. **A. Al-Ezzi:** None. **I. Man:** None. **D. Buennagel:** None. **X. Wu:** None. **N. Astraea:** None. **R. Kloner:** None. **X. Arakaki:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.39/LBP069

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

Support: Alzheimer's Association Grant (AARG-24-1309896 to AS-P)
Fundación Ramón Areces (Research Fellowship to NR-L)

Title: Real-World Comparison of Brain [^{18}F]FDG-PET Imaging with CSF AD Biomarkers in a Tertiary Memory Clinic Setting

Authors: *N. RABANEDA-LOMBARTE[1], J. FERRARI-SOUZA[1,2], A. SERRANO-POZO[1]; [1]Massachusetts General Hospital & Harvard Medical School, Boston, MA; [2]Universidade Federale do Rio Grande do Sul, Porto Alegre, Brazil

Abstract: Background: While brain [^{18}F]FDG-PET imaging remains widely used to evaluate cognitive decline worldwide, data on its diagnostic performance against gold-standard CSF Alzheimer's disease (AD) biomarkers are scarce. We assessed the agreement between brain [^{18}F]FDG-PET and CSF AD biomarker results in a real-world tertiary memory clinic setting. **Methods:** We queried Mass General Brigham electronic health records to capture patients with cognitive concerns and both [^{18}F]FDG-PET brain imaging and CSF AD biomarkers. [^{18}F]FDG-PET results were categorized as Normal, Abnormal Non-conclusive, Abnormal Not AD-like, or Abnormal AD-like, based on narrative reports. CSF AD biomarker panel results were classified as Not Consistent with AD, Equivocal, or Consistent with AD following lab report. Performance of [^{18}F]FDG-PET against CSF AD biomarkers was tested with Fisher's exact and kappa agreement tests. The correlation between [^{18}F]FDG-PET and CSF AD biomarker results was further examined via regression models. **Results:** Among 360 eligible individuals, 151 had a CSF Consistent with AD, 136 Equivocal, and 73 Not Consistent with AD. 73/151 (48.3%) subjects with CSF Consistent with AD had an Abnormal AD-like [^{18}F]FDG-PET pattern, whereas 30/73 (41.1%) with CSF Not Consistent with AD had a Normal [^{18}F]FDG-PET scan. However, 19/151 (12.6%) individuals with CSF Consistent with AD had a Normal [^{18}F]FDG-PET scan (false negatives) and 8/73 (11.0%) with CSF Not Consistent with AD had an Abnormal AD-like [^{18}F]FDG-PET scan (false positives), resulting in 0.48 sensitivity, 0.84

specificity, 0.68 PPV, 0.69 NPV, and κ=0.334 (fair agreement). An Abnormal AD-like [^{18}F]FDG-PET independently predicted a CSF Consistent with AD (OR=4.82, p<0.001) and a lower Amyloid-Tau Index (β=-0.43, p<0.001). [^{18}F]FDG-PET false positives were later diagnosed with FTLD (n=3), DLB (n=1), DLB+AD (n=1), vascular dementia (n=1), and mood plus alcohol use disorder (n=1); all [^{18}F]FDG-PET false negatives were finally diagnosed with AD. Posterior cingulate gyrus hypometabolism independently predicted an Abnormal AD-like [^{18}F]FDG-PET result (OR=6.38, p<0.0001) and a CSF Consistent with AD (OR=2.47, p=0.0004), whereas frontal hypometabolism predicted a Not AD-like [^{18}F]FDG-PET result (OR=5.95, p<0.0001) but did not predict a CSF Not Consistent with AD (OR=0.41, p=0.0022). **Conclusions:** [^{18}F]FDG-PET imaging has high specificity but limited sensitivity to identify AD as defined by CSF biomarker criteria. Although a typical AD-like [^{18}F]FDG-PET pattern of hypometabolism predicted a positive CSF AD biomarker panel, in this clinical setting the agreement between both tests was only fair.

Disclosures: N. Rabaneda-Lombarte: None. **J. Ferrari-Souza:** None. **A. Serrano-Pozo:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.40/LBP070

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

Support: NIH GR1053713
Zilkha Neurogenetic Institute

Title: Repeated FUS+MB induced BBB opening in young (2-4mo) C57BL/6J and Tg5XFAD mice using DCE-MRI

Authors: *N. S. SANTA MARIA[1], S. W. LIN[2], X. LIU[3], T. NGUYEN[4], R. E. JACOBS[2]; [1]Physiology and Neuroscience, University of Southern California, Los Angeles, CA; [2]Zilkha Neurogenetic Institute, USC Keck School of Medicine, Los Angeles, CA; [3]University of California, San Francisco, San Francisco, CA; [4]School of Engineering and Applied Science, University of California, Los Angeles, Los Angeles, CA

Abstract: Focused ultrasound with intravenously injected microbubbles (FUS+MB) have been shown to transiently open the blood-brain barrier (BBB) allowing drugs and diagnostic agents to cross into the brain. We determined whether there are lasting effects in BBB permeability using dynamic contrast enhanced MRI (DCE-MRI) following repeated FUS+MB induced BBB opening in young (2- to 4-months-old) control C57BL/6J and Tg5XFAD mice. We measured hippocampal permeability constant (Ktrans, 1/min) using DCE-MRI in a 7T MRI scanner (MR Solutions) as a quantitative correlate of BBB integrity, before and after administration of repeated FUS+MB. The ultrasound system has an eight-element annular array transducer

(diameter= 25 mm, natural focal point = 20 mm; aperture (F) = 0.8), center frequency = 1.5 MHz) coupled to the shaven mouse head with ultrasound gel (Aquasonic). The ultrasound parameters were 0.44 - 0.51 MPa pressure accounting for skull attenuation (18%), 10 ms pulse duration (1% duty cycle), and 1 Hz pulse repetition frequency for 90 pulses. To target FUS+MB to the bilateral dorsal hippocampus regions we used a 3D FLASH sequence with the following parameters: TR/TE=ms/5ms, FOV=32x32x32mm, FA=15, matrix size = 96x96x32, NA=4. DCE-MRI involved a 2D T1-weighted variable flip angle FLASH (to generate bias corrected T1 map) and a 2D dynamic FLASH with the following parameters: TR/TE=19ms/4ms, FA=15, temporal resolution = 3.7s, FOV=15x15mm, matrix size = 192x192, 1mm slice thickness, with a 15 min total scan duration (3 min baseline and 12 min post Gd-DTPA (1:6 dilution in saline, 0.3-0.4 mmol/kg) injection via the tail vein). To characterize FUS+MB parameters and BBB opening duration, 2mo C57BL/6J mice (n=9) underwent DCE-MRI before, and 1hr, 24hr, and 1-2weeks after FUS+MB. We observed hippocampal Ktrans significantly increased 1 hour following sonication (0.00416 ± 0.00019 1/min) compared to baseline (0.00146 ± 0.00096 1/min). At 24h (Ktrans = 0.00191 ± 0.00153 1/min) and 1-2 weeks (Ktrans = 0.00124 ± 0.00082 1/min) post FUS+MB, Ktrans values were comparable to baseline values. To determine whether repeated FUS+MB induced openings affect BBB permeability over time in Tg5XFAD mice, we measured DCE-MRI Ktrans in the cortical and hippocampal regions at the focus sites at pre (2mo) and post (4mo) timepoints after two FUS+MB (3.5 weeks apart). No significant differences were observed between the baseline Ktrans at 2mo and at 4mo following repeated FUS+MB in control C57BL/6J and Tg5XFAD. We demonstrate FUS+MB parameters that allow repeated transient BBB opening without lasting alterations in BBB integrity in young C57BL/6J and Tg5XFAD mice.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.41/LBP071

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

Support: MBD Fellowship, Georgia State University

Title: Sex-Dependent Gray Matter Atrophy in Alzheimer’s Disease Progression

Authors: *C. MUKHERJEE[1], M. DHAMALA[1], S. BAJAJ[2], B. M. ADHIKARI[3];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder marked by cognitive and functional decline, with **mild cognitive impairment (MCI)** as a transitional stage. This study examined **sex-specific grey matter volume (GMV) differences** across healthy controls (HC), MCI, and AD using high-resolution structural MRI data from 332 participants in the Alzheimer's Disease Neuroimaging Initiative. Whole-brain parcellation into 82 regions revealed a significant **group-by-sex interaction** [$F(164, 488) = 1.42$, $p = 0.002$, $\eta p^2 = 0.32$], with ten regions showing notable sex-dependent effects. Volumetric trajectories revealed clear sex-specific patterns across disease stages. In HC, males and females had comparable GMVs. From HC to MCI, females showed relative stability, while males exhibited moderate decline. However, from MCI to AD, females experienced steep and widespread GMV loss, in contrast to the slower, region-specific changes seen in males. Females showed significantly greater GMV reductions than males, notably in the **left frontal pole** during AD progression [$F(1,243) = 10.68$, $p < 0.001$, $\eta p^2 = 0.14$] and in the **right caudal middle frontal cortex** during MCI [$F(1,243) = 10.62$, $p < 0.001$, $\eta p^2 = 0.14$]. Females exhibited more widespread associations between grey matter volume (GMV) and cognitive and functional outcomes, as assessed by regression analyses with Mini-Mental State Examination (MMSE) and Functional Activities Questionnaire (FAQ) scores. Specifically, positive relationships were found between GMV and MMSE scores, indicating better global cognitive performance, while negative relationships were identified between GMV and FAQ scores, indicating greater functional independence.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.42/LBP072

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

Support: KHIDI HI22C1464
NIH Grant U01 AG024904

Title: Predicting amyloid beta deposition in the brain using a mathematically informed deep learning model

Authors: B. JEONG[1], ***H.-G. JEONG**[2], D. KIM[3], M. KAISER[4], C. E. HAN[3];
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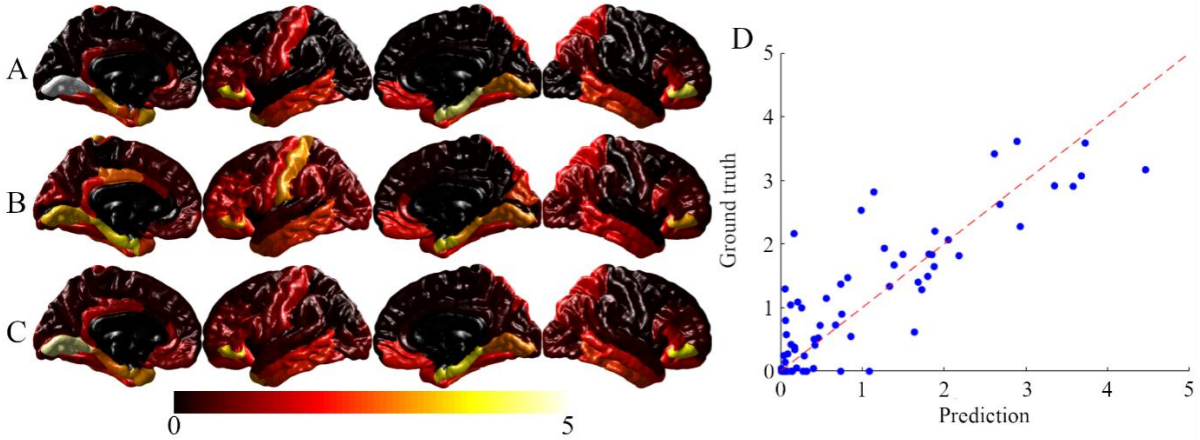
Abstract: Amyloid-β accumulation and propagation are central features of Alzheimer's disease (AD). Characterizing these dynamics is essential for understanding AD pathogenesis and progression. Computational models have been developed to simulate amyloid-β spread, yet each

has limitations: mathematical models are interpretable but inflexible, while deep learning offers predictive accuracy but often lacks biological plausibility.To address these challenges, we developed a **mathematically informed neural network (MINN)** that integrates biological mechanisms with data-driven learning to model the spatiotemporal propagation of amyloid-β in the human brain. The architecture embeds modules representing amyloid-β generation, clearance, and network-based diffusion, inspired by differential equations. Trained on longitudinal multimodal neuroimaging data, MINN simulated monthly changes in regional amyloid-β burden, accurately predicted future deposition, and reproduced established spatial staging patterns.Notably, MINN uncovered biologically plausible dynamics—such as saturation effects, delayed clearance, and declining generation and clearance rates with increasing amyloid-β burden—without explicit constraints. These emergent properties are consistent with prior clinical observations, highlighting both the interpretability and robustness of the model.By embedding domain knowledge into a neural network structure, MINN achieves predictive accuracy while preserving biological plausibility. This approach provides a data-efficient and biologically grounded framework for simulating pathological protein propagation, offering potential utility for understanding AD progression and informing therapeutic strategies.



Disclosures: B. Jeong: None. **H. Jeong:** None. **D. Kim:** None. **M. Kaiser:** None. **C.E. Han:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.43/LBP073

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

Support: NIH Grant 5T32AG076411-04

Title: Interaction of smoking and Aβ status on hippocampal volume and cognition

Authors: *A. P. RAMOS-ROLÓN[1], Z. SHI[2], S. DAS[3], J. S. PHILLIPS[3], J. A. DETRE[3], C. E. WIERS[2];
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Abstract: Significance: Alzheimer's disease (AD) is neuropathologically characterized by amyloid-β (Aβ) plaques and tau neurofibrillary tangles, yet not all Aβ+ individuals develop clinical AD or tau pathology. Tobacco smoking is a significant risk factor for AD, but the neurobiological mechanisms underlying this vulnerability remain unclear. Hippocampal atrophy, a biomarker of AD and a strong predictor of cognitive decline, is also observed in smokers, even in younger and cognitively normal populations. Therefore, smoking may exacerbate hippocampal atrophy in Aβ+ individuals already at risk for AD. **Methods:** We analyzed data from 164 participants from the Aging Brain Cohort study of the University of Pennsylvania Alzheimer's Disease Research Center, grouped as follows: 38 Aβ- never-smokers; 63 Aβ- ever-smokers; 39 Aβ+ never-smokers; 24 Aβ+ ever-smokers. We used the Automatic Segmentation of Hippocampal Subfields toolbox to quantify the gray matter volume of the anterior and posterior hippocampus. We then evaluated the smoking × Aβ status interaction on Montreal Cognitive Assessment (MoCA) scores and on the anterior and posterior hippocampal volumes. Covariates included age and sex for all models, and intracranial volume for hippocampal volume models. Lastly, we tested whether hippocampal volumes mediated the relationship between Aβ status and MoCA scores, and if this mediation was moderated by smoking status. **Results:** There was a significant smoking × Aβ status interaction on MoCA scores [$F_{1,158} = 8.2$, $p = 0.0048$], such that MoCA scores were lower in ever-smokers compared to never-smokers within the Aβ+ group, but not within the Aβ- group. We also found a similar smoking × Aβ status interaction for posterior (but not anterior) hippocampal volume [$F_{1,156} = 4.5$, $p = 0.0345$]: Aβ+ ever-smokers had lower posterior hippocampal volume than Aβ+ never-smokers, whereas no such difference was observed in the Aβ- group. Lastly, posterior hippocampal volume significantly mediated the relationship between Aβ status and MoCA score, with the mediation effect being more pronounced among ever-smokers than never-smokers. **Conclusion:** Smoking is associated with poorer cognitive performance and lower posterior hippocampal volume in Aβ+ individuals. Posterior hippocampal volume mediates the relationship between Aβ status and cognition, suggesting that posterior hippocampal atrophy may be a marker of increased vulnerability to cognitive impairment in AD due to smoking. Future studies should examine whether smoking contributes to hippocampal atrophy through AD-related pathology (Aβ/tau) or through non-AD pathways such as vascular or ischemic processes.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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

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NIH/NIMH BRAIN Initiative grant U01 MH117079
NIH/NIMH BRAIN Initiative grant RF1MH128888

Title: Mapping Axonal Pathology in AD Mice at Single-Neuron Resolution with Ultrasparse Labeling and Light-Sheet Imaging

Authors: *C. LEE[1,2], C. S. PARK[1,2], M. S. AKRAM[1,2], A. S. DE LA ROCHA[1,2], X. YANG[2,1,3]; [1]Center for Neurobehavioral Genetics, Semel Institute of Neuroscience and Human Behavior, University of California, Los Angeles, Los Angeles, CA; [2]Dept. Psychiatry and Biobehavioral Science, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA; [3]Brain Research Institute, University of California, Los Angeles, Los Angeles, CA

Abstract: A common feature of neurodegenerative disorders is the selective degeneration of distinct sets of vulnerable neurons; however, how neurons with complex dendritic and axonal processes undergo progressive degeneration across different diseases remains poorly understood. Here, we describe an integrated, scalable systems-level approach to label and image single-neuron, brainwide morphology and pathology in amyloid-bearing AD mice. To sparsely label single neurons, we utilized MORF3, which drives Cre-dependent stochastic expression of a membrane-bound ultrabright reporter (Veldman et al., 2020; PMID: 32795398) and previously enabled our lab to map the dendritic morphologies of over 3,700 striatal D1- and D2-neurons (Park et al., 2024; PMID: 39484488). We crossed MORF3 mice with Etv1-CreER mice and subsequently with 5xFAD mice, resulting in sparse genetic labeling of individual cortical Layer 5 Etv1+ pyramidal neurons (L5-PNs), including their complete dendritic and axonal processes. Intact brain hemispheres from double (MORF3/Etv1-CreER) and triple (MORF3/Etv1-CreER/5xFAD) transgenic mice at 4 and 7 months of age were processed using automated tissue clearing, immunostaining for the MORF reporter, and high-resolution light-sheet imaging. Our single L5-PN morphological analyses demonstrated that 5xFAD mice, but not age-matched wild-type controls, exhibit robust axonal spheroid pathology. This pathology is enriched in distinct brain regions and progressively accumulates with age. The relationships between axonal spheroids and amyloid plaques appear complex, as some spheroids are distant from plaques. Current studies are focused on deploying next-generation MORF mouse lines that enable complete dendritic and axonal imaging across diverse neuronal cell types and support genetic perturbations of labeled neurons. In parallel, we are developing a suite of bioinformatic tools to process and analyze terabyte-scale single-neuron imaging datasets, providing a streamlined systems biology framework to study single-neuron morphology and pathology.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.45/LBP075

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

Support: NIH R21AG085055

Title: Impact of Western diet-induced liver changes on Alzheimer's disease pathology in APP^{SAA}-knock-in mice

Authors: *G. C. ROULES[1], D. V. CHANDRASHEKAR[1], N. JAGADEESAN[1], J. CHU[2], M. DAHILIG[1], D. HAN[2], R. K. SUMBRIA[1,3];
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Abstract: Alzheimer's disease (AD) and obesity are linked health challenges, with obesity driven by high-fat and sugar Western diets (WD) being a major AD risk factor. Up to 90% of obese individuals develop non-alcoholic fatty liver disease (NAFLD). Liver steatosis, a hallmark of NAFLD, upregulates hepatic amyloid precursor protein (APP) and downregulates lipoprotein receptor-related protein 1 (LRP1), a key receptor for peripheral amyloid-beta (Aβ) clearance. These changes may dysregulate peripheral Aβ homeostasis, elevate brain Aβ, and exacerbate AD pathology. While the liver's role in peripheral Aβ regulation is known, how obesity-induced hepatic changes contribute to AD is unclear. Our study seeks to clarify this relationship. Two-month-old female APP^{SAA} knock-in (KI) mice carrying human Swedish, Arctic, and Austrian mutations of the APP gene, and wild-type (WT) mice were fed a WD or control diet (CD) for 4 months. APP-WT mice without SAA mutations were also used as controls. Mice were monitored for weight gain and feed intake for 4 months, and brain, liver, and plasma were assessed for Aβ and inflammation. Plasma cholesterol and body weights were significantly increased in all WD-fed mice compared to CD-fed mice. Hepatic neprilysin was significantly elevated ($p<0.05$) in WD-fed APP^{SAA}-KI and APP-WT mice. Compared to CD, WD-fed APP^{SAA}-KI mice had significantly higher soluble ($p<0.05$) and insoluble ($p<0.01$) brain Aβ40 and Aβ42, and plasma Aβ42 ($p<0.001$), an effect not observed in WD-fed APP-WT mice. Though both WD-fed APP^{SAA}-KI ($p<0.001$) and APP-WT mice ($p<0.001$) showed increased liver-to-body weight ratio compared to controls, indicative of liver injury, only the WD-fed APP^{SAA}-KI mice had elevated liver proinflammatory cytokines and plasma ALT ($p<0.05$) compared to respective CD-fed mice. Analysis of the hepatic-plasma-brain axis revealed that plasma IL-2 was negatively correlated ($p<0.05$), whereas plasma TNF-α and liver-to-body weight ratio were positively correlated ($p<0.05$), with insoluble brain Aβ40 and Aβ42. Our findings show that APP^{SAA}-KI mice are more susceptible to liver injury and brain Aβ increase than APP-WT mice, and liver injury was associated with brain Aβ. This highlights the liver-brain axis in obesity-induced AD pathology and the need to explore systemic metabolic contributions to AD.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.46/LBP076

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

Support: Larry L. Hillblom Foundation, Grant/Award Number: 2020-A-001-NET

Title: Amyloid-beta Toxicity in Human and Nonhuman Primate Neuronal Cell Cultures: Insights into Human Susceptibility to Alzheimer's Disease

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Abstract: Despite the fact that closely related species tend to experience the same, or similar, diseases, previous research suggests that Alzheimer’s disease (AD), a devastating neurodegenerative disease, may be unique to humans. Extracellular plaques composed of amyloid-beta (Aβ) are one of the hallmark pathologies of AD at the cellular level. We used an MTT cell viability assay to investigate survival differences in iPSC-derived neurons from 2 healthy human controls, 3 AD patients, 2 great ape species (chimpanzee and bonobo), and 1 catarrhine monkey species (rhesus macaque) following application of two Aβ isoforms (Aβ42 and Aβ40) commonly found in the brains of AD patients as well as typically aging primates. Two rounds of MTT assay were performed and, for each round, 8 replicates were used for each cell line/condition. Percent viabilities were then calculated against the vehicle control condition. We also quantified neuritic beading, an early hallmark of neuronal toxicity, and synaptic puncta density in human and nonhuman primate neurons to further assess variations in Aβ-induced toxicity between species. Quantification of neuritic beading was performed on fluorescence microscopy images of Map2 stained neurons imaged at 40X. 5 fields for each subject/condition were imaged. Quantification of puncta density was performed on confocal microscopy images of synapsin and Map2 stained neurons. 3 fields per sample were imaged at 63X and only puncta outlining Map2 positive neurites were counted. All quantifications of neuritic beading and puncta density were performed by an investigator blind to species/disease status. For additional insight into neuronal molecular response to Aβ-induced toxicity across species we performed RNA sequencing. Our results demonstrate an increase in cell death following application of Aβ42 in human compared to macaque cells. Additionally, neuritic beading is increased and synaptic puncta density decreased following application of Aβ42 in human, chimpanzee, and bonobo cells compared to the macaque. Analysis of RNA sequencing data reveals differences in the expression of genes involved in Aβ metabolism, apoptosis, autophagy, and cellular stress

between human and macaque cells, which may be relevant to observed differences in neuronal sensitivity to Aβ. Taken together, these results demonstrate an increased sensitivity to Aβ-induced toxicity in human neurons when compared to the macaque. These findings enhance our understanding of the neurobiology of aging across species and may offer valuable insights into the pathogenesis of AD in humans, potentially guiding the development of novel therapeutic strategies.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.47/LBP077

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

Support: NIH Grant R15GM148964

Title: Distinct aggregate structures of lysozyme exhibit differential toxicity

Authors: E. R. PICKENS[1], D. Y. DURUR[1], K. UPTON[2], J. GUSTAFSON[2], M. DIMITRUCK[2], Y. LABH[2], ***A. TIWARI**[2];
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Abstract: Over the last decade, there has been a growing emphasis on understanding the varying toxicity of protein aggregates using different model proteins. However, the toxic mechanisms involved and the differences in toxicity among various aggregated proteins remain a topic of intense debate. To investigate the link between aggregate structure diversity and toxicity, we used a non-neurodegenerative disease protein, lysozyme, as a model. To generate aggregates, 40 μM lysozyme protein at pH 7.2 was incubated at 37 °C or 65 °C, in the presence or absence of 10 mM Tris(2-carboxyethyl) phosphine hydrochloride (TCEP; a disulfide-bond reducing agent), for either 1 day or 7 days. After the incubation was complete, the aggregates were washed with MQ water to remove any dissolved buffer, salts, and other small-molecular-weight compounds. The aggregates after washing were either plated on Scanning Electron Microscope (SEM) stubs and imaged or suspended in the cell media at a range of concentrations (5 to 40 μM or higher) before treating the SH-SY5Y cells to test their effect on cell viability using the MTS assay. Our results show that the fresh lysozyme or its aggregates prepared in the absence of disulfide reducing agent, TCEP, were not toxic or very mildly toxic, irrespective of their length of incubation (1 day or 7 days) or concentrations. However, the aggregates formed under disulfide-reducing conditions exhibited concentration-dependent toxicity for both 1-day and 7-day aggregate samples when incubated at either 37 °C or 65 °C. As per Field Emission Scanning Electron Microscope (FESEM) imaging, while the general morphology of TCEP-treated lysozyme aggregates for 1 day or 7 days remains amorphous, the temperature of incubation

affects the nature of these amorphous aggregates. The lysozyme incubated at 37 °C, irrespective of the length of incubation, forms a large, amorphous, agglomerated structure. Whereas the lysozyme incubated at 65 °C forms an organized amorphous network-type structure with a smaller agglomerated structure connected to each with a prefibrillar-like structure. These aggregates formed at 37 °C or 65 °C also differ in their physical properties; aggregates at 37 °C form soft aggregates that resuspend easily in buffer upon mixing, whereas aggregates formed at 65 °C are much more challenging to resuspend. These studies offer insight into the unique physicochemical properties of aggregated proteins, which may influence cellular toxicity.

Disclosures: E.R. Pickens: None. **D.Y. Durur:** None. **K. Upton:** None. **J. Gustafson:** None. **M. Dimitruck:** None. **Y. Labh:** None. **A. Tiwari:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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Program #/Poster #: LBP071.48/LBP078

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

Support: NIH Grant R24AG073198

Title: Single cell epigenome profiling of the aging dog brain reveals gene regulatory programs associated with neurodegeneration

Authors: *K. WONG[1], J. CHIU[2], N. R. ZEMKE[3], P. LAU[4], W. BARTOSIK[5], B. M. GARDUÑO[6], N. C. BERCHTOLD[7], Z. TAN[8], E. VELAZQUEZ[9], B. YANG[4], K. VU[4], X. XU[10], B. REN[4];
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Abstract: Aging is the primary risk factor for neurodegenerative disorders such as Alzheimer’s disease, Parkinson’s disease, and amyotrophic lateral sclerosis. Yet, the most widely used model organism—mice—does not naturally develop Alzheimer’s-like pathology, underscoring the need for alternative models. Unlike mice, dogs spontaneously accumulate amyloid plaques and hyperphosphorylated tau with age, accompanied by cognitive decline that becomes prominent after 11 years of age. To define the aging gene regulatory programs in the dog brain, we generated single-nucleus profiles of gene expression, chromatin accessibility, DNA methylation, and 3D genome organization across three brain regions—the prefrontal cortex (PFC), temporal cortex (TC), and ventral hippocampus (vHIP)—from 24 animals spanning the canine lifespan (1-14 years). Aging was marked by sharp declines in GABAergic and glutamatergic neurons, astrocytes, oligodendrocyte precursors, and endothelial cells. Thousands of genes showed age-

associated dynamics, including reduced expression of cell type-specific functions and increased neuroinflammatory signatures. Epigenomic analysis revealed age-dependent gains in accessibility of bZIP transcription factor motifs, including AP-1 and CEBP, alongside widespread reprogramming of DNA methylation in glial cells of the TC and vHIP. Strikingly, aging microglia exhibited robust activation of senescence-associated gene programs. Together, our multi-omic profiling of the aging dog brain reveals cell type- and region-specific transcriptomic and epigenomic changes that parallel hallmarks of human neurodegeneration, establishing the dog as a powerful natural model for age-related cognitive dysfunction.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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Program #/Poster #: LBP071.49/LBP079

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

Support: NIH R01 AG073826-01A1

Title: Long-Term Vitamin A Supplementation Decelerates Cognitive Deficits and Anxiety-Like Phenotypes in the J20 Alzheimer’s Mouse Model

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Abstract: Previous research has demonstrated that the activity of all-trans retinoic acid (ATRA), a metabolite derived from vitamin A (VA, retinol), is compromised in human Alzheimer’s Disease (AD). ATRA has been reported to enhance α-secretase activity, thereby promoting non-amyloidogenic processing of amyloid precursor protein (APP) and potentially reducing amyloid plaque formation. We hypothesized that long-term VA supplementation decelerates AD progression and cognitive decline in an AD mouse model. Here, we utilized the J20 AD mouse model, which overexpresses human APP with familial AD-linked mutations. In this model, amyloid beta (Ab) plaque deposition becomes detectable in the hippocampus and neocortex by

~5 months of age and increases with age. J20 AD mice were weaned onto either a VA-enriched diet (20 IU/g) or a control diet (4 IU/g) and underwent a behavioral test battery at 14 ± 1 months. Cognitive, behavioral, and motor performance were evaluated using the Open Field Test (OFT), Novel Object Location and Recognition tasks (NOL/NOR), Water T-maze (WTM), and Rotarod. In the OFT, J20 mice exhibited increased locomotion and decreased time in the center zone relative to wild-type (WT) controls ($p<0.001$, 3-way RM ANOVA), consistent with an anxiety-like phenotype. During the NOL/NOR trials, discrimination indices did not significantly differ across genotypes or diet groups; however, J20 mice on the control diet spent significantly more time in the center than WT and VA-supplemented J20 mice, suggesting reduced neophobia that was normalized by VA supplementation. In the WTM, both genotype ($p<0.001$) and diet ($p=0.006$) significantly influenced latency to locate the platform during the simple discrimination phase. J20 mice on the VA-enriched diet showed significantly reduced latency compared to control-fed J20 mice ($p=0.003$), indicating improved spatial learning. During reversal learning, J20 mice exhibited increased latency ($p<0.001$), with no diet effect (ns, 3-way RM ANOVA). Main effects of sex ($p=0.001$) and genotype ($p=0.032$) were observed to affect time spent on rotarod, but performance did not significantly vary by diet group (ns, 3-way RM ANOVA). Confocal imaging revealed abundant plaques in J20 mice at 14 months; further analyses are ongoing to determine the effect of VA supplementation on Ab plaque burden. Collectively, these findings support the potential of dietary VA sufficiency in mitigating cognitive deficits and reducing amyloid pathology in a transgenic AD model. Further studies are warranted to evaluate VA as a preventive or therapeutic intervention in human AD.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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

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UND SMHS funds

Title: Sex Dependent Effects of Alzheimer’s APP Mutations on Colorectal Tumorigenesis

Authors: *T. ISHIDA-TAKAKU, M. SOHRABI, C. K. COMBS;
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Abstract: Cancer and Alzheimer's disease (AD) are among the most common age-associated disorders. Epidemiological studies consistently reveal an inverse association between AD and several cancer types, suggesting overlapping but antagonistic biological mechanisms. However, the molecular basis of this negative correlation remains poorly defined. One potential contributor is biological sex, a key determinant of disease risk and progression in both conditions. Nearly two-thirds of AD patients are women, whereas men experience higher incidence and mortality of colorectal cancer. Clinical data further indicate that APP expression influences colorectal cancer prognosis, with elevated APP levels linked to poorer overall survival in both sexes. However, relapse-free outcomes diverge, correlating with higher APP expression in males and lower APP expression in females. These observations imply that APP and its AD-causing mutations may actively shape tumor biology in a sex-dependent manner, yet few experimental studies have tested this possibility.In this study, we investigated the role of familial AD mutations in colorectal cancer using the $APP^{NL\text{-}G\text{-}F}$ knock-in mouse model, which harbors three pathogenic mutations in the endogenous App gene. Colitis-associated colorectal cancer (CAC) was induced by azoxymethane (AOM) and dextran sulfate sodium (DSS). Interestingly, APP mutations enhanced tumor initiation and progression in male mice, whereas female mice showed suppressed tumor burden and reduced inflammatory pathology. Transcriptomic profiling revealed sex-specific alterations in neuronal markers, steroid hormone signaling, and immune pathways, while immune characterization uncovered divergent macrophage subsets and neuronal features in the colon. Importantly, CAC induction also altered brain Aβ accumulation in both male and female $APP^{NL\text{-}G\text{-}F}$ mice, suggesting bidirectional interactions between peripheral tumorigenesis and AD pathology.Together, these findings provide the first experimental evidence that APP mutations shape colorectal cancer development in a sex-dependent manner while also influencing brain pathology.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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Program #/Poster #: LBP071.51/LBP081

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

Support: NINDS/NIA Grant K22 NS123507
AHA Grant 23SCEFIA1155595

Title: Impact of Angiotensin II on Tau Phosphorylation in vitro and Cognitive Function in vivo

Authors: *J. N. VELÁZQUEZ[1], S. REASONOVER[2], I. BLANCO[3], M. M. SANTISTEBAN[2]; [1]University of Puerto Rico Rio Piedras, San Juan, PR; [2]Medicine, Vanderbilt University Medical Center, Nashville, TN; [3]Clinical Pharmacology, Vanderbilt University Medical Center, Nashville, TN

Abstract: Hypertension (>130/90mmHg), affects over half of the adult population in the United States and is the highest modifiable risk factor for age-related cognitive decline including Alzheimer's disease (AD). Previous research has shown that hypertension is associated with increased tau phosphorylation in amyloid negative elderly adults over a 5 year follow up. A key link between hypertension and cognitive decline may be overactivation of the Renin-Angiotensin System (RAS). Supporting this, angiotensin receptor blockers (ARBs) are associated with longitudinal decrease in both tau and phospho-tau in participants with mild cognitive impairment. Thus, in this study, we wanted to (1) elucidate the molecular basis of how hypertension contributes to tau phosphorylation *in vitro* and (2) determine how brain RAS overactivation affects cognitive abilities *in vivo*. We hypothesized that elevated levels of Ang II promotes tau phosphorylation *in vitro* and worsens cognitive function *in vivo*. Engineered human induced pluripotent stem cells derived neurons (iNeurons) were treated with Ang II (300nM or 1uM) and were collected at varying timepoints to assess the effect on various tau phosphorylation sites using Western blots. For the *in vivo* study, we leveraged the sRA mouse model, a double-transgenic model of brain-specific RAS characterized by elevated expression of human angiotensinogen and neuronal specific expression of human renin. Blood pressure was measured by tail-cuff plethysmography followed by neurobehavioral testing (Y-maze, Novel object recognition, Barnes maze, and Nest building) at 20 weeks of age. We found that Ang II treatment did not significantly increase tau phosphorylation at the tested timepoints *in vitro*. However, sRA mice showed deficits in the learning trials of the Barnes Maze and in Nest building behavior, indicating possible cognitive deficits in spatial learning and memory and ability to perform the activities of daily life. Our findings may suggest that brain-specific RAS activation contributes to cognitive dysfunction. Future studies will expand sample size, extend *in vitro* time points, assess whether tau phosphorylation occurs in sRA mice, and test potential mechanisms through GSK3β. By understanding the mechanisms of how Ang II contributes to tau phosphorylation, we seek to unravel the involvement of the RAS in AD pathology and its impact on cognitive health, thus identifying potential targets for therapeutic intervention.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

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BrightFocus ADR A20183775
Brown Foundation 2020 Healthy Aging Initiative
Pilot Grant support from UTHealth McGovern Medical School

Title: NON-MUTATED HUMAN TAU STIMULATES ALZHEIMER'S DISEASE-RELEVANT NEURODEGENERATION IN A MICROGLIA-DEPENDENT MANNER

Authors: *W. CAO;
University of Texas Health Science Center at Houston, Houston, TX

Abstract: Objectives The accumulation of abnormal, non-mutated tau protein is a key pathological hallmark of Alzheimer's disease (AD). Despite its strong association with disease progression, the mechanisms by which wild-type tau drives neurodegeneration in the brain remain poorly understood. **Methods** We selectively expressed either wild-type or mutant human microtubule-associated protein tau (hMAPT) in neurons throughout the mouse brain using an AAV-based approach, and systematically evaluated the resulting structural, cellular, and molecular changes over time. In addition, we applied this tauopathy model to FIRE mice, which are genetically engineered to lack microglia, to examine how the absence of microglia influences the progression of neurodegeneration induced by wild-type tau. **Results** We observed neurodegeneration in the hippocampus, especially associated with non-mutated human tau. Single-nuclei RNA sequencing confirmed a selective loss of hippocampal excitatory neurons by the wild-type tau and revealed the upregulation of neurodegeneration-related pathways in the affected populations. The accumulation of phosphorylated tau was accompanied by cellular stress in neurons and reactive gliosis in multiple brain regions. Notably, the lifelong absence of microglia significantly and differentially influenced the extent of neurodegeneration in the hippocampus and thalamus. **Conclusions** Our study established an AD-relevant tauopathy mouse model, elucidated both neuron-intrinsic and neuron-extrinsic responses, and highlighted critical and complex roles of microglia in modulating tau-driven neurodegeneration.

Disclosures: W. Cao: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

Support: R01AG084473
R01AG071782

Title: Consideration of *APOE* genotype reveals differences in the mechanisms by which amyloid β-peptide and proinflammatory cytokines suppress glucose uptake in astrocytes

Authors: *N. BEGUM[1], S. W. BARGER[1,2,3];
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Abstract: The gene for apolipoprotein E (*APOE*) makes the largest impact of any gene on the risk for developing Alzheimer's disease (AD); individuals carrying the ε4 allele have 3- to 15-fold higher odds compared to those homozygous for ε3. Carriers of ε4 also show lower rates of cerebral glucose utilization, a key component of AD pathogenesis. This appears to be at least partially dependent on glucose uptake rates in astrocytes, and we previously found lower levels of glucose uptake in astrocytes expressing the ε4 variant of *APOE* compared to the ε3 variant. Moreover, we found a decrease in glucose uptake in cultured astrocytes after exposure to oligomeric amyloid β-peptide (oAβ) or proinflammatory cytokines (an IL-1β/TNF combination).Here, we compare the mechanistic elements of the oAβ and cytokine effects. Primary astrocytes were cultured from mice subjected to targeted replacement of the murine Poe gene with human *APOE* ε3 or ε4 variants. In some cases, microglia were thoroughly removed by sequential treatment with cytosine arabinoside (AraC) and L-leucine methyl ester (LME). To induce hypoxia, cells were placed in a chamber containing 5% CO2 and 95% nitrogen for 2 hours, followed by a 6-hour recovery in normoxia. Glucose uptake was assayed with a fluorescent glucose analog. Compared to normoxia, hypoxia/reoxygenation elevated glucose uptake in *APOE* ε4astrocytes that were otherwise untreated, as well as those treated with oAβ. Although hypoxia/reoxygenation alone did not elevate uptake in *APOE* ε3 astrocytes, it did elevate uptake in *APOE* ε3 astrocytes treated with oAβ. The suppression of glucose uptake by cytokines was not impacted by hypoxia but did abate after removal of microglia from *APOE* ε4 astrocyte cultures; this manipulation did not prevent the effects of cytokines in *APOE* ε3 cultures. Together, these findings suggest that suppression of glucose uptake by Aβ and proinflammatory cytokines occurs through different mechanisms. Our results provide insight into astrocytic glucose transport, a crucial component of AD pathogenesis. These findings might contribute to therapeutic strategies that could be effective downstream of Aβ production and, perhaps, accumulation.

Disclosures: N. Begum: None. **S.W. Barger:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

Support: NIH Grant R01AG083941

Title: The PLX5622 supplementation impacts the diet consumption and body weight based on different diet backgrounds in male *App*$^{NLGF\ KI/WT}$ mice

Authors: *M. KURKELA[1], T. TCW[1], D. KSHATRIYA[2], M. PELLIZZON[2], J. TCW[1,3]; [1]Department of Pharmacology, Physiology, Boston University Chobanian & Avedisian School of Medicine, Boston, MA; [2]Research Diets Inc., New Brunswick, NJ; [3]Bioinformatics Program, Faculty of Computing & Data Sciences, Boston University, Boston, MA

Abstract: Alzheimer's disease (AD) is impacted by metabolic health; Type-2 diabetes individuals carrying one *APOE4* allele display 3-fold increased risk and those with two *APOE4* alleles display 12-fold increased risk for AD. AD mice on Western Diets (WD, high-sucrose, high fat) display cognitive decline and increased Aβ plaques and ApoE protein loads in the brain. Under the WD, *APOE3* AD mice display increased cognitive impairment, whereas cognitively impaired *APOE4* AD mice display no impact on cognitive functions through the diet. This suggests that WD could induce detrimental effects in AD mice. PLX5622 that depletes microglia from the central nervous system, is usually administered in high sucrose (50%) AIN-76A purified rodent diet, which mimics WD and might mask beneficial effects of PLX5622. Therefore, we hypothesized that low sucrose (4%) open standard diet (OSD, purified) could reduce confounding variables.
5 month-old *App*$^{\text{NLGF KI/WT}}$ males (n = 4 per group) were used considering higher susceptibility to metabolic dysfunction over females. The mice were placed on PLX5622-supplemented diets (1200 ppm) for 14 days either AIN-76A or OSD, or control diets, after which a glucose tolerance test (GTT) challenged by 2 μg/g glucose injection post 6-h fasting was performed. The blood glucose level was monitored for 2 h to determine the impact of diet backgrounds and PLX5622 on glucose tolerance. To assess the efficacy of PLX5622 in OSD, the microglial depletion rate was determined for 14 days of diet consumption, and the microglial repopulation rate was determined for 14 days post-end of PLX5622-supplemented diet consumption.
PLX5622 in both AIN-76A and OSD was equally efficient in microglial depletion in cortex and hippocampus. GTT did not reveal significant differences between diet backgrounds. However, PLX5622 in both AIN-76A and OSD reduced diet consumption compared with its control, respectively ($p < 0.05$). This effect was stronger in AIN-76A than OSD and resulted in weight loss of animals on PLX5622 in AIN-76A ($p < 0.01$). This indicates that mice on the PLX5622-supplemented OSD display reduced confounding variability in metabolic outcomes compared to those fed a control diet. The depletion of microglia on OSD reached 90% after 14 days, and the repopulation of microglia to the CNS took 7 days.
Our results indicate administering PLX5622 in OSD is efficient in depleting microglia. Importantly, it reduces the difference in metabolic phenotypes minimizing confounding factors of metabolic differences between control and PLX5622 treatment. Because metabolic health is intertwined with the severity and progression of AD, we suggest using OSD in future studies instead of AIN-76A.

Disclosures: M. Kurkela: None. **T. Tcw:** None. **D. Kshatriya:** A. Employment/Salary (full or part-time); Research diets Inc. **M. Pellizzon:** A. Employment/Salary (full or part-time); Research diets Inc.. **J. Tcw:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

Support: NIH grant 5R01HL71515-3
R24 HL114473
75N92019R002

Title: APOE e4-Linked Disruptions in Phasic Sawtooth Event Coordination and REM Sleep Synchrony

Authors: *T. DESEL[1], C. BROWN[1], C. CHEN[1], M. P. WALKER[2];
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Abstract: Motivation: Phasic REM sleep, marked by rapid eye movements, cortical activation, and synchronized cortico-thalamic activity, reflects a highly coordinated brain state. Sawtooth waves, a hallmark of this stage, are tightly coupled to these dynamics and may index REM-specific synchrony. REM sleep is essential for memory consolidation and large-scale network coordination, and reduced REM duration has been linked to Alzheimer's disease and genetic risk in APOE ε4 carriers. Yet, beyond overall duration, REM microstructure offers a more sensitive indicator of early neural vulnerability. Whether APOE ε4 carriers exhibit disruptions in phasic REM events remains unknown. Sawtooth waves may therefore serve as a marker of REM synchrony, with APOE ε4 carriers hypothesized to show early disruptions in this coordination.
Methods: Overnight polysomnographic EEG recordings from 558 adults (mean age 45.6 ± 13.6 years; 37.8% female) with APOE genotyping were obtained from the National Sleep Research Resource. Sawtooth delta waves were detected using established algorithms during phasic and tonic REM periods. Phase-locking value (PLV) was computed across frequency bands and averaged across channel pairs.
Results: Phasic REM exhibited greater phase synchrony (PLV) across all frequency bands than tonic REM (all $p < 0.01$). Across participants, higher sawtooth density was associated with increased phasic synchrony in the delta (rho = 0.10, $p = 0.01$) and theta (rho = 0.14, $p = 0.004$) bands, independent of band power. APOE ε4 carriers exhibited lower delta-band PLV ($U = 29{,}183.0$, $p = 0.03$) and lacked a significant association between sawtooth density and REM synchrony (all $p > 0.30$), confirming the second hypothesis. Non-carriers, in contrast, showed robust coordination in delta (rho = 0.15, $p = 0.001$), theta (rho = 0.17, $p = 0.0001$), and gamma band (rho = 0.10, $p = 0.02$). These effects persisted after adjusting for age and sex and were absent in NREM sleep (all $p > 0.05$), indicating specificity to REM sleep.
Conclusion: These findings reveal genotype-specific alterations in REM physiology. APOE ε4 carriers show disrupted coordination between phasic sawtooth events and network synchrony, which may affect REM-dependent memory consolidation. Sawtooth activity and REM synchrony may serve as early functional markers of Alzheimer's disease vulnerability.

Disclosures: T. Desel: None. **C. Brown:** None. **C. Chen:** None. **M.P. Walker:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

Support: NIH/NIA Program Project Grant - P01 AG073082

Title: Synergistic Interaction of ApoE4 and Amyloid-β Pathology Drives Prodromal Behavioral, Cellular, and Gene Network Disruption

Authors: *J. SHIN[1], E. BRADY[2], S. R. MILLER[3], X. JIANG[4], D. MALLEN[5], K. LAUDERDALE[6], J. HERBERT[2], J. J. PALOP[7];
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Abstract: Current transgenic mouse models used in Alzheimer's disease (AD) research, such as the widely employed 5xFAD line, face limitations due to overexpression of amyloid precursor protein (APP) and the resulting non-physiological protein levels. In contrast, knock-in models introduce precise genetic modifications that yield more biologically relevant systems for modeling late-onset AD (LOAD). In this study, we investigated a double knock-in model carrying two major AD risk factors: humanized ApoE4 and App^{NL-F} (E4NLF), which harbors Swedish and Iberian familial AD mutations. At 13-15 months, when amyloid pathology is present but spatial memory and cognition remain intact, our objective was to characterize prodromal-stage dysfunction and assess how ApoE4 and Aβ pathology interact to shape disease progression.Behaviorally, E4NLF mice exhibited reduced locomotion, impaired habituation, and increased thigmotaxis in the open field. Using Variational Animal Motion Embedding (VAME), an unsupervised machine learning approach, we further identified fragmented directional movement, elevated transitions into unassisted rearing, and center-avoiding grooming, patterns of behavioral disorganization not captured by standard metrics. Histopathological analyses revealed that these abnormalities tracked with amyloid deposition in App^{NL-F} mice but were exacerbated in E4NLF, where ApoE4 uniquely intensified microgliosis and synaptic disruption. Finally, single-cell RNA-seq combined with high-dimensional co-expression network analysis (hdWGCNA) uncovered interneuron-selective impairments in lysosomal and adhesion pathways, changes that differential expression alone failed to detect.Together, these results demonstrate that ApoE4 and Aβ pathology synergistically drive prodromal dysfunction across behavior, pathology, and gene networks. This work underscores the value of humanized knock-in models for elucidating complex genetic interactions underlying LOAD and establishes a scalable analytic framework for detecting early circuit instability, when intervention is most likely to be effective.

Disclosures: J. Shin: None. **E. Brady:** None. **S.R. Miller:** None. **X. Jiang:** None. **D. Mallen:** None. **K. Lauderdale:** None. **J. Herbert:** None. **J.J. Palop:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.57/Web Only

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

Title: Computational Design of Lipid-soluble ApoE N-terminal Segment Using Reverse-QTY Code

Authors: *T. KARAGÖL, A. KARAGÖL;
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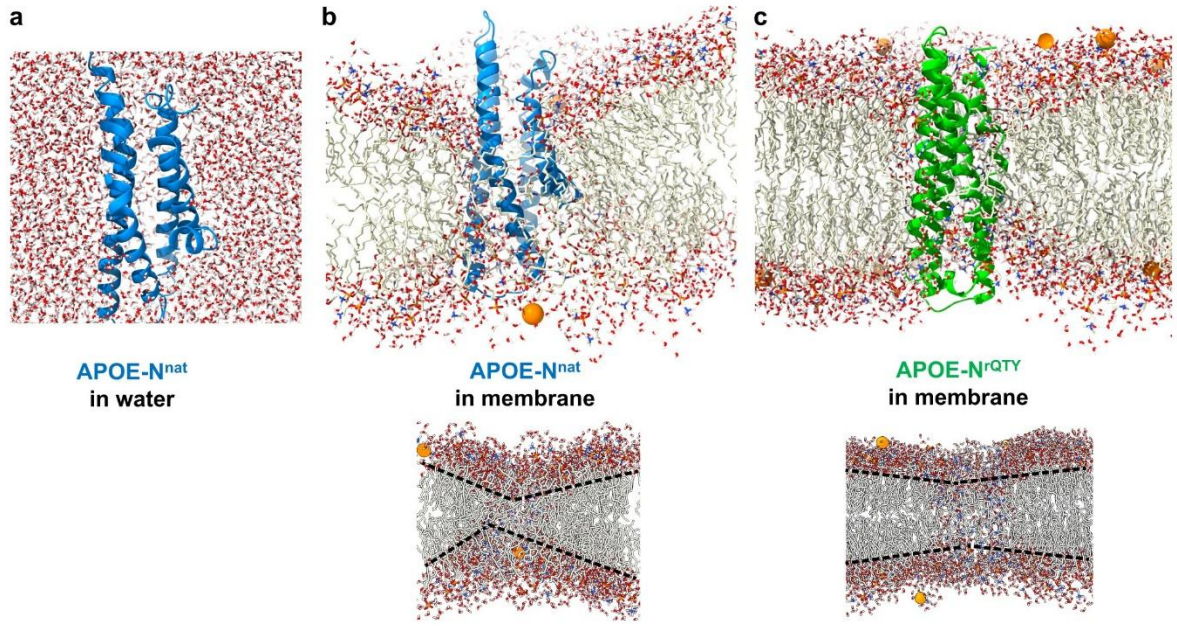
Abstract: Apolipoprotein E (ApoE) is the principal lipid and cholesterol carrier in the brain, and the ε4 allele is the strongest genetic risk factor for late-onset Alzheimer's disease (AD). ApoE recently understood to drive multiple mechanisms beyond amyloid-β pathology; including neuroinflammation and tau degeneration. Structural studies reveal three distinct regions: an N-terminal domain with receptor-binding helices, a C-terminal lipid-binding region, and a flexible hinge. Modulating ApoE's interaction with membranes represents an unexplored target for altering its biological functions and mitigating AD risk. Here, we introduce a reverse-QTY (rQTY) protein-engineering strategy to selectively enhance ApoE's membrane affinity. We previously used the original QTY code (Zhang et al.) to improve water-solubility of integral neuronal membrane proteins, and rQTY has been used to increase hydrophobicity in serum albumin. We applied rQTY substitutions (Q, T, Y → L, V, F) to ApoE's N-terminal helices, aiming to strengthen membrane anchoring without compromising C-terminal lipid binding. To validate this concept, we followed multi-level computational workflow, including AlphaFold3 predictions, 300ns all-atom molecular dynamics simulations, hydropathy and membrane calculations applying neuronal vesicle lipid compositions and a highly mobile membrane model. Our results demonstrate that rQTY code effectively modulated the hydrophobicity (ΔGRAVY: 0.88) and improved membrane binding. The rQTY variant exhibited greater stability and reduced membrane pitting (Figure 1). Furthermore, it did not destabilize the overall fold and C-terminal. These findings establish domain-specific rQTY engineering as a framework for reprogramming ApoE interactions. We provide a blueprint for designing synthetic ApoE peptides modulating lipid trafficking and neuroinflammatory pathways. Beyond advancing ApoE biology, this work shows a generalizable strategy for precision engineering of lipid-interacting proteins, with implications for novel therapeutic interventions.



Disclosures: T. Karagöl: None. **A. Karagöl:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.58/LBP087

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

Title: RNAase-H active antisense oligonucleotides (ASOs) targeting APOE and TREM2 microglial cells for Alzheimer’s disease therapy

Authors: *M. LU;
iLab Research Institute, Fremont, CA

Abstract: RNAase-H active antisense oligonucleotides (ASOs) targeting *APOE* and *TREM2* inmicroglial cells for Alzheimer’s disease therapyRoy D. Lao, Mason LuAlzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by memoryloss and cognitive decline. Its pathogenesis involves the accumulation of amyloid-β plaques andtau tangles in the brain. Despite ongoing efforts, developing effective therapy tools against ADremains challenging. Antisense oligonucleotide (ASO)-based drugs, which have beeninvestigated in other central nervous system disorders, may offer an opportunity for targeting ADpathology and application in AD treatment.Microglia, the primary immune cells of the central nervous system, play critical roles inmaintaining brain health and responding to injury and diseases. *APOE* and *TREM2* are essentialgenes expressed by microglia to help mediate their functions. These genes link the importantroles of microglial cells and AD pathogenesis.To investigate transcriptome

changes of ASO-induced attenuation of*APOE* and *TREM2*, theGSE219284 designed RNAase-H active antisense oligonucleotides (ASOs) to selectively bindand degrade human *APOE* and *TREM2* mRNA. These ASOs were applied to the hESC-derivedhuman microglia cells brain Xenotransplant mouse model (App-NL-G-F). At 1 and 4 weeksfollowing cerebrospinal fluid injections of *APOE* and *TREM2*-targeting ASOs, both human andmouse CD11b+/CD45+ microglia were FACS sorted for RNA extraction and sequencing.Principal component analysis (PCA) graphs of human-derived and mouse-resident microglialcells revealed clear separations between Vehicle control and *APOE* or *TREM2* ASO-treatedgroups in human-derived microglial cells. Such distinctions were absent in mouse-residentmicroglial cells at both 1 week and 4 weeks post treatment, indicating the ASOs therapies last forat least 4 weeks. Differential expression gene (DEG) analysis reveals the key genes significantlyup and down-regulated after 1 week and 4 weeks *APOE* or *TREM2* ASOs treatment, along withassociated pathways. Most importantly, cross comparison of DEGs across *APOE* and *TREM2*treatment yielded a new list of DEGs commonly regulated by both *APOE* and *TREM2*. Thesegenes and the relevant pathways may serve as biomarkers to monitor *APOE* and *TREM2* ASOtreatment or to serve as new therapeutic targets in AD.In conclusion, ASOs targeting human *APOE* and *TREM2* effectively reduced the expression of*APOE* and *TREM2* for up to 4 weeks. The RNAseq data analysis revealed significant DEGs andaffected pathways, highlighting the potential of ASO target therapies for modulating keymolecular processes in Alzheimer's disease.

Disclosures: M. Lu: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.59/LBP088

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

Title: Sex specific metabolic remodeling in the hypothalamus during early Alzheimer’s disease

Authors: *M. RAMEZAN[1], M. ALIAHMADI[1], A. C. SHIN[2];
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Abstract: Alzheimer’s disease (AD) disproportionately affects women, yet the biological basis for this disparity remains incompletely understood. Brain glucose metabolism, particularly in the hypothalamus, may play a key role in mediating sex differences in AD vulnerability. We investigated sex-dependent alterations in hypothalamic glucose metabolism across mouse and neuronal cell models of early AD in an exploratory study. Eight-month-old male and female APP/PS1 AD mice and wild-type littermates (n=10/group/sex) were used, with females sacrificed in diestrus to minimize hormonal variability. Gene expression analyses were conducted in the hypothalamus, cortex, and hippocampus by RT qPCR. Additionally, Seahorse metabolic assays were performed on neuronal cell lines derived from adult male and female

mouse hypothalamus (mHypoA-BMAL1-WT) exposed to either oligomeric amyloid-beta (oAβ) or media as a control (n=6/group/sex). Sample sizes were determined by power analysis. There was a trend toward upregulation of glucose transporter 1 and 4 and some glycolytic enzymes in the hypothalamus of both sexes of APP/PS1 mice. However, males showed a significant upregulation of Ndufs1 - an electron transport chain complex I component - and a trend of increased expression of mt-co1, a complex IV component, whereas females exhibited downregulation of Ndufs1. In parallel, both sexes of the hypothalamic neuronal cell lines increased glycolysis under oAβ stress, but only female cells showed impaired mitochondrial respiration and ATP production, an effect that disappeared under pyruvate deprivation, indicating inefficient mitochondrial pyruvate oxidation or import. Hypoxia-inducible factor 1-alpha (HIF1-α), an upstream regulator of glycolysis, was upregulated in the hypothalamus of male APP/PS1 mice and male cells but unchanged in females, indicating sex-dependent HIF1-α induction within the hypothalamus in response to amyloid pathology. Regional comparisons showed that some cortical glucose metabolic genes were upregulated in APP/PS1 males, whereas there was no change or downregulation of some mitochondrial metabolic genes in females. The hippocampus underwent broad suppression of glucose metabolic pathways in both sexes, with females more severely affected. This work identifies the hypothalamus as a critical node for glucose metabolic abnormalities in AD. We demonstrated for the first time an upregulation of glycolysis in response to Aβ pathology in both sexes and a sex-specific metabolic remodeling of mitochondrial pyruvate metabolism, which makes both processes potential therapeutic targets.

Disclosures: M. Ramezan: None. **M. Aliahmadi:** None. **A.C. Shin:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.60/Web Only

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

Title: Altered heme and redox homeostasis underpin late-onset Alzheimer's disease

Authors: *L. ZHANG;
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Abstract: Early-onset Alzheimer’s disease (EOAD) is associated with highly penetrant mutations in genes such as PSEN2, whereas the strongest genetic risk factor for late-onset Alzheimer’s disease (LOAD) is the APOE4 allele. Despite intense research efforts, how neuronal dysfunction is initiated in LOAD cases and how the initiating events for EOAD and LOAD differ remain to be clarified. Using biochemical measurements of energy metabolism, heme and redox homeostasis, in combination with RNA-Sequencing analysis, we characterized biochemical and transcriptome differences in neurons differentiated from human EOAD and LOAD iPSC-derived neural stem cells, relative to their respective control neurons. Strikingly, we found that LOAD neurons, not EOAD neurons, are defective in heme and redox homeostasis.

The levels of multiple proteins and enzymes involved in heme synthesis, degradation, and oxidative phosphorylation are preferentially decreased in LOAD neurons, not EOAD neurons. Likewise, heme transport is decreased in LOAD neurons. ROS generation is strongly increased in LOAD neurons, not EOAD neurons. Further, many genes involved in heme and redox homeostasis, as well as cellular energy generation, are downregulated in LOAD neurons, not EOAD neurons. Together, these results strongly suggest that altered heme and redox homeostasis in LOAD neurons underlie the initiation of neurological deficits.

Disclosures: L. Zhang: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.61/LBP089

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

Title: Intracellular sigma peptide reduces Aβ levels and boosts neuron differentiation in a murine model of Alzheimer’s disease.

Authors: *S. AYGAR;
MGH, Charlestown, MA

Abstract: In vitro models of Alzheimer’s disease (AD) commonly implement amyloid-β (Aβ) elevations to elicit disease-associated changes in cell cultures. However, AD involves multifactorial mechanisms beyond Aβ. Alterations in the composition of the extracellular matrix (ECM), especially the perineuronal net (PNN), contribute to synaptic dysfunction and disease progression. Here, we examined how inhibiting chondroitin sulfate proteoglycan (CSPG) signaling by intracellular sigma peptide (ISP) affects Aβ levels, viability, and neuronal differentiation in cultures exposed to varying concentrations of CSPGs, a key ECM component. Mouse embryonic cortical progenitors were seeded on plates coated with CSPGs (0, 0.1, 1, 10 μg/ml). Plates were treated with 2.5 μM ISP or scrambled peptide (SCR) as a control. Cell viability, Aβ40 & Aβ42 levels, and neuronal differentiation (NeuN, Olig2) were assessed by LIVE/DEAD assay, ELISA, and immunocytochemistry, respectively. Preliminary results suggest that ISP treatment consistently reduced soluble Aβ40 and Aβ42 levels, attenuating Aβ production. In SCR-treated cultures, increasing CSPG concentrations led to dose-dependent increases in Aβ40 and Aβ42, with the highest levels at 10 μg/ml CSPGs. This occurred despite significant reductions in cell viability and density at higher CSPG concentrations, suggesting CSPGs enhance Aβ production under neurotoxic conditions. ISP treatment maintained neuronal viability across all CSPG concentrations compared to SCR. Neuronal differentiation, as measured by NeuN/DAPI ratios, was not significantly affected by CSPGs in SCR-treated cultures. In ISP-treated cultures, NeuN/DAPI ratios were significantly increased at 0.1 μg/ml ($p<0.05$) and 10 μg/ml ($p<0.001$) CSPG relative to 0 μg/ml, indicating that ISP promotes neuronal differentiation in response to CSPGs. Given that the CSPG receptor protein tyrosine

phosphatase sigma (PTPσ) binds to amyloid precursor protein (APP) and may potentiate Aβ production, inhibiting the CSPG signaling pathway via ISP offers a promising approach to modulate AD pathology by protecting against CSPG-induced neurotoxicity and reducing Aβ levels. Additional replicates and expanded sample sizes will be essential to validate the robustness and translational relevance of these observations.

Disclosures: S. Aygar: 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.; NervGen Pharma. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); NervGen Pharma.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

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

Support: MODEL-AD U54AG054345
TREAT-AD U54AG065181
ADDF-HDI U01AG088802

Title: Acute Pharmacological Inhibition of SHIP-1 Modulates the Inflammatory Response in a Humanized Amyloid-β Mouse Models of Alzheimer’s Disease

Authors: *J. KWON[1], I. H. CABALLERO FLORAN[2], D. SONI[3], C. RANGEL-BARAJAS[2], A. OBLAK[4];
[1]Emory University, Atlanta, GA; [2]Medical and Molecular Genetics, Indiana University, indianapolis, IN; [3]Medical neuroscience, indiana university, Indianapolis, IN; [4]Stark Neurosciences Research Institute, Indianapolis, IN

Abstract: Genome-wide association studies have identified multiple genetic loci strongly associated with Alzheimer's disease risk, especially in relation to the regulation of microglial inflammatory response. Among these is the phosphatidylinositol 3,4,5-trisphosphate 5-phosphatase 1 (Inpp5d) gene, which encodes the SHIP-1 protein that has been linked to the clearance of amyloid beta. Previously, our research group demonstrated that SHIP-1 haplodeficiency prevented cognitive decline in the amyloidogenic 5xFAD mouse model. Thus, investigating pharmacological inhibition of SHIP-1 in a translational model like the APP-SAA knock-in (SAA) mouse may advance our understanding of SHIP-1 involvement in AD pathology and neuroinflammatory profiles and enable the development of new therapeutic strategies. In this study, we analyzed gene and protein expression profiles following 3-dose oral administration of the selective SHIP-1 inhibitor TAD-0000032, provided by the TREAT-AD Center. To ensure scientific rigor, we utilized blinding for treatment group and control group sampling.

Experiments were conducted using 6 and 14 month old SAA mice of both sexes. Pharmacokinetic profiling of TAD-0000032 was performed. Once presence of drug was validated, we assessed SHIP-1 expression along with key markers of inflammatory response. A comprehensive set of analyses was employed, including immunohistochemistry to evaluate AD-related pathology, Meso Scale Discovery (MSD) for sensitive multiplex biomarker quantification, western blotting for protein expression analysis, and NanoString technology for detailed transcriptomic profiling. Our results indicate that the acute in vivo inhibition of SHIP-1 for 24h did not significantly alter the SHIP-1 expression levels. However, changes observed in both gene and protein expression of key markers, such as interleukin-1β and Clec7a, suggest that SHIP-1 inhibition with TAD-0000032, may reduce neuroinflammation and modulate microglial activation state. In qPCR results, interleukin-1β levels were significantly decreased in 6mo treatment group. Clec7a results were significant in 6mo as well. When analyzing MSD results, significance was noted in the TNF-α proinflammatory cytokine level in 6mo with trending data observed among 14mo groups. Notably, these effects were evident at both early and late stages of AD progression. These data suggest that SHIP-1 inhibition could offer therapeutic benefits across disease stages. Acute pharmacological inhibition of SHIP-1 modulates key neuroinflammatory markers at both genetic and protein levels, supporting its potential as a therapeutic strategy in AD across disease stages.

Disclosures: J. Kwon: None. **I.H. Caballero Floran:** None. **D. Soni:** None. **C. Rangel-Barajas:** None. **A. Oblak:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.63/LBP091

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

Support: NIH Grant R01AG073230

Title: A Novel AI-Powered Nest-Building Assay Provides Insights Into the Cerebrovascular Effects of the K_{Ca} Channel Activator SKA-31 on Aging and Alzheimer's-Related Behavioral Decline

Authors: *F. E. L. MIOT[1], Z. SHIH[1], S. SALLOUM[2,3,4], P. CHUM[4], E. J. BEHRINGER[4]; [1]Basic Sciences, Loma Linda University, Loma Linda, CA; [2]Université d'Aix-Marseille, Marseille, France; [3]Université des Antilles, Pointe à Pitre, Guadeloupe; [4]Loma Linda University, Loma Linda, CA

Abstract: Alzheimer's disease (AD) is characterized by progressive cognitive and behavioral decline, with mounting evidence pointing to cerebrovascular dysfunction as an early contributor. Nest building is a complex, species-typical behavior that reflects cognitive and motor function, offering a valuable preclinical research tool. We developed an AI-powered image analysis

pipeline to quantify nest complexity in 3xTg-AD mice and wild-type controls, and used this platform to test the cerebrovascular potassium channel ($K_{Ca}2$ and $K_{Ca}3.1$) activator SKA-31 (10 mg/kg). Mice (N=93) were randomly assigned to a treatment or vehicle group within each age and genotype cohort. Nest building was assessed at baseline and again after a nine-week treatment period where SKA-31 was administered daily via palatable agar gel cubes while controls received vehicle-infused (ethanol) cubes. For each assessment, photos were taken across multiple timepoints (0.5-24 hrs) to track nesting progress. Nest complexity was analyzed using a validated convolutional neural network (ResNet18) pipeline, which was trained on human-scored pilot data, assigning scores from 1-5. Cross-sectional results confirmed that age and AD genotype impaired nesting, consistent with prior literature. Longitudinal analysis of the percentage change in performance, normalized to baseline, showed no statistically significant improvement in SKA-31-treated mice compared to controls. This indicates the tested dose and method of administration were not sufficient to improve the complex behaviors required for nest building in this model. These results suggest consistent dosing and combinatorial therapeutics (e.g., senolytics and anti-inflammation) that can aid the dysfunctional cerebrovascular system may be required. The AI assay proved to be a highly robust, objective, and generalizable tool for detecting nuanced behavioral changes in preclinical studies.

Disclosures: F.E.L. Miot: None. **Z. Shih:** None. **S. Salloum:** None. **P. Chum:** None. **E.J. Behringer:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.64/LBP092

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

Title: A novel role for FLCN in neuronal mTORC1 and tauopathy

Authors: *K. PARK[1], H. XU[2], V. M. LEE[3], Z. ARANY[2];
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Abstract: The mechanistic target of rapamycin complex 1 (mTORC1) plays a key role in cellular metabolism and is involved in various physiological processes. As such, it is studied across multiple fields, including Alzheimer’s disease (AD) research. AD is a neurodegenerative disorder characterized by the accumulation of intracellular neurofibrillary tangles (NFTs). Due to the diverse functions of mTORC1, its direct targeting for therapy has limitations. Our group has previously shown that folliculin (FLCN), an upstream regulator of mTORC1, can selectively control a non-canonical branch of mTORC1 signaling. This occurs through inhibition of TFEB/TFE3 activation, which regulates the CLEAR pathway and mitochondrial function. Inhibiting FLCN reduced lipotoxicity and ameliorated non-alcoholic fatty liver disease (NAFLD)

without disrupting the canonical anabolic pathway of mTORC1. We are now investigating whether this mechanism is conserved in neurons. To model AD pathology, we injected tau lysates into neuronal FLCN knockout (KO) mice's hippocampus. Immunohistochemistry revealed increased pathological markers, but behavioral performance was unexpectedly improved. Given the significant differences observed, we propose that FLCN inhibition modulates neuronal function in a unique way. Overall, our findings suggest a novel role for FLCN in neuronal cells and highlight its potential relevance to AD pathology in the context of translational research.

Disclosures: K. Park: None. **H. Xu:** None. **V.M. Lee:** None. **Z. Arany:** None.

Late-Breaking Poster

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

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Title: Loss of REST associated with Alzheimer's disease is ameliorated by NAD^+

Authors: *B. ESCOBAR DONCEL[1], M. LAGARTOS DONATE[1], S. ZHANG[1], N. VILLASECA[2], A. ANISIMOV[1], N. MONTALDO[3], D. CAPONIO[1], H. NILSEN[3,4], E. F. FANG[1,5];
[1]University of Oslo and Akershus University Hospital, Oslo, Norway; [2]Universidad de Castilla-La Mancha, Albacete, Spain; [3]Oslo University Hospital, Oslo, Norway; [4]CRESCO, Oslo, Norway; [5]NO-Age and NO-AD networks, Oslo, Norway

Abstract: Downregulation and inactivation of the Repressor Element 1-Silencing Transcription factor (REST) has been implicated in Alzheimer's disease (AD), yet the mechanisms remain unclear. We analyzed REST expression and localization in postmortem entorhinal cortex and hippocampal samples across different Braak stages of tauopathy and identified stage-dependent reductions in nuclear REST. Using a cross-species approach, we show that REST overexpression improves cognitive function, reduces amyloid beta (Aβ) deposition and accumulation of misfolded and phosphorylated tau, and restores mitochondrial and synaptic homeostasis. Mitochondrial dysfunction is a key driver of AD progression. Enhancing mitophagy via the nicotinamide adenine dinucleotide (NAD^+)-dependent pathway represents a promising therapeutic strategy. In AD models, elevating NAD^+ levels increases REST expression, linking NAD^+ metabolism to transcriptional regulation of mitochondrial quality control. Mechanistically, the NAD^+/SIRT1 axis modulates REST expression through chromatin remodeling in the promoter region of REST, leading to changes in the expression of REST target genes involved in mitophagy and synaptic function. These findings reveal a new mechanism of action for NAD^+ and highlight REST as a promising therapeutic target for AD.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

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

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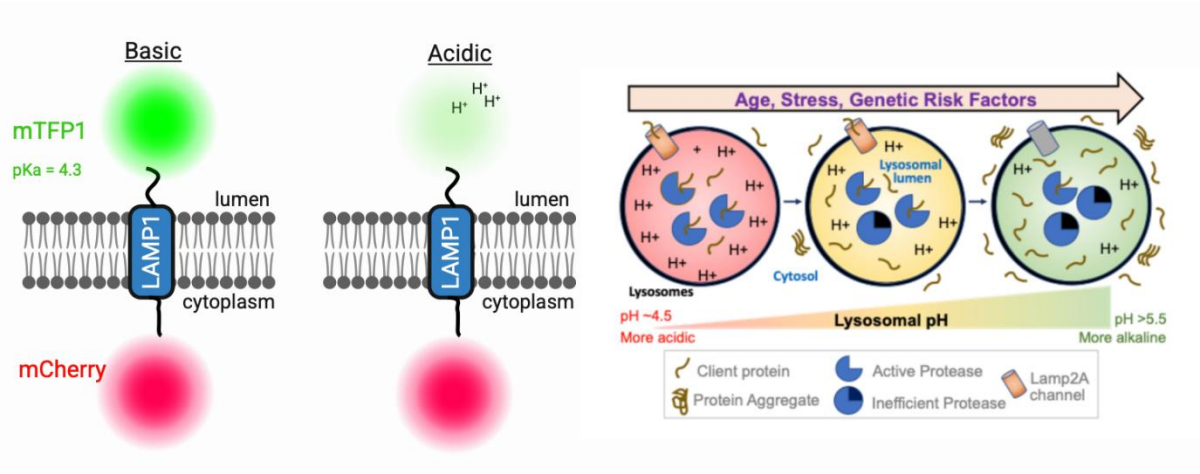
Title: Using a novel mouse model to investigate lysosomal pH differences across cell type, brain region, and age

Authors: *A. W. SMITH, C. LANE-DONOVAN, A. W. KAO;
Neurology -- Memory and Aging Center, University of California, San Francisco, San Francisco, CA

Abstract: Lysosomal dysfunction is implicated in age-related neurodegenerative disorders like Alzheimer's Disease (AD), Frontotemporal Dementia (FTD), and Parkinson's Disease (PD), among others. The lysosome is a catabolic, acidic organelle that processes waste and misfolded proteins and requires a low, acidic pH for optimal function. In both yeast and C. Elegans, lysosomal pH has been shown to rise with age; however, it is unknown if this occurs in mammalian systems. To answer this question, we developed a novel mouse model that expresses a genetically-derived pH sensor. Fluorescent Indicator REporting pH in Lysosomes (FIRE-pHLy) is a ratiometric fluorescent pH indicator tagged to lysosomes that contains a cytosolic, pH-insensitive mCherry domain and an intraluminal, pH-sensitive mTFP marker with a pKa of 4.5 optimal for studying the lysosome (see Figure). Utilizing an inducible flox promoter design, FIRE-pHLy expression can be selectively driven in the mouse brain with specific Cre driver lines. In young adult FIREpHLy mice, we found variation in resting neuronal lysosomal pH, with certain brain regions that are vulnerable to neurodegeneration showing elevated lysosomal pH. Additionally, utilizing viral mediated expression of FIRE-pHLy in aging mice, we have observed elevated lysosomal pH with aging in cortex. Overall, the FIRE-pHLy mouse is a novel, flexible tool to investigate lysosomal pH in vivo in fixed tissue. In the future, we aim to use this tool to explore lysosomal pH in disease models.



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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.67/LBP095

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

Support: American Heart Association, pre-doctoral fellowship; 24PRE1196641
5R01AG057555-03

Title: Targeting α-1 adrenergic receptor and phosphoglycerate kinase 1 with Terazosin improves cognition and pathology in a transgenic AD rat model

Authors: *S. PATTANASHETTY GANGADHARAPPA[1], P. A. SERRANO[2], P. ROCKWELL[3], M. E. FIGUEIREDO-PEREIRA[4];
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Abstract: The locus coeruleus (LC), the brain's major source of norepinephrine (NE), is among the earliest regions to degenerate in Alzheimer's disease (AD), contributing to profound cognitive decline. In parallel, AD brains exhibit marked deficits in cellular energy metabolism. Here, we tested whether **terazosin (TZ)—**an α1-adrenergic receptor antagonist and activator of phosphoglycerate kinase 1 (PGK1)—could counteract both noradrenergic dysfunction and energetic failure in AD. TgF344-AD rats received TZ (0.5 mg/kg/day) from 5-11 months of age. TZ-treated rats displayed **improved spatial memory** on the active place avoidance task compared to untreated littermates. Immunohistochemistry revealed **reduced hippocampal Aβ plaque burden,** accompanied by increased amoeboid microglia, suggesting enhanced plaque clearance in both sexes. Notably, TZ reduced hippocampal hyperphosphorylated tau in females only, pointing to **sex-specific effects.** Moreover, TZ **rescued hippocampal noradrenergic fiber loss** at 11 months. RNAseq analyses further identified sex-dependent transcriptional changes, including **upregulation of cell survival pathways in females** and **downregulation of β-secretase mRNA stabilizing protein in males,** indicating potential mechanistic pathways.Together, these findings highlight TZ's **dual actions**—modulating α1-adrenergic signaling and enhancing energy metabolism—as drivers of cognitive and neuropathological improvement, while revealing **sex-specific therapeutic pathways** that may guide precision approaches to AD treatment.

Disclosures: S. Pattanashetty Gangadharappa: 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.; American Heart Association, pre-doctoral fellowship. **P.A. Serrano:** None. **P. Rockwell:** None. **M.E. Figueiredo-Pereira:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.68/LBP096

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

Title: Structural determinants of sirt2 function: implications for ran regulation in neurodegeneration

Authors: *S. JARBOU;
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Abstract: Sirtuin 2 (SIRT2) is a NAD^+-dependent deacetylase that controls nuclear transport and cytoskeletal dynamics. Dysregulated acetylation by SIRT2 has been connected to neurodegenerative diseases, including Alzheimer's and Parkinson's. One key substrate is the small GTPase RAN, which SIRT2 deacetylates at lysine 71, a modification that can affect nucleocytoplasmic transport, a pathway often disturbed in neurodegeneration. Aimed to compare the activity of wild-type (WT) SIRT2 with a deletion mutant lacking residues 292-303 (Δ292-303) to figure out whether this region is required for RAN deacetylation and neurodegeneration-relevant function. SIRT2 variants were expressed in E. coli BL21 (DE3) following IPTG induction and genetic code expansion for TFAcK incorporation. Proteins were purified by immobilized metal affinity chromatography (IMAC) and size-exclusion chromatography (SEC), with purity confirmed by SDS-PAGE. Deacetylase activity was measured by incubating purified SIRT2 with acetylated RAN over a 0-120 min time course, followed by anti-acetyl-lysine Western blot and densitometric analysis. All results were confirmed across independent replicates with WT and mutant controls. The SDS-PAGE confirmed successful expression and purification of both SIRT2 variants. SEC improved purity and yielded monomeric fractions. Western blot analysis showed time-dependent RAN deacetylation by WT SIRT2, whereas Δ292-303 showed no measurable activity. Quantification confirmed complete loss of activity in the mutant, highlighting the functional importance of this structural region. Results identify residues 292-303 of the SIRT2 as essential for the deacetylation of RAN. Given SIRT2's role in neuronal protein regulation, these findings provide insight into how specific structural elements contribute to enzymatic activity and can guide the design of selective SIRT2 inhibitors for neurodegenerative disease therapeutics.

Disclosures: S. Jarbou: None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.69/LBP097

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

Support: NIH Grant 5P20GM152335-02

Title: Novel PRNP polymorphisms associated with neurodegenerative Chronic Wasting Disease in Montana mule deer and implications for protein misfolding

Authors: *A. SEERLEY[1], A. GRINDELAND PANTER[2];
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[2]Weissman Hood Institute at Touro; McLaughlin Research Institute, Great Falls, MT

Abstract: Transmissible spongiform encephalopathies (TSEs), also known as prion diseases, are a class of fatal neurodegenerative diseases that progress over time and have no cure. These diseases occur in a variety of mammals including humans. While species barriers seem to rarely be crossed, there are few cases where genetic variations played a huge role. Bovine Spongiform Encephalopathy (BSE) gave rise to the human disease Variant Creutzfeldt-Jakob (vCJD) and other studies have shown that polymorphisms can result in strain emergences affecting multiple species within the cervid (deer, elk, moose, and reindeer) family. Additionally, one position within the cervid gene has been identified to be equivalent to that of the human prion gene, raising concerns for the possibility of species transmission. Chronic Wasting Disease (CWD) is a prion disease of cervids and is the most infective of all TSEs due to peripheral shedding of misfolded PrP^{Sc} from infected animals through bodily fluids and excrement. Our laboratory sequenced and analyzed the *PRNP* sequence in over 400 mule deer samples obtained from Montana Fish, Wildlife, & Parks (MT FWP) in the 2017, 2018, and 2022 hunting seasons. This analysis led to a discovery of novel genetic variants, V12F and R40Q, which correlate with CWD status in the Montana mule deer population. Based on computational analysis, we believe that these single non-synonymous nucleotide substitutions alter the PrP folding characteristics, and therefore, disease outcomes. Our novel variant at amino acid 12 resides in the N-terminal region of the immature protein prior to cleavage during posttranslational modifications. Alterations to the protein structure in the N-terminus, may affect intracellular trafficking and PrP misfolding resulting in a reduced threshold of PrP^{res} corruption from another CWD animal. Additionally, biochemical changes because of the mutation could disrupt the structure causing steric clashes, enhanced interactions with other hydrophobic residues, and alter protein stability, all leading to misfolding. Similar computational modeling of amino acid 40 reveals the polymorphism lies in a disordered region of the protein which makes it difficult to predict structural impact. Using RT-QuIC assays, our lab also sought to understand seeding characteristics of the emerging *PRNP* genetic variants to assess the impacts the polymorphisms have on spontaneity of misfolding, disease progression and manifestation, and species barriers. While our investigations are focused on the proteinopathy of the cervid prion protein, this

information is critical in understanding the future and evolution of prion diseases across multiple species.

Disclosures: A. Seerley: None. **A. Grindeland Panter:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.70/LBP098

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

Support: NIH COBRE award 5P20GM152335-02

Title: Advancing early detection of a transmissible spongiform encephalopathy through comprehensive phenotypic profiling analysis in transgenic mouse models

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Abstract: Chronic Wasting Disease (CWD) is a fatal transmissible spongiform encephalopathy affecting cervids (deer, moose, elk, and reindeer) which is caused by the misfolded prion protein (PrP). CWD shares key properties with human neurodegenerative conditions such as Alzheimer's, Parkinson's, Huntington's disease and frontal-temporal dementia. Although CWD is currently thought to be confined to cervids, it provides a unique portal into understanding neurodegeneration in humans and other species in relationship to basic biological properties including protein misfolding and neuropathology. Investigations that are focused on understanding clinical and neuropathological biomarkers and phenotypes such as ours, are significant in that they provide insight into mechanisms that influence susceptibility and disease progression. Accurate antemortem testing techniques currently available for many neurodegenerative diseases and especially prion diseases are extremely limited. The identification of diagnostic and prognostic biomarkers at all stages of CWD disease progression is becoming exceedingly critical as these diseases continue to increase in prevalence. This study investigated neurological biomarkers and neurobehavioral manifestations in cervidized transgenic mice recapitulating CWD in various disease stages. Neurofilament light chain (NFL) as a marker of neuronal injury, glial fibrillary acidic protein (GFAP) as a marker of brain inflammation, and creatine kinase (CK) as a marker of muscle damage were assessed together under the hypothesis that combined biomarker signatures more reliably reflect CWD-related neurodegeneration and disease progression. Brain and plasma samples from mice representing three age groups were analyzed for biomarker levels using immunoblotting techniques with appropriate controls. Preliminary analyses at 90, 168, and 230 days post-CWD inoculation show distinct biomarker patterns integrated with neurobehavioral impairments, where NFL and GFAP were significantly elevated in the CWD group by 168 days. While individual markers may

fluctuate due to injury or stress, the combined elevation of NFL, GFAP, and CK provides a more consistent signal of CWD, highlighting the potential of a multi-biomarker signature to improve the reliability of future field-based diagnostic testing. Disease biomarkers that can be analyzed through blood will support less invasive testing in live cervids, where reliable signatures could enable earlier disease detection in cervids, assist with disease management, and be useful for determining human transmission if suspected.

Disclosures: A. Grindeland Panter: None. **A. Seerley:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.71/LBP099

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

Title: Novel phase transition pathways of TDP-43 and hnrnp H1 from soluble and aggregated states to liquid state

Authors: *T. WANG, A. R. MUDLIAR, J. WANG;
Allele Biotechnology, San Diego, CA

Abstract: Cytotoxic inclusions of TAR DNA-binding protein 43 (TDP-43) have been identified in amyotrophic lateral sclerosis, frontotemporal lobar degeneration, and other neurodegenerative diseases. It has been well documented that TDP-43, mainly through its C-terminal low-complexity domain (LCD), forms aggregates/fibrils as well as undergoes liquid-liquid phase separation (LLPS). These phase transitions parallel pathological mislocalization and aggregation in the cytoplasm. But what decides TDP-43 to enter either the solid aggregate or liquid droplet state, and how? Understanding the underlying mechanism will help illustrate the cellular toxicity of TDP-43 and likely other similar proteins, including the large family of RNA-binding proteins. We first succeeded in creating recombinant proteins of full-length TDP-43 without a solubility tag, which is known to be difficult to prepare, and TDP-LCD, both remain soluble at sub-mg/ml working concentration by incorporating urea addition and slow removal. For comparison, we also generated another RNA-binding protein, hnRNP H1, which features 3 RNA recognition motifs and its own LCDs with disease relevance. The purified soluble proteins were then induced to form solid aggregates by varying electrostatic conditions such as pH and salt. These assemblies were characterized using amyloid-specific Thioflavin-T and Congo Red dyes, and visualized by brightfield and confocal microscopy. With sufficient soluble proteins we were able to carefully track the physical chemical properties and the dynamics of the aggregate formation at a controlled pace. We then investigated the transitions among all 3 phases, namely, soluble, solid fibrils, and liquid droplets, in all directions.
The current paradigm states that TDP-43 LLPS droplets age into hydrogels, inclusions, and amyloid fibrils. LLPS acts as a scaffold accelerating solid aggregate formation, often leading to direct amyloidosis. Our hypothesis is that the phasing-out of the soluble form starts with a “seed”

area in a protein-specific manner, which can then lead to LLPS or fibrils depending on the charge of this region. We inadvertently found that SDS, which can add net charge to the whole protein, drove phase transitions into liquid droplets, either directly from soluble protein or, to our surprise, through a novel reversal pathway from aggregates. We further show the protein-specific seeding effects by using sophisticated combinations of fluorescent labeling schemes.
Our findings represent an unusual reversal of the conventional liquid-to-solid maturation of protein condensates and reveal the role of electrostatic charge in regulating LLPS in vitro.

Disclosures: T. Wang: None. **A.R. Mudliar:** None. **J. Wang:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.72/LBP100

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

Support: Cure Sanfilippo Foundation
National MPS Society

Title: Hematopoietic stem cell gene therapy for Mucopolysaccharidosis type IIIC

Authors: *R. A. BADELL-GRAU[1], J. SCHENCK[2], A. SIVAKUMAR[3], A. CORL[4], J. ESKO[5], J. SCHLACHETZKI[6], S. CHERQUI[3];
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Abstract: Mucopolysaccharidosis type IIIC (MPSIIIC) is a severe neurodegenerative lysosomal storage disorder (LSD) caused by loss-of-function of the lysosomal transmembrane protein acetyl-CoA:heparan-α;-glucosamine N-acetyltransferase (HGSNAT). MPSIIIC is characterised by accumulation of the Heparan Sulfate (HS), developmental delay, dementia and neuronal cell loss leading to death from severe neurodegeneration. Our group has previously shown that transplantation of hematopoietic stem cells (HSCs) rescue cystinosis, another LSD due to mutations in a transmembrane lysosomal protein. One of the mechanisms of rescue involved lysosomal cross-correction from HSC-derived macrophages to the disease cells via tunnelling nanotubes. We believe that the same principles could be used to treat MPS IIIC.We generated a new MPSIIIC mouse model and confirmed disease phenotypes such as HS accumulation, splenomegaly, neurological defects, and presence of disease specific non-reducing end carbohydrates (NREs). To explore a new therapeutic strategy, we transplanted wild type (WT) HSCs into lethally irradiated 2-month-old MPSIIIC mice and analyzed the impact 6 months later. Transplanted HSCs differentiated into macrophages in tissues and microglia-like cells in the brain. This resulted in partial restoration of MPSIIIC expression and enzymatic activity along

with the significant reduction of the MPSIIIC-specific. In addition, WT HSC transplant resulted in improved neurological defects, reduction in splenomegaly and urine retention.For the clinical translation of this approach, we are developed an autologous transplantation of *ex vivo* gene modified HSCs. We have generated self-inactivated (SIN)-lentivirus vector containing human *HGSNAT* cDNA (NM_152419) and performed *in vitro* characterization. Following transduction of murine and patient cells lines, we observed a recovery in *HGSNAT* expression and activity as well as HGSNAT lysosomal localization and decreased HS storage. We also transplanted gene-modified HSCs in MPSIIIC mice, and have confirmed successful engraftment with vector copy number between 1.2 and 3.6. Our data showed improvement in locomotor phenotypes in MPSIIIC. Additionally, RNA-seq analysis revealed increased expression of inflammatory genes as well as an upregulation in synapse pruning, microglial activation and lysosomal gene expression in the MPSIIIC mice compared to WT mice. Notably, this phenotype was ameliorated following transplantation of gene-modified HSCs. These data support HSC transplantation as a promising therapeutic avenue for MPSIIIC and represent the first step towards a clinical translation.

Disclosures: R.A. Badell-Grau: None. **J. Schenck:** None. **A. Sivakumar:** F. Consulting Fees (e.g., advisory boards); Papillon Therapeutics. **A. Corl:** None. **J. Esko:** None. **J. Schlachetzki:** None. **S. Cherqui:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Founder of Papillon Therapeutics. Other; Advisory board in Cystinosis Research Foundation.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.73/LBP101

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

Support: NIA R03AG081865

Title: Repetitive Mild Traumatic Brain Injury Exacerbates Cognitive Deficits in a Mouse Model of Cerebral Amyloid Angiopathy

Authors: V. PULIDO-CORREA[1], A. HERNANDEZ[2], C. VOGEL[2], B. C. ALBENSI[3], ***L. S. ROBISON**[2];
[1]Department of Neuroscience, Nova Southeastern University, Fort Lauderdale, FL; [2]Psychology and Neuroscience, Nova Southeastern University, Fort Lauderdale, FL; [3]Pharmaceutical Sciences, Nova Southeastern University, Fort Lauderdale, FL

Abstract: Traumatic brain injury (TBI) affects around 69 million people each year, with mild TBIs (mTBIs) making up the majority of cases. These injuries, often sustained during contact sports, military service, or incidents of domestic violence, typically involve brief or no loss of consciousness and few immediate symptoms. However, repeated occurrences significantly

elevate the risk for long-term complications, including dementia. While repetitive mTBI is strongly linked to chronic traumatic encephalopathy (CTE) and Alzheimer's disease (AD), the relationship with cerebral amyloid angiopathy (CAA), characterized by the accumulation of amyloid peptides in the cerebral vasculature, remains understudied. Given that CAA significantly contributes to dementia and stroke risk, it is critical to investigate whether and how repetitive mTBIs exacerbate the development and progression of CAA pathology and associated cognitive-behavioral deficits. In this study, male and female Tg-SwDI mice (CAA model) and wild-type (WT) C57BL/6J controls were exposed to repetitive mTBIs (one hit daily using a modified weight drop method over five consecutive days) starting at approximately two months of age (late adolescence/early adulthood). Cognitive-behavioral outcomes (open field, elevated zero maze, novel object recognition, object placement test, y-maze, and Barnes maze) were assessed 7 days or 3 months post-injury. Repetitive mTBIs resulted in significant impairments in several cognitive tests, with deficits being genotype-, sex-, and time- dependent, with more severe deficits resulting from mTBI in Tg-SwDI mice, females, and at the later time-point. Our results suggest that even mTBI can result in cognitive deficits and exacerbate symptoms associated with CAA, warranting further investigation of the mechanisms responsible to help identify novel therapeutic targets.

Disclosures: V. Pulido-Correa: None. **A. Hernandez:** None. **C. Vogel:** None. **B.C. Albensi:** None. **L.S. Robison:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.74/LBP102

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

Support: NIH Grant P30AG072931
Charitable Gift from Sarns' Family

Title: An Isoform-Specific Signal in Extracellular Vesicle BDNF Identifies Early Alzheimer’s-Related Cognitive Changes

Authors: S. CHONG[1], C. MAZO[2], M. VESIA[1], *J. HAUS[1];
[1]University of Michigan, Ann Arbor, MI; [2]University of Wisconsin, Madison, WI

Abstract: Background: As the prevenance of dementia increases, early diagnosis of Alzheimer’s disease is crucial to prevent and slow the progression of irreversible neuronal damage. Neurotrophic factors such as brain derived neurotrophic factor (BDNF) are implicated in Alzheimer’s disease related dementia (ADRD) pathogenesis and circulating concentrations are altered across the cognitive impairment continuum. Further, extracellular vesicles (EVs) may be an important source of circulating BDNF. The association of circulating and EV derived BDNF with clinical and functional hallmarks of ADRD pathogenesis has not yet been established.

Purpose: This study aimed to determine whether plasma and EV-derived BDNF protein levels, particularly isoform-specific abundance, are associated with cognitive status and brain structure across the ADRD spectrum. **Methods:** Samples were acquired from the University of Michigan Alzheimer's Disease Research Center (n=44 control (CON), n=20 mild cognitive impairment (MCI), and n=24 amnestic multidomain related dementia (AMDS)). All participants underwent cognitive assessments, structural brain imaging (via magnetic resonance imaging (MRI)) and blood sampling. Plasma BDNF was assessed, EVs were isolated via size exclusion chromatography and EV BDNF protein abundance was measured. **Results:** No differences ($p<0.05$) in plasma BDNF, EV concentration or EV size were detected between groups. Patients with MCI displayed 42% more 25kD BDNF isoform within EVs when compared to AMDS ($p=0.02$). Plasma and EV BDNF protein were not associated with cognitive function scores or brain volumetrics. **Conclusion:** The data indicated that clinical cognitive disease status is not influenced by plasma BDNF. However, elevations in EV 25kD BDNF protein may be an early indicator of clinical cognitive impairment manifestation. Further research is necessary to determine the function in the isoform in the progression of ADRD.

Disclosures: S. Chong: None. **C. Mazo:** None. **M. Vesia:** None. **J. Haus:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.75/LBP103

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

Support: NIH R61 / AG075725
TARCC grant

Title: Blood-based RNA profiling reveals common disease risk factors in Alzheimer’s disease and multiple sclerosis

Authors: *E. CHOI[1], W. WU[1], M. RIPPEE-BROOKS[1], K. KHATKAR[1], L. LIU[2], E. LIU[2], I. LEE[2], L. LI[3], K. QUICK[4], X. FANG[4], X. BAO[1];
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Abstract: Background: Early and non-invasive detection of Alzheimer’s disease (AD) and multiple sclerosis (MS) is crucial for timely intervention. In this study, we explored blood-based biomarkers by profiling mRNA and small RNA expression in buffy coat samples from healthy individuals as well as AD and MS patients. **Methods**: Buffy coat samples were collected from patients with AD (n=4), MS (n=4), and healthy controls (n=5). Both mRNA and small RNAs were sequenced and analyzed for differential expression and functional enrichment (Gene Ontology (GO) analysis). **Results**: In AD, resting NK cells and monocytes were significantly

decreased, while neutrophils and T cells showed a nonsignificant increase and decrease, respectively. In MS, monocyte levels also tended to decrease, though not significantly. Gene Ontology (GO) analysis revealed that genes upregulated in AD were associated with viral response, kinase activity, and single-stranded RNA binding. Downregulated genes were enriched in pathways related to leukocyte cell-cell adhesion, RNA complex biosynthesis, and T cell regulation. In MS, upregulated genes were linked to viral response and the IgA immunoglobulin complex, whereas genes involved in lumen and granule functions were downregulated. Both diseases exhibited shared molecular signatures, including upregulation of viral response pathways and downregulation of immune regulatory processes such as T cell function and intracellular vesicle trafficking. Small RNA analysis identified OSBPL1A as commonly upregulated, while several miRNAs and piRNAs were consistently downregulated in both diseases. OSBPL1A may serve as a molecular link between cholesterol metabolism and the intracellular processing and trafficking of amyloid precursor protein (APP), potentially influencing Aβ production, a pathological hallmark of AD. **Conclusion**: Despite the preliminary nature of this study and its limited sample size, our findings suggest that immune dysregulation and viral responses are common molecular features shared by Alzheimer's disease and multiple sclerosis. Future studies with larger cohorts and experimental validation are essential to confirm these candidate biomarkers' predictive and diagnostic potential.

Disclosures: E. Choi: None. **W. Wu:** None. **M. Rippee-Brooks:** None. **K. khatkar:** None. **L. Liu:** None. **E. Liu:** None. **I. Lee:** None. **L. Li:** None. **K. Quick:** None. **X. Fang:** None. **X. Bao:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.76/LBP104

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

Title: A Multiscale Systems Biology Framework Integrating ODE-Based Kinetics and MD-Derived Structural Affinities to Model mBDNF-proBDNF-Mediated Bifurcation Dynamics in CNS Neurotrophin Signaling

Authors: *E. LIU[1], A. MURTHY[2], A. RAMANI[3], K. MOORJANI[4], S. CHOI[5];
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Abstract: *All authors contributed equally to this project. Brain-Derived Neurotrophic Factor (BDNF), a key member of the neurotrophin family, is implicated in the regulation of synaptic plasticity, neuronal differentiation, and long-term survival in the Central Nervous System (CNS). The dualistic signaling pathways mediated by the mature form of BDNF(mBDNF) via TrkB receptors and the precursor form (proBDNF) via p75NTR introduce a dynamic molecular axis that governs a balance between neurogenesis and programmed cell death. In this study, we

developed a multi-computational framework incorporating a system of ordinary differential equations (ODEs) representing concentrations of proBDNF, BDNF, TrkB, p75NTR, tPA (cleavage enzyme), and the protein-receptor complexes. To parameterize the ODE system with biophysically accurate constants, Molecular Dynamics (MD) simulations were used to resolve energetically favorable conformations and receptor-binding affinities. Notably, these simulations enabled de novo structural elucidation of a previously uncharacterized isoform of proBDNF, increasing the biological relevance of the ODE model with heightened accuracy. A hill-type sigmoid function was then applied to the ODE system to create a nonlinear representation of the interaction between TrkB and p75 activation, translating directly to the topological rewiring of the neuronal model via modulation of edge weights for determination of overall neuronal death or survival. This model provides insights towards emergent phenomena such as neurotrophin-dependent synaptic pruning, and it facilitates the identification of bifurcation thresholds in the proBDNF:mBDNF ratios that can signify early-stage neurodegeneration and can serve as biomarkers for various neurodegenerative diseases. The model also holds translational potential for therapeutic target discovery as well, and can be utilized to analyze the implications of different drugs on the neurotrophic ratio, hence providing further information on neurodegenerative states.

Disclosures: E. Liu: None. **A. Murthy:** None. **A. Ramani:** None. **K. Moorjani:** None. **S. Choi:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.77/LBP105

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

Title: Distinct spatiotemporal dynamics of DNA methylation in familial and sporadic Alzheimer’s disease mouse models

Authors: *C. CAO[1], R. N. DILGER[1], S. K. SILVERMAN[2], Z.-P. LIANG[3], K. C. LI[4], G. E. ROBINSON[5], D. A. LLANO[6], F. LAM[2];
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Abstract: Alzheimer’s disease (AD) encompasses both familial and sporadic forms, each driven by distinct genetic and molecular mechanisms. Epigenetic regulation, particularly DNA methylation, has emerged as an important mechanism influencing gene expression and disease trajectory in AD. Unlike amyloid β and tau, methylation changes have long-term effects on brain function thus may provide earlier biomarkers of disease-related changes. With our long-term

goal of establishing a non-invasive epigenetic imaging technology (eMRI), we sought to characterize the spatiotemporal patterns of global DNA methylation in two distinct mouse models--familial 5xFAD and sporadic APOE4 knock-in--to determine how this key mechanism might diverge across disease types and brain regions. We analyzed APOE4/APOE3 knock-in mice at 5/6, 9, and 12/13 months of age (n = 3-7 per group) and 5xFAD/wild-type (WT) mice at 1, 2, and 3 months of age (n = 3-6 per group). DNA was extracted from cortex, hippocampus, striatum, midbrain, and cerebellum, and regional global methylation levels were quantified by ELISA. APOE4 mice exhibited consistent hypermethylation than APOE3 controls ($P < 0.05$ or 0.01, two-way ANOVA) in hippocampus, striatum, and midbrain (except at 9 months), but showed hypomethylation in the cerebellum (except at 12-13 months). In contrast, 5xFAD mice displayed consistent hypomethylation relative to WT ($P < 0.05$ or 0.01, two-way ANOVA) in the hippocampus, midbrain, cerebellum, and (at 1 month only) cortex, whereas the striatum showed transient hypermethylation at 3 months. Notably, the hippocampus, a region highly vulnerable in AD, together with the midbrain, demonstrated opposite methylation trajectories between the two models, suggesting that methylation dynamics reflect not only AD progression but also underlying etiology. Importantly, these differences emerged as early as 1 month of age for 5xFAD, supporting DNA methylation as a potential early marker. At the same time, convergent patterns in striatum and cerebellum suggest partial overlap in downstream epigenetic remodeling across familial and sporadic AD contexts. Our findings reveal distinct spatiotemporal signatures of DNA methylation in familial vs sporadic AD mouse models, underscoring both divergent and shared epigenetic alterations. Our findings also further support the use of DNA methylation as a dynamic--but model-specific--biomarker, and strengthen the rationale for using non-invasive imaging (eMRI) as a novel way to study AD in animals and humans longitudinally. We plan to employ additional AD mouse models to better characterize and understand the strikingly discordant patterns observed thus far.

Disclosures: C. Cao: None. **R.N. Dilger:** None. **S.K. Silverman:** None. **Z. Liang:** None. **K.C. Li:** None. **G.E. Robinson:** None. **D.A. Llano:** None. **F. Lam:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.78/LBP106

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

Title: Molecular and phenotypic evaluation of bioenergetic stress-induced cholinergic neuron disease in mice

Authors: *S. SAHA[1], A. PAPANERI[1], W. GLADWELL[1], D. SPINA[2], L. R. WILSON[1], J. D. CUSHMAN[1], G. CUI[1];
[1]National Institute of Health, Durham, NC; [2]Bio-Rad Laboratories, Inc., Hercules, CA

Abstract: Optimum “bioenergetic balance” in the mitochondria, the powerhouse of neurons, is a key factor for proper brain functioning. The brain's inability to produce or use energy proficiently, referred to as bioenergetic stress, is primarily driven by mitochondrial dysfunction, which precedes and contributes to a wide array of neurodegenerative disorders, such as Alzheimer’s disease (AD) and Amyotrophic Lateral Sclerosis (ALS). Interestingly, both of these diseases are characterized by degeneration of cholinergic neurons (CN). Knowing that mitochondrial transcription factor A (Tfam) plays indispensable roles in regulating cellular bioenergetics by reducing oxidative stress and maintaining mitochondrial DNA and health, we sought to elucidate the etiopathogeneses of AD and ALS, which remain unknown, by studying the direct role of bioenergetic stress via Tfam deletion in CN. Therefore, we developed a new cholinergic Tfam global knockout (KO) mouse strain (ChAT-cre;Tfam$^{-/-}$, abbreviated as ChTf) to evaluate bioenergetic stress-induced molecular and phenotypic effects. In these ChTf mice, a progressive loss of mitochondrial function in CN was observed. Compared to littermate controls, KO mice exhibited a rapid decrease in body weight following 13.5 weeks of age. As they approached the 16th week of age, they showed stooped posture and limited mobility in their home cages, potentially due to weakened muscle activity. Behaviorally, ChTf mice showed decreased exploratory behavior and ambulation, and reduced motor performance and coordination in Phenotyper and rotarod tests, respectively. Furthermore, the ChAT staining histological analysis of CN revealed damage to the basal forebrain CN and striatal cholinergic interneurons in an age-dependent manner. Using a novel multiplex Droplet Digital™ PCR (ddPCR™) assay design (Bio-Rad Laboratories), we quantified gene expression differences between KO and control mice for targets relevant to neurodegeneration, including APP and ChAT. Histopathology of the spinal cord and in vivo fiber photometry using ATP and cholinergic fluorescent sensors are planned to confirm the perturbed bioenergetic dynamics in multiple brain regions of this mouse model. Taken together, the findings implicate that bioenergetic stress-induced damage to CNs resulted in the development and/or progression of movement dysfunctions. This model bestows a new perspective on the susceptibility and treatment of CN diseases, indicating that differential bioenergetics is an important mechanism underlying CN degeneration.

Disclosures: S. Saha: None. **A. Papaneri:** None. **W. Gladwell:** None. **D. Spina:** None. **L.R. Wilson:** None. **J.D. Cushman:** None. **G. Cui:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.79/LBP107

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

Support: NIH Grant R01 AG089169
NIH Grant P50 AG047366

Title: Motor-based Biomarkers for Detection of Mild Cognitive Impairment and Alzheimer's Disease

Authors: *A. ZHOU, J. HUANG, N. SCHUETZ, M. DANIEL, D. BAHMANI, F. V. LIN, V. W. HENDERSON, E. ADELI;
Stanford University, Stanford, CA

Abstract: Background: Early detection of Alzheimer's Disease (AD) is essential, as interventions are most effective before advanced neurodegeneration. Widely used cognitive screeners, such as the Montreal Cognitive Assessment (MoCA), are influenced by education, language, and socioeconomics; often fail to capture early deficits; and rely on subjective scoring. In contrast, motor function provides a promising, largely untapped source of predictive biomarkers. Declines in coordination, gait, and motor skills can emerge in prodromal AD, reflect underlying neurodegeneration in motor and associative networks, and are less influenced by culture or education. We systematically examined three motor test batteries for their ability to discriminate among healthy controls (HC), mild cognitive impairment (MCI), and AD: Luria motor sequences combined with a test of finger praxis, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UDPRS) Part III, and the Short Physical Performance Battery (SPPB).
Methods: Data were obtained from 673 Stanford Alzheimer's Disease Research Center participants. After filtering to a representative visit per participant, we retained valid scores on Luria's (n=238), MDS-UPDRS-III (n=417), and SPPB (n=408). For each battery, we fit logistic regression models with age and sex as covariates, and evaluated diagnostic discrimination (HC, MCI, and AD) using stratified 5-fold cross-validation, with mean AUC ± SD as primary metrics. To identify the most informative subtests, we applied elastic net regression for feature selection.
Results: Luria showed the strongest performance, with AUCs of 0.63 ± 0.06 (HC vs. MCI), 0.75 ± 0.09 (MCI vs. AD), and 0.87 ± 0.03 (HC vs. AD). MDS-UPDRS-III demonstrated AUCs of 0.57 ± 0.04 (HC vs. MCI), 0.60 ± 0.08 (MCI vs. AD), and 0.72 ± 0.07 (HC vs. AD). SPPB performed near chance, with AUCs of 0.57 ± 0.04 (HC vs. MCI), 0.48 ± 0.08 (MCI vs. AD), and 0.51 ± 0.10 (HC vs. AD). Elastic net feature selection consistently highlighted fine motor and sequencing sub-tests from the Luria composite and MDS-UDPRS-III, underscoring the value of probing coordination and motor planning. The highest coefficients were for Luria sequences performed with verbal mediation, a finger praxis task, and MDS-UPDRS-III postural stability.
Conclusion: Motor tasks hold promise as complementary biomarkers for early detection of cognitive impairment. While categorical assessments have limited predictive power, the signal we observed highlights the potential of fine-grained motor analysis. Future work leveraging computer vision and sensor approaches may enable scalable biomarkers to augment current screeners.

Disclosures: A. Zhou: None. **J. Huang:** None. **N. Schuetz:** None. **M. Daniel:** None. **D. Bahmani:** None. **F.V. lin:** None. **V.W. Henderson:** None. **E. Adeli:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.80/LBP108

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

Title: EEG spectral and network biomarkers differentiate Alzheimer’s disease, frontotemporal dementia, and normal aging across public datasets

Authors: *Y. CAI[1], S. ERTLMAIER[2];
[1]Johns Hopkins, Baltimore, MD; [2]Computer Science, Johns Hopkins University, Baltimore, MD

Abstract: Background
Accessible biomarkers for dementia remain limited. Imaging provides diagnostic accuracy but is costly and invasive. Electroencephalography (EEG) is inexpensive, widely available, and sensitive to neural dynamics. Although slowing of oscillations and disrupted connectivity have been reported in Alzheimer’s disease (AD) and frontotemporal dementia (FTD), validation across independent datasets is rare.
Methods
We analyzed EEG from 88 participants in open datasets (AD=36, FTD=23, cognitively normal [CN]=29). Signals were filtered (0.5-45 Hz), re-referenced, and segmented into 5-s epochs. Features included (i) relative band power, theta/alpha ratio, and alpha peak frequency; (ii) sample entropy; and (iii) functional connectivity via weighted phase-lag index in theta and alpha bands. Connectivity matrices were summarized using graph measures: efficiency, clustering, eigenvector centrality, and modularity. Classification tasks were (A) CN vs. dementia (AD+FTD) and (B) AD vs. FTD. Random Forest, XGBoost, and logistic regression were evaluated with leave-one-subject-out cross-validation.
Results
For CN vs. dementia, Random Forest achieved AUC=0.87 and accuracy=0.77. For AD vs. FTD, performance was lower but clinically informative (AUC=0.77, accuracy=0.73). Results were consistent across datasets. Combining spectral slowing with network measures yielded higher reproducibility than either feature set alone.
Conclusions
EEG captures reproducible and interpretable markers of dementia. Integrating oscillatory features with graph-theoretic metrics provides discrimination between normal aging, AD, and FTD. Use of public datasets and standardized pipelines supports rigor and cross-cohort generalizability, highlighting EEG as a scalable tool for dementia research and potential clinical screening.
Rigor and Reproducibility
Open, de-identified datasets; standardized preprocessing; subject-level cross-validation; transparent reporting of sample sizes and metrics.

Disclosures: Y. Cai: None. **S. Ertlmaier:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.81/LBP109

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

Support: NIH AF1 AG082216
NIH R01 AG080587

Title: Detection of Alzheimer's disease at early stage of brain dysfunction by AI-based assessment of auditory evoked cortical potential

Authors: I. IQBAL, C. LIANG, T.-Y. ZHAI, Z.-R. ZHAO, ***H.-B. ZHAO**;
Yale University Medical School, New Haven, CT

Abstract: Alzheimer's disease (AD) is a progressive neurodegeneration disease, starting from synaptic dysfunction to eventually neuronal degeneration. Early detection of AD at the stage of functional changes in synapses and brain is still a big challenge, even though this is important for AD prevention and treatment. Our previous study demonstrated that the auditory-evoked cortical potential (AECP) is sensitive to dysfunction in the central auditory system and other brain areas as well and could capture AD related changes (Mei et al., 2021, Front Aging Neurosci. 13;13:710317.). However, AECP is very complex and hard to identify and assess by regular traditional analyses. In this study, we adopted AI-technique to analyze AECPs recorded from APP/PS1 AD mice and wildtype (WT) mice from 1 month old to 1.5 years old. The convolutional neural network (CNN) was used and trained with Barlow Twins on z-scored waveforms using morphology-preserving augmentations. After per-feature standardization, we applied supervised UMAP (Uniform Manifold Approximation and Projection) to visualize tasks. Cluster quality was quantified by the silhouette score. To aid interpretation, we computed permutation-based features for the domain features. Domain features analysis demonstrated two clearly separated AD and WT clusters. UMAP embeddings showed two compact, non-overlapping genotype regions, even at 1 month old, when APP/PS1 mice have no apparent AD phenotypes. The silhouette score is ~0.60. Hybrid features further markedly improved separation to 0.92 of silhouette score. The hybrid gains indicate that the SSL (self-supervised learning) embeddings add complementary, distributed waveform information beyond these audiology-informed markers. The data demonstrated that by AI-based assessment, AECP as a non-invasive recording can efficiently detect AD at the early stage of synapse and brain functional changes and assess AD development and progression.

Disclosures: I. Iqbal: None. **C. Liang:** None. **T. Zhai:** None. **Z. Zhao:** None. **H. Zhao:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.82/LBP110

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

Support: NIH grant # R01AG062006 from the National Institute on Aging to CM.

Title: Mobility Impairment and Cognitive-Olfactory Dysfunction in Preclinical Alzheimer's Disease

Authors: *T. BICAKCI[1,2], C. MURPHY[3];
[1]Psychology, Palo Alto University - Stanford University Consortium, Palo Alto, CA; [2]Psychology, San Diego State University, San Diego, CA; [3]San Diego State University/UC San Diego, San Diego, CA

Abstract: Mobility impairment may be an early marker of brain abnormalities and predict later cognitive decline in Alzheimer's disease (AD) (Tian et al., 2023). Preliminary evidence also suggests an association between mobility impairment and olfactory dysfunction (Yuan et al., 2024), an early indicator of AD pathology (Murphy, 2019). To support early identification and prevention of AD, this study examined mobility and physical activity impairments as modifiable risk factors for cognitive and olfactory decline in genetically at-risk ApoE ε4 carrier older adults. Participants were 613 community-dwelling older adults (≥60 years) from the Rancho Bernardo Study of Healthy Aging who completed the Quality of Well-Being Scale, the Mini-Mental State Examination, the National Geographic Smell Survey, and ApoE genotyping. Multivariate linear regressions examined associations between mobility/physical activity impairments and cognitive and olfactory function, as well as ApoE ε4 interaction effects, adjusting for age, sex, education, and antidepressant/anxiolytic use. Greater mobility impairment was associated with worse cognitive function ($\beta = -.127$, $p = .011$), and ε4 carriers with greater physical activity impairment exhibited worse function than non-carriers ($\beta = -.093$, $p = .039$). Greater physical activity impairment was also associated with worse olfactory function ($\beta = -.160$, $p = .020$). Findings suggest that mobility limitations and reduced physical activity are potential risk factors for cognitive and olfactory decline, particularly in genetically at-risk older adults. As impaired mobility can restrict physical activity and social engagement—both important for cognitive stimulation and olfactory preservation (Shrestha et al., 2023; Zhao et al., 2023)—improving mobility may help mitigate early declines in at-risk populations for AD.

Disclosures: T. Bicakci: None. **C. Murphy:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.83/LBP111

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

Support: NIH K99/R00 Grant MH121355
BBRF Young Investigator Award
NIH Grant R35GM142836

Title: Mitochondrial DNA copy-number in neurodegenerative disorders: a meta-analysis

Authors: *S. BOUYADJERA[1], R. MATHEWS[1], J. DONEGAN[2], J. HAVIRD[3];
[1]University of Texas at Austin, Austin, TX; [2]Psychiatry, Dell Medical School at UT Austin, Austin, TX; [3]Integrative Biology, University of Texas at Austin, Austin, TX

Abstract: Neurodegenerative disorders are chronic conditions marked by the progressive loss of neuronal integrity in the CNS and affect nearly 50 million adults worldwide. Neural mitochondria have commonly been referred to as potential drivers for neurodegeneration, especially when they become dysfunctional. Mitochondrial DNA copy-number (mtDNA-CN) is directly linked to mitochondrial function and has been proposed as a biomarker for multiple diseases, including neurogenerative disorders. However, inconsistent findings make it unclear whether study-specific factors contribute to the link between mtDNA-CN and neurodegeneration. Therefore, we conducted a systematic review and meta-analysis of 61 relevant articles that compared mtDNA-CN, determined as a ratio of a mitochondrial gene copy number to a single-copy nuclear gene, in various neurodegenerative disorders to control populations. Effect sizes were calculated using the log of the response ratio. We then applied a weighted random-effects model to account for the variability between studies. We observed that mtDNA-CN was ~15% lower in patients with neurodegenerative disorders than controls ($p = 0.005$). Yet, the moderator analyses revealed the magnitude of this association differed depending on the disease: Alzheimer's disease (AD) and Amyotrophic Lateral Sclerosis (ALS) had the most significant decrease in mtDNA-CN ($p < 0.001$). The effects were also different depending on which tissue was used to quantify the mtDNA-CN. Leukocytes and brain tissue had particularly low mtDNA-CN ($p = 0.02$). Our analysis reveals that while mtDNA-CN levels tend to be lower in patients with neurodegenerative disorders, much variation exists that remains to be explained. By investigating mtDNA-CN, we may identify disease-specific thresholds that serve as early indicators and guide for timely therapeutic intervention.

Disclosures: S. Bouyadjera: None. **R. Mathews:** None. **J. Donegan:** None. **J. Havird:** None.

Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.84/LBP112

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

Support: NIH Grant 839788

Title: Elevated REM Theta Activity Predicts Lower Medial Temporal Lobe Dynamic Connectivity in Cognitively-Healthy Older Adults

Authors: *P. WHITE[1], S. MOALLEMIAN[2], M. BUDAK[3], V. PARUZEL[4], B. A. MANDER[5], B. A. FAUSTO[6], M. A. GLUCK[7];
[1]Rutgers University-Newark, Newark, NJ; [2]Rutgers-Newark, Roselle, NJ; [3]CMBN, Rutgers University-Newark, Newark, NJ; [4]Rutgers University-Newark, East Hanover, NJ; [5]Psychiatry and Human Behavior, University of California, Irvine, Irvine, CA; [6]Center for Molecular & Behavioral Neuroscience, Rutgers University–Newark, Newark, NJ; [7]Center for Neuroscience, Rutgers University Newark, Newark, NY

Abstract: Background: Rapid eye movement (REM) sleep disturbances are among the earliest indicators of Alzheimer's disease (AD) risk. Elevated theta oscillations during REM sleep may reflect an overall increase in lower frequencies and less desynchrony than expected during this stage and has been linked to AD progression. Medial temporal lobe (MTL) flexibility, a measure of time-varying network interactions, is sensitive to cognitive decline in this key memory-related region implicated in AD. Obesity is another modifiable AD risk factor, linked with both sleep disturbances and neuropathology. Higher body mass index (BMI) has been linked to higher risk of sleep disorders as well as AD pathology. Little is known about how REM sleep oscillatory activity links with MTL flexibility. This study aims to identify whether differences in theta activity are detectable in cognitively healthy older adults. We hypothesized that, consistent with previous evidence on later-stage AD, higher theta activity during REM sleep will be significantly associated with lower MTL flexibility.**Method:**15 subjects (79.50% female; mean age 68.97±5.82 years) from an ongoing longitudinal study at Rutgers University-Newark. Subjects were cognitively normal based on the Montreal Cognitive Assessment (MoCA) cutoff scores (M*ean±SD = 22.90±3.75*) adjusted for race and education. Sleep measures were collected from a home-based sleep monitoring device. REM relative theta activity was calculated as the ratio of the activity within the theta frequency range (4-8Hz) divided by the total activity across all bands. MTL flexibility was measured from the resting state functional MRI. Spearman correlation was applied on the data to characterize a relationship between BMI and relative theta activity and a relationship between MTL flexibility and relative theta activity within the REM sleep.**Result:**Relative theta activity during REM sleep was negatively correlated with MTL flexibility (r_s = -.58, p-value = .031) and positively correlated with BMI (r_s = .547, p-value = .035). **Conclusion:**Theta activity during REM sleep is related to early changes in the brain sensitive to AD pathophysiology. The positive association with BMI links theta activity with

obesity, an established risk factor for AD, potentially due to consequences of obesity-associated neurological insults including hypoxemia and cerebrovascular pathology. These preliminary findings indicate that higher theta activity during REM sleep is associated with lower MTL flexibility during daytime generalization learning, potentially serving as a non-invasive, accessible biomarker for early detection of AD pathophysiological progression.

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Late-Breaking Poster

LBP071: C.02. Alzheimer's Disease and Other Dementias

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP071.85/LBP113

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

Title: Unlocking Insights in Alzheimer’s Disease from Archived Brain Tissue Samples with High Sensitivity Spatial Transcriptomics

Authors: *M. RAY, R. CHEN, S. TATTIKOTA, J. HE, B. WANG, B. YANG, T. WIGGIN, L. MAZIASHVILI, S. WANG, G. EMANUEL, J. HE;
Vizgen, Cambridge, MA

Abstract: The advent of tools enabling researchers to easily perform spatial transcriptomics with single-cell resolution has enabled a revolution in the understanding of the nervous system. However, samples with degraded RNA or extensive crosslinking remain challenging for spatial transcriptomic measurements. The majority of human brain samples are archived using fresh frozen methodologies, but the RNA quality is often too low for useful transcriptome analysis due to variable collection conditions. To accurately map gene expression in frozen brain tissue in situ, a spatial transcriptomics technique with high detection efficiency is required. Multiplexed Error Robust in situ Hybridization (MERFISH) 2.0 directly profiles the transcriptome of intact tissues with high sensitivity and accuracy. The 3cm2 imageable area allows measurement from multiple samples on the same slide, removing batch effects and other artifacts when studying paired conditions. Here we demonstrate spatial transcriptomics from normal and Alzheimer’s Diseased (AD) human cortical tissue simultaneously.
The improved chemistry and workflow accurately profiled gene expression in situ and mapped cell types in archival human brain samples from both normal and AD tissues. Each sample was profiled using an 815-plex gene panel containing markers for both cell typing and neurodegeneration pathways. The high sensitivity MERFISH data enabled robust identification of cell types in all samples. We showed differential cell type distribution and differentially expressed genes within these cell types between disease vs normal states.
In addition, we simultaneously performed protein co-staining for Aβ plaques. We calculated the cell types present by distance from Aβ plaques, and the difference in gene expression associated with proximity to plaques. These types of measurements are only possible through the

combination of spatial imaging, gene expression quantification, and protein detection. Spatially resolved transcriptomic profiling of low-quality samples at single-cell level provides enormous opportunities in understanding the structure, function and disease of human brain. The improved sensitivity and throughput of the platform will enable new genomic inquiries into previously intractable diseases such as AD, leading to new insights into disease progression.

Disclosures: **M. Ray:** A. Employment/Salary (full or part-time); Vizgen. **R. Chen:** A. Employment/Salary (full or part-time); Vizgen. **S. Tattikota:** A. Employment/Salary (full or part-time); Vizgen. **J. He:** A. Employment/Salary (full or part-time); Vizgen. **B. Wang:** A. Employment/Salary (full or part-time); Vizgen. **B. Yang:** A. Employment/Salary (full or part-time); Vizgen. **T. Wiggin:** A. Employment/Salary (full or part-time); Vizgen. **L. Maziashvili:** A. Employment/Salary (full or part-time); Vizgen. **S. Wang:** A. Employment/Salary (full or part-time); Vizgen. **G. Emanuel:** A. Employment/Salary (full or part-time); Vizgen. **J. He:** A. Employment/Salary (full or part-time); Vizgen.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.01/LBP114

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

Support: Wellcome Trust (RE20960)

Title: Psilocin promotes differentiation during neurogenesis of human hippocampal progenitor cells in vitro

Authors: ***Z. HANIFF**[1], S. THURET[2];
[1]King's College London, London, United Kingdom; [2]Department of Basic and Clinical Neuroscience, Kings College London, London, United Kingdom

Abstract: Major depressive disorder is linked to altered adult hippocampal neurogenesis (AHN), a process of generating new neurons in the dentate gyrus: crucial for mood, memory, and learning. Reduced neuroplasticity and AHN, including impaired neuritogenesis, is associated with clinical depression and antidepressants may potentially restore it. Psilocybin, a serotonergic psychedelic, rapidly improves mood and promotes neuroplasticity, increasing neurogenic markers, such as doublecortin (DCX), in mice. Its active metabolite, psilocin, activates 5-HT2a receptors and enhances BDNF-trkB signaling, promoting neuritogenesis, dendritogenesis and synaptogenesis. However, psilocin's impact on AHN-related molecular pathways in humans remains unknown.
This study investigates the effect of psilocin on prolonged differentiation of human hippocampal progenitor cells (HPCs) in an *in vitro* assay of neurogenesis.
Human foetal-derived HPC03A/07 cells proliferated in media containing growth factors (EGF/bFGF/4-OHT). At 24h post-seeding, proliferation media was exchanged. After 48h, media

was exchanged for differentiation media (no growth factors) and cells were allowed to differentiate for 7 days. After a week, cells were treated once only with psilocin 0.5μM or 1μM and differentiated for a further 12 days before being fixed with 4% paraformaldehyde. Immunocytochemistry staining was completed to detect neurogenesis (DCX, MAP2) and proliferation (Ki67) markers and included parameters of neurite outgrowth. Immunofluorescence was quantified via High Content Imaging and neurite analysis conducted using Harmony software.
Twelve days after treatment, 0.5μM and 1μM psilocin promote neuronal differentiation of week-old hippocampal neurons by increasing expression of proliferation marker Ki67, as well as, DCX, MAP2 and neuritogenesis - including number of segments, length to cells and maximum length of neurites. These results are derived from one biological sample. This may suggest that modulation of hippocampal neurogenesis could play a role in psilocybin-induced neuroplasticity observed in humans.

Disclosures: Z. Haniff: None. **S. Thuret:** None.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.02/LBP115

Topic: C.03. Parkinson's Disease

Support: Aligning Science Across Parkinson's (ASAP-000350)

Title: Decoding the Mitophagic Stress Response: a stress dependent pathway modulating mitochondrial quality control in neurons

Authors: *B. BASAK, E. HOLZBAUR;
Physiology, University of Pennsylvania, Philadelphia, PA

Abstract: Mutations in genes regulating mitophagy, a central mitochondrial quality control pathway, are causative for neurodegenerative diseases, including Parkinson's disease. In this study, we unravel a neuron-specific pathway activated by mitochondrial damage, termed as 'Mitophagic Stress Response (MitoSR)'. We show that induction of MitoSR triggers the graded, coordinated degradation of negative regulators of autophagy, such as Myotubularin-related phosphatases 5 and 2 (MTMR5/MTMR2) and Rubicon, via the ubiquitin-proteasome system. MitoSR functions in parallel with classical Pink1/Parkin-mediated mitochondrial quality control; and exclusively targets the negative regulators of autophagy upon mitochondrial stress. We find that the negative regulators, MTMR5 and MTMR2 inhibit autophagosome biogenesis, whereas Rubicon suppresses lysosomal function, thereby impeding autophagosome maturation. Targeted depletion of these negative regulators via MitoSR activation significantly enhances mitophagic flux in diseased neurons, increasing both autophagosome formation and mitophagosome-lysosome fusion. Importantly, our data also suggest that Rubicon depletion can rescue

autophagosomal defects associated with the LRRK2^{G2019S} mutation, a common pathogenic variant in familial Parkinson's disease, indicating that Rubicon represents a convergent therapeutic target across multiple PD-linked pathways. Collectively, our work provides mechanistic insight into neuron-specific mitochondrial quality control pathways and identifies Rubicon as a potential target for therapeutic intervention to enhance mitophagy in the context of genetic and stress-associated Parkinson's disease.

Disclosures: B. Basak: None. **E. Holzbaur:** None.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.03/LBP116

Topic: C.03. Parkinson's Disease

Title: TLC for the Ca2+ dishomeostasis Neurodegeneration model

Authors: *M. A. THOMAS, T. HUGHES;
Montana Molecular, Bozeman, MT

Abstract: Calcium homeostasis is a critical process in the neuron requiring precise spatiotemportal control of intracellular Ca2+ concentrations. The regulation is dependent on dynamic interactions between organelles and their membrane contact sites. The Ca2+ dishomeostasis model posits that disrupted crosstalk among the endoplasmic reticulum ER, mitochondria, and lysosomes drives disease pathogenesis. The transient receptor potential channel mucolipin 1 (TRPML1), a Ca2+ permeant channel, plays a critical role in maintaining lysosomal function. TRPML1 dysfunction leads to impaired lysosomal activity, Ca2+ dyshomeostasis and ultimately neurodegeneration. Importantly, synthetic TRPML1 agonists such as ML-SA5 and MSK-83 have been shown to rescue Alzheimers and Parkinson's disease cellular models, and TRPML1 has become an increasingly interesting drug target (Tsunemi et al. 2019; Tedeschi et al. 2024; Tedeschi et al. 2019). Recent work in iPSC derived human cortical neurons expressing APOE4 demonstrated a significant decrease in TRPML1-induced endolysosomal CA2+ release (Somogyi et al. 2023).
Our goal was to develop a robust assay for the TRPML1 channel function, an assay that could be deployed in an automated drug discovery laboratory. To create a fluorescent biosensor for TRPML1, we positioned a fluorescent green Ca2+ sensor at the cytosolic surface of the lysosome by fusing it directly to the TRPML1 channel. This TRPML1 - Lysosomal - Ca2+ (TLC) sensor was then packaged in BacMam virus. Expressed in HEK293 cells, the agonists for TRPML1 produced strong, bright signals that were readily detected on standard fluorescence plate readers (384 well). Rapamycin, MSK-83, and ML-SA5 produced prolonged (~60 min) responses with unusual, prolonged response waveforms. ML-SA5 is often used as the reference agonist for the TRPML1 channel, but in our experiments it produced a response that can only be

partially blocked by MLS-13, while MSK-83 appears to be more specific and completely blocked by MLS-13. This is consistent with recent reports of off-target effects of ML-SA5.

Disclosures: M.A. Thomas: A. Employment/Salary (full or part-time); Montana Molecular. **T. Hughes:** A. Employment/Salary (full or part-time); Montana Molecular.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.04/LBP117

Topic: C.03. Parkinson's Disease

Support: NIH Grant NS123405

Title: Reduced DJ-1-F1Fo ATP synthase interaction correlates with midbrain dopaminergic neuron vulnerability in idiopathic Parkinson's disease

Authors: *K. N. ALAVIAN[1], A. ALI[1], H. BAE[2], M. TSUJISHITA[1], E. A. JONAS[3], P. J. SMITH[4], S. BALAKRISHNAN[1], A. ABULIMITI[2];
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Abstract: Disruption of neuronal and synaptic metabolic homeostasis is a key driver of neurodegeneration in Parkinson's disease (PD). Mitochondrial activity, biomass, and efficiency together maintain this balance. While activity and biomass are well characterized in PD, mitochondrial metabolic efficiency remains insufficiently explored. We previously showed that the protein product of the PD-associated gene DJ-1 modulates metabolic efficiency through its interaction with the F1Fo ATP synthase β subunit (β-sub). Here, using proximity ligation assay (PLA), we compared mitochondrial DJ-1-β-sub association across distinct mesencephalic dopaminergic (mesDA) neuronal subpopulations and their intracellular compartments in postmortem brains from PD cases and controls. In PD, DJ-1-β-sub PLA signal was lower than control in substantia nigra pars compacta (SNpc) somata and neurites, but was unchanged in ventral tegmental area (VTA) neurons. Across both PD and control groups, the PLA signal was reduced in distal neurites of SNpc neurons relative to VTA neurons. These region- and compartment-specific differences indicate that a deficit in the DJ-1-F1Fo ATP synthase interaction, and thus impaired mitochondrial efficiency, may contribute to the selective vulnerability of mesDA neurons in PD. Our findings highlight a subcellular mechanism linking DJ-1 to mitochondrial bioenergetics in human PD tissue and suggest a targetable pathway for protecting the most vulnerable dopaminergic populations.

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Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.05/LBP118

Topic: C.03. Parkinson's Disease

Support: NIH RF1-NS103873
NIH S10-OD023592

Title: Determination of α-Synuclein Protein Interactions by μMap Photo-proximity Labeling

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Abstract: Fibrillar aggregates of the natively disordered protein α-synuclein are hallmarks of Parkinson's disease and related neurodegenerative disorders termed synucleinopathies. Here, we used μMap photo-proximity labeling to determine the interactomes of α-synuclein monomers and fibrils in mouse brain lysate to better understand both the loss of healthy function and gain of toxic function aspects of synucleinopathies. Several α-synuclein variants were synthesized and characterized, showing that the small size (1 kDa) of the photocatalyst makes it minimally-perturbing to α-synuclein with a narrow labeling radius that allows one to identify interactome differences between different regions of α-synuclein. Monomer and fibril interactomes were compared to each other and to previous proximity labeling data sets for validation and examples of further investigations are demonstrated, including μMap in primary neurons and comparisons of the effects of α-synuclein post-translational modifications on interactomes.

Disclosures: E. Petersson: None.

Late-Breaking Poster

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Location: SDCC Hall B

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Support: Department of Veterans Affairs [Merit Review I01-BX003748 (D.K.C.)
Department of Veterans Affairs [Merit Review I01-BX005079 (J.E.D.)]

Title: Bioengineered Neural Tissue Testbed to Study Human Alpha Synuclein Pathology and Cell-to-cell Spread in the Nigrostriatal Pathway

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Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the accumulation of alpha-synuclein (aSyn) protein, leading to disruption in normal cellular functions and eventually cell death. Intercellular propagation of aSyn pathology across neural networks has been studied in various animal models. However, understanding the exact mechanisms of cell-to-cell spread in humans requires an anatomically-relevant human model. We have developed an *in vitro* 3D model using human iPSC-derived dopaminergic (DA) and striatal medium spiny neurons (MSNs) connected via long dopaminergic axons that mimics the native nigrostriatal pathway. The current study used this tissue engineered nigrostriatal pathway (TE-NSP) as a testbed to induce aSyn pathology to understand cell-to-cell spread of pathological aSyn protein across neuronal populations spanned by 2cm long axonal tracts. Recombinant pre-formed fibrils of aSyn were directly injected into DA neuronal population and the TE-NSP was later seeded with MSNs. Next, we did compartment specific analyses to evaluate the presence of pathologic aSyn via immunohistochemistry (IHC) staining of phosphorylated (pS129) aSyn and tyrosine hydroxylase (TH; key marker of DA neurons). The presence of aggregated aSyn and their capacity to seed fibrillization in each compartment were assessed by ELISA and seed amplification assay (SAA), respectively. IHC results showed evidence of early synucleinopathy in 40-50% cells (pS129+) in both neuronal populations in comparison to unseeded controls. ELISA results revealed relatively higher aggregated aSyn in all three compartments, namely, DA neurons, DA axon tracts and MSNs in comparison to their respective healthy controls. Interestingly, the axonal compartment of the testbed showed the highest concentration of aggregated aSyn protein. Further, SAA results exhibited significantly higher levels of seed-competent aSyn in all three compartments when compared to controls, indicating aSyn propagation and the capacity to spread pathological aSyn protein. Our novel 3D human testbed presents a promising platform for further investigations in pathophysiology of PD and the potential evaluation of therapeutic targets.

Disclosures: D. Chouhan: None. **G.T. Kannarkat:** None. **K.D. Browne:** None. **F. Laimo:** None. **S. Karandikar:** None. **D. Cullen:** None. **J. Duda:** None.

Late-Breaking Poster

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Topic: C.03. Parkinson's Disease

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SFB1286 (B8)
LT000559/2021-L

Title: Synphili-1 as a modulator of alpha-Synuclein assembly

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Abstract: The assembly of alpha-synuclein (aSyn) into intracellular inclusions called Lewy bodies (LBs) is a hallmark of Parkinson's disease (PD) and related synucleinopathies, yet the cellular mechanisms underlying this process remain incompletely understood. Existing models of aSyn aggregation often fail to capture its complexity, underscoring the need for new approaches. Here, we introduce a novel cell-based model to study aSyn aggregation and identify synphilin-1 (Sph1) as a pivotal modulator. Using bimolecular fluorescence complementation, we show that Sph1 interacts with aSyn to promote inclusion formation. These inclusions undergo fusion and fission, consistent with liquid-liquid phase separation (LLPS), and are regulated by altering Sph1 or aSyn expression or by disrupting their interaction. To validate these findings, we used complementary assays, including Seeding Amplification, which confirmed that Sph1 accelerates aSyn aggregation. Inclusions localized near trafficking hubs such as the trans-Golgi network and endo-lysosomal system, and their formation impaired vesicle trafficking and reduced aSyn release, suggesting consequences for intracellular transport and intercellular propagation. Importantly, molecular chaperones such as Hsp70 decreased inclusion size and number, highlighting the dynamic regulation of these assemblies within the proteostasis network. Together, our work demonstrates that Sph1 is a critical determinant of aSyn assembly, shaping both the spatial organization and functional impact of inclusions. These findings establish a robust model for studying aSyn aggregation and open new avenues for targeting the Sph1-aSyn interaction as a therapeutic strategy in PD and related synucleinopathies.

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Late-Breaking Poster

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Topic: C.03. Parkinson's Disease

Support: Aligning Science Across Parkinson's (ASAP-020551) through the Michael J. Fox Foundation for Parkinson's Research (MJFF)
Parkinson's Disease Foundation (PDFPF-RCE-1948)
National Institutes of Health (NIH, U19: 5U19NS104649-03)
NARSAD Young Investigator Grant from the Brain & Behavior Research Foundation (30086)

Title: A Vulnerable Subtype of Dopaminergic Neurons Drives Early Motor Deficits in Parkinson's Disease

Authors: *A. FUSHIKI[1], D. NG[2], Z. R. LEWIS[1], A. YADAV[3], T. SARAIVA[4], L. A. HAMMOND[5], C. WIRBLICH[6], B. TASIC[1], V. MENON[3], J. ALVES DA SILVA[7], R. M. COSTA[1];
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Abstract: In Parkinson's disease, dopaminergic neurons (DANs) in the midbrain gradually degenerate, with ventral substantia nigra pars compacta (SNc) DANs exhibiting greater vulnerability. However, it remains unclear whether specific molecular subtypes of ventral SNc DANs are more susceptible to degeneration in PD, and if they contribute to the early motor symptoms associated with the disease. We identified a subtype of *Sox6*+ DANs, *Anxa1*+, which are selectively lost earlier than other DANs, and with a time course that aligns with the development of motor symptoms in MitoPark mice. We generated a knock-in Cre mouse line for *Anxa1*+ DANs and showed differential anatomical inputs and outputs of this population. Further, we found that the inhibition of transmitter release in *Anxa1*+ neurons led to bradykinesia and tremor. This study uncovers the existence of a selectively vulnerable subtype of DANs that is sufficient to drive early motor symptoms in Parkinson's disease.

Disclosures: A. Fushiki: None. **D. Ng:** None. **Z.R. Lewis:** None. **A. Yadav:** None. **T. Saraiva:** None. **L.A. Hammond:** None. **C. Wirblich:** None. **B. Tasic:** None. **V. Menon:** None. **J. Alves Da Silva:** None. **R.M. Costa:** None.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.09/LBP122

Topic: C.03. Parkinson's Disease

Title: Temporal interference stimulation effectively reduces Parkinsonian beta band activity in a computational model of the basal ganglia network

Authors: *A. STOLLE, D. B. DORMAN;
Neuroscience, Hope College, Holland, MI

Abstract: Parkinson's disease (PD) is a progressive neurological disorder characterized by the degeneration of dopaminergic neurons, leading to impaired motor function and disrupted activity in the basal ganglia circuit. One of the most effective treatments currently available is deep brain

stimulation (DBS), which targets specific deep brain regions to restore normal firing patterns. However, this approach requires invasive surgery to implant electrodes into the deep brain structures, which poses surgical risks and limits accessibility for many patients. As a result, there is growing interest in non-invasive alternatives that can achieve similar therapeutic outcomes without the need for surgery. Transcranial temporal interference stimulation (tTIS) is a novel technique that delivers two high-frequency electrical currents through electrodes placed on the scalp. These currents overlap to produce a low-frequency "beat" that can reach deep brain structures without directly stimulating off-target regions. This mechanism enables tTIS to modulate neuronal activity in a non-invasive manner. Due to its non-invasive nature, tTIS is being explored as a potential alternative to DBS for treating neurological disorders such as PD. The objective of this study is to develop a computational model of the basal ganglia capable of simulating tTIS, and to compare its effectiveness with DBS as a treatment for PD. In this study, we developed a computational model of the basal ganglia using NetPyNE, a Python-based interface for NEURON, to simulate Parkinsonian network dynamics and investigate the effects of tTIS and DBS. We modified parameters from an existing model to reflect Parkinsonian conditions and incorporated tTIS to stimulate the subthalamic nucleus. Spectral analysis focused on beta-band activity (12-30 Hz), as it is associated with PD severity. Preliminary spectral analysis results show that both DBS and tTIS reduce excessive beta-band oscillations and restore activity closer to a healthy range. Optimal tTIS parameters (an amplitude of 0.04 mV and carrier frequencies of 1000 Hz and 1100 Hz) reduced beta-band power by 78.8% relative to PD and differed only 3.3% from healthy levels. Furthermore, the mean firing rate (MFR) data aligned with patterns typically observed in human Parkinsonian conditions. These findings suggest that tTIS is comparably effective to DBS in modulating network activity and has strong potential as a cost-effective, non-invasive treatment option for PD. Future work will involve validating these findings in experimental models and optimizing stimulation parameters for greater biological accuracy.

Disclosures: A. Stolle: None. **D.B. Dorman:** None.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

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Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

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Topic: C.03. Parkinson's Disease

Support: R01NS097782
RF1MH121373

Title: Inter-subject variability in a canonical spatio-spectral map of Parkinson's disease predicts clinical phenotype

Authors: *K. MIRPOUR, A. ALIJANPOUROTAGHSARA, N. POURATIAN;
UTSW, Dallas, TX

Abstract: *Background:* Parkinson's disease (PD) is characterized by excessive beta-frequency (13-35 Hz) oscillations in the cortico-basal ganglia network. However, this stereotyped neurophysiological finding is difficult to reconcile with the disease's profound clinical heterogeneity. We sought to resolve this paradox by proposing a "canonical map + deviation" framework, hypothesizing that a consistent, core spatio-spectral pattern of neural activity defines the parkinsonian state, while patient-specific deviations from this pattern systematically encode clinical variability. *Methods:* We acquired intraoperative local field potentials (LFP) from sensorimotor cortex using Electrocortical leads (ECoG), subthalamic nucleus (STN), and globus pallidus internus (GPi) in 75 PD patients and 17 Essential Tremor (ET) controls. We constructed spatio-spectral maps of oscillatory power and cortico-subcortical coherence. The statistical significance, consistency, and disease-specificity of these maps were rigorously tested using permutation analyses and multivariate pattern analysis (MVPA). We used Partial Least Squares (PLS) regression to correlate neurophysiological variability with motor symptom severity (UPDRS-III) and unsupervised clustering to identify neurophysiological subtypes. *Results:* We identified a statistically robust and highly consistent canonical map in PD, characterized by prominent pre-central beta power and strong beta-band coherence between the cortex and both STN and GPi. This pattern was specific to PD, allowing for accurate classification against ET controls (81.5% accuracy, p=0.004, using a linear support vector machine classifier). Crucially, inter-subject variability was not random; spatio-spectral regions with the highest variance across patients were also the most strongly correlated with individual motor impairment. Unsupervised clustering based on these features revealed distinct neurophysiological subgroups associated with significantly different overall clinical profiles. *Conclusion:* Our findings validate a unifying framework where a canonical spatio-spectral map defines the core parkinsonian state, and quantifiable, patient-specific deviations from this map encode the severity and nature of the clinical phenotype. This model reconciles the stereotyped pathophysiology and clinical heterogeneity of PD and provides a quantitative foundation for developing personalized neuromodulation therapies.

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Late-Breaking Poster

LBP072: C.03. Parkinson’s Disease

Location: SDCC Hall B

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Program #/Poster #: LBP072.11/LBP124

Topic: C.03. Parkinson’s Disease

Support: Aligning Science Across Parkinson's (ASAP)

Title: Investigating Striatal Dysfunction Using iPSC Derived Neurons from Parkinson’s Patients with SNCA Triplication

Authors: *H. NOOR[1,2], K. M. L. CRAMB[3,2], L. HANDUNNETTHI[4], R. WADE-MARTINS[3,2]; [1]Nuffleid Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom; [2]Aligning Science Across Parkinson's (ASAP) Collaborative Research Network, Chevy Chase, MD; [3]Department of Physiology, Anatomy & Genetics, University of Oxford, Oxford, United Kingdom; [4]Centre for Human Genetics and Department of Psychiatry, University of Oxford, Oxford, United Kingdom

Abstract: Background: Parkinson's disease (PD) is a common neurodegenerative disorder driven by loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), which heavily innervates the striatum. Medium spiny neurons (MSNs), the predominant postsynaptic targets of these dopaminergic inputs, populate ~90% of the striatum. Despite representing an integral component of the network responsible for movement modulation that becomes compromised in PD, our understanding of the role of MSNs in PD pathophysiology remains limited. **Methods:** To investigate dysfunction in human MSNs, we differentiated induced pluripotent stem cells (iPSCs) from patients with *SNCA* triplication mutation and healthy controls into GABAergic MSNs, confirmed by immunocytochemistry and RT-qPCR. Calcium dynamics were measured using the ratiometric indicator Fura-2AM, neurotransmitter release was probed with the genetically encoded sensor iGABASnFR2, and electrophysiological properties were assessed by whole-cell patch clamping. **Results:** iPSC-derived MSNs with *SNCA* triplication exhibited significantly reduced glutamate-evoked calcium transients compared to controls. Preliminary pharmacological testing with selective agonists suggests that impaired NMDA receptor function may contribute to this blunted response. Functionally, these cells displayed impaired GABA release upon depolarising glutamatergic stimulation, despite normal synaptic density, spine number and neurotransmitter content. In contrast, electrophysiological recordings indicated unaltered passive membrane properties. **Conclusion:** These findings reveal a functional deficit in iPSC-derived *SNCA* triplication MSNs, where disrupted calcium signalling diminishes the coupling of excitatory glutamatergic input from inhibitory GABAergic output. Such dysfunction may contribute to an imbalance of striatal output and lead to circuit dysfunction in PD. Ongoing work aims to dissect the specific contributions of NMDA receptor subtypes to the calcium defect and to identify molecular pathways linking calcium dysregulation to impaired neurotransmitter release. Future studies will employ an iPSC-based microfluidic model that recapitulates the cortico-striato-nigral connectivity to evaluate how this MSN dysfunction propagates within the PD-relevant network.

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Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

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Program #/Poster #: LBP072.12/LBP125

Topic: C.03. Parkinson's Disease

Title: PET-informed modeling of levodopa redistribution across monoaminergic systems in progressive Parkinson's disease

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Abstract: Background: Levodopa (LD) is the most effective treatment for Parkinson's disease (PD) but its benefit shortens with progression. Reed et al., 2012 showed mechanistically that LD enters both dopaminergic (SNc) and serotonergic neurons and is converted to dopamine (DA), with 5-HT terminals releasing DA without autoregulation as SNc terminals are lost. Longitudinal ^18F-dopa PET demonstrates region-specific decline beyond striatum, indicating progressive redistribution of LD among monoaminergic systems (Pavese et al., 2011). We aimed to quantify how this redistribution shapes striatal DA dynamics across PD stages. We extended Reed's ODE framework by adding an extrastriatal compartment and splitting BBB LD influx among four destinations: SNc terminals, striatal 5-HT terminals, DRN cell bodies, and extrastriatal nuclei. Routing weights were set from PET influx constants (Ki) and updated annually using reported declines in early PD (Pavese et al., 2011: n=10 patients, 6M/4F, mean age 57±7 y, disease duration ~26 mo; 11 healthy controls, mean age 67±6 y). We simulated a 75 mg/h×3 h LD infusion at dopaminergic fractions f_dop=0.42,0.6,0.8, computing peak DA, T_max, duration above baseline, AUC, a Redistribution Index (extrastriatal÷[SNc+5-HT+striatum]), uptake-pathway fractions, and progression slopes. Results: Redistribution strongly governed the striatal time course. As f_dop fell, LD was rerouted from SNc toward serotonergic/extrastriatal pools: modeled SNc routing declined from ~0.78 to ~0.41; RI rose 0.11→0.41. Striatal DA peaks increased 0.00049→0.00086 mg/L, T_max shortened 4.3→3.8 h, and duration above baseline contracted 8.7→7.6 h; AUC rose modestly 0.0037→0.0048 mg·h/L. The 5-HT contribution to extracellular DA increased 5%→30%. Uptake balance shifted slightly away from DAT (0.95→0.94) toward SERT (0.004→0.008). SNc routing declined ~5.3%/yr, close to PET striatal Ki loss ~8%/yr (Pavese et al., 2011); extrastriatal routing increased ~0.026/yr. Conclusions: Levodopa redistribution—from SNc to serotonergic and extrastriatal pathways—drives higher but shorter DA surges and the progressive narrowing of benefit. The framework links imaging-measured regional decline to therapeutic dynamics and supports ^18F-dopa PET for guiding dosing and trial design.
DisclosuresThis project was unfunded. The authors report no conflicts of interest.

Disclosures: H. Abdurakhimov: None. **J. Jung:** None. **W.W. Lytton:** None.

Late-Breaking Poster

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Program #/Poster #: LBP072.13/LBP126

Topic: C.03. Parkinson's Disease

Support: SIP20253588-IPN
SIP20250893-IPN

Title: Dopaminergic denervation in the rat external globus pallidus produces thermal and mechanical allodynia that is reversed by pramipexol.

Authors: H. GARCÍA JAUREGUI[1], P. V. CORREA LOPEZ[2], *E. CHUC-MEZA[3], M. GARCIA-RAMIREZ[4];
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Abstract: The external globus pallidus (GP) has been proposed as an integrative nucleus, not just a relay nucleus, in the basal ganglia. It receives dopaminergic innervation from the substantia nigra compacta (SNc) and appears to be involved in pain modulation. Thermal and mechanical allodynia and pain are evident from the early stages of Parkinson's disease (PD). This study aimed to determine whether dopamine loss in the GP increases thermal and mechanical allodynia. We also aimed to find out if this is reduced by treatment with dopamine agonists. To meet our objectives, we administered MPP+ locally to the GP (10 µg/0.5 µL) in male Wistar rats. Thirty days after the surgery, we measured thermal and mechanical allodynia using a hot plate (Ugo Basile) and Voy Frey filaments, respectively. Subsequently, we administered different concentrations of pramipexole (0.03, 0.3, and 3 mg/kg via sc). One group of rats received only SSI. After treatment, we extracted the rats' brains to determine the number of TH(+) neurons in the SNc. Rats that received MPP+ in the GP developed thermal and mechanical allodynia. Both types of allodynia were reduced by pramipexole in a dose-response relationship. TH(+) neurons in the SNc were reduced by 35% compared to the control side. In conclusion, the GP participates in pain response and administering a D2/D3 agonist such as pramipexole can reverse the allodynia caused by dopamine reduction. The pain response observed in PD may be due to a reduction of dopamine at the GP level.

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Late-Breaking Poster

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Topic: C.03. Parkinson’s Disease

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Title: Nuclear morphometric patterns in a lipopolysaccharide-based endotoxemia rat model.

Authors: *J. CORTÉS CORTINA[1], W. MONTEJO LÓPEZ[2], A. SÁNCHEZ GARCÍA[3], R. NADELLA[4], Y. FLORES-MARTINEZ[5], A. A. BARRIENTOS BONILLA[6], P. B. PENSADO GUEVARA[7], G. VARELA CASTILLO[8], D. HERNANDEZ-BALTAZAR[9];
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Abstract: In cells, the degree of spatial confinement can be determined by their largest and stiffest organelle, the nucleus. Nuclear shape is a result of the balance between the chromatin organization and nucleoskeleton. Although there are various immunostaining techniques for diagnostic studies using hematoxylin-eosin, the analysis of neuronal nuclear patterns has been neglected till date. To determine the nuclear morphometric patterns in a lipopolysaccharide (LPS)-based endotoxemia rat model, male adult Wistar rats were used. Cellular stress was induced by LPS (500 mg/Kg, i.p.), an immune response activator. The Brain tissue sections (5-10 μm) were immunostained with Hoechst-33342 (nuclear marker), CD11b/c-OX-42 (microglial marker) and tyrosine hydroxylase (dopaminergic phenotype marker). The evaluation of shape, size, number and hyper/hypochromic features of cell nuclei was performed by segmentation algorithm followed by an automatic thresholding analysis from ImageJ software. During inflammation, degeneration and cell death processes in substantia nigra, details regarding the nuclear patterns were identified in LPS-induced nuclear spatial constraints during neuronal injury. The analysis of nuclear patterns contributes to the understanding of cellular processes such as cell communication, cell survival, and neuronal homeostasis in stress-based animal models.

Disclosures: J. Cortés Cortina: None. **W. Montejo lópez:** None. **A. Sánchez García:** None. **R. Nadella:** None. **Y. Flores-Martinez:** None. **A.A. Barrientos Bonilla:** None. **P.B. Pensado guevara:** None. **G. Varela Castillo:** None. **D. Hernandez-Baltazar:** None.

Late-Breaking Poster

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Topic: C.03. Parkinson's Disease

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Instituto Politecnico Nacional Grant 20254178

Title: Toluene exacerbates motor deficits in a murine model of Parkinson's disease induced by MPP+

Authors: I. FERIA-FIGUEROA[1], S. MONTES[2], *N. PAEZ-MARTINEZ[1,3];
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Abstract: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra, leading to reduced dopamine levels and impaired motor function. Environmental factors, such as exposure to industrial solvents, may contribute to PD development. Toluene, widely used in paints and commercial products, is readily available and can also be abused recreationally. Some reports suggest that individuals with occupational exposure to toluene may develop PD, although direct evidence is limited. This study aimed to evaluate the effects of repeated toluene exposure on motor deficits in an experimental PD model induced by MPP+ in mice. Animals were injected with MPP+ or saline intra caudate putamen. Afterwards, they were repeatedly exposed to toluene (0 or 2000 ppm, twice daily for 7 days). Motor coordination and fatigue were assessed using the rotarod test, in which animals walk on a rotating rod to maintain balance; the latency to the first fall and the number of falls were recorded. Forelimb strength and endurance were evaluated with the wire hanging test, in which mice hang from a horizontal bar and the duration of hanging was measured. Toluene exposure and MPP+ by themselves significantly reduced the latency to the first fall and increased the number of falls in the rotarod test; however, the co-administration of toluene with MPP+ exacerbated both responses. In the wire hanging test, toluene-exposed mice showed shorter hanging times; nevertheless, the combination of toluene with MPP+ resulted in a response similar to that of control mice. These behavioral findings suggest that motor deficits induced by repeated exposure to toluene act as an environmental factor that exacerbates motor impairments in MPP+-treated mice. Thus, these data highlight the importance of considering solvent exposure as a relevant risk factor that may worsen Parkinson-like motor deficits.

Disclosures: I. Feria-Figueroa: None. **S. Montes:** None. **N. Paez-Martinez:** None.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.16/LBP129

Topic: C.03. Parkinson's Disease

Support: Italian Ministry of University and Research

Title: Targeting p75NTR in microglial cells ameliorates oxidative stress and inflammation in rotenone-induced Parkinson's phenotype

Authors: A. VALENZA[1,2], D. PENSABENE[3], M. MUZZI[3], I. MONTALI[1], F. RENDINA[1], A. FRACASSI[4], M. SEGATTO[3], *S. MORENO[1,2,5];
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Abstract: Parkinson's disease (PD) is associated with progressive degeneration of mesencephalic dopaminergic neurons. Among pathogenic mechanisms, oxidative stress and neuroinflammation involve microglia, whose role in disease progression, encompassing neuroprotective and neurotoxic phenotypes, remains incompletely elucidated. Neurotrophins (NT), acting via Trk receptors, or p75 neurotrophin receptor (p75NTR), are important modulators in PD. The involvement of p75NTR in apoptotic signaling cascades has stimulated the development of selective modulators of its activity. Among these, LM11A-31 promotes survival, while suppressing neurodegeneration pathways (Varone et al., 2024). We explored the potentially protective role of LM11A-31 in a rotenone (Rot)-based BV2 microglial cell model of PD, after preliminarily assessing p75NTR induction by the pesticide. Immunofluorescence (IF) analysis shows Rot-mediated induction of IBA1, TNF-α, and IL-6 vs. control (Ctrl) ($p<0.0001$, $p<0.001$), indicating microglial activation and pro-inflammatory signaling, abrogated by LM11A-31 treatment. Rot exposure caused a dramatic rise in TUNEL-positive apoptotic cells ($p<0.0001$), associated with altered cell morphology, as assessed by scanning electron microscopy (SEM), and cytoskeletal derangement, shown by α-tubulin IF. All these changes were restored by LM11A-31 treatment. We then detected by IF increased oxidative damage to nucleic acid (8-OH(d)G) and lipids (4-HNE) (both $p<0.05$, Rot vs. Ctrl), reduced by LM11A-31 ($p>0.001$). Redox imbalance may derive from activation of pro-oxidant enzymes, such as NOX4 and ACOX1 (Rot vs. Ctrl $p<0.01$ and $p<0.0001$, respectively), blunted by LM11A-31 ($p<0.01$, vs. Rot). To cope with excess ROS, antioxidant response involving NRF2 is elicited, as its IF levels are significantly induced by Rot ($p<0.01$). Consistently, its targets catalase and glutathione reductase (GSR), involved in H2O2 detoxification, are significantly increased by Rot. Conversely, glutathione and other antioxidants, such as superoxide dismutase (SOD) 1 and 2, decrease following Rot treatment, as if these molecules are themselves damaged by the insult. Co-treatment with LM11A-31 restores values of IF levels close (SOD2), equal (SOD1, CAT) or even higher (GSH), than Ctrl. Overall, our data provide novel evidence on pro-survival and anti-apoptotic actions of LM11A-31 against Rot-induced microglial damage, via p75NTR modulation. Such protective mechanisms are related to redox balance restoration. We support the potential of LM11A-31 as a candidate for developing innovative therapeutic strategies targeting microglia-mediated mechanisms in PD.

Disclosures: A. Valenza: None. **D. Pensabene:** None. **M. Muzzi:** None. **I. Montali:** None. **F. Rendina:** None. **A. Fracassi:** None. **M. Segatto:** None. **S. Moreno:** None.

Late-Breaking Poster

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Topic: C.03. Parkinson's Disease

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Title: Elucidating a Novel Binding Site for a Positive Allosteric Modulator of the D_1Dopamine Receptor

Authors: *S. DIMOVA[1], J. HANSON[2], K. WANG[3], A. MORITZ[2], A. N. NILSON[2], K. D. LUDERMAN[2], R. FREE[2], L. SHI[4], D. R. SIBLEY[2];
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Abstract: The D1 dopamine receptor (D1R) is a G protein-coupled receptor involved in dopamine (DA) signaling and is necessary for movement, cognition, and reward. Therefore, it represents a drug target for treating several neuropsychiatric disorders including Parkinson's Disease and schizophrenia. Current therapeutic approaches target the orthosteric pocket of the

D1R to improve DA signaling, which can reduce motor symptoms and/or enhance cognition. However, orthosteric agonists of the D1R exhibit cardiovascular side effects and they can cause the development of tolerance in patients. Due to these drawbacks, we have explored the use of positive allosteric modulators (PAMs) to selectively target the D1R and enhance endogenous signaling to overcome the shortcomings of current D1R agonists. Previously, our lab conducted a high throughput screen of 400,000+ compounds and identified compound MLS6585 as a novel D1R PAM. Using maximally effective concentrations, MLS6585 increased the potency (EC_{50}) of DA for the D1R by ~5-fold but had minimal effect on DA efficacy (Emax), as observed using functional assays measuring beta-arrestin recruitment to the receptor. To improve and optimize MLS6585 potency and efficacy, we synthesized and tested over 100 analogs. From this, we identified two compounds with improved PAM activity, UNC9815 and UNC10062. In beta-arrestin recruitment assays, UNC9815 increased DA potency ~10-fold but exhibited minimal efficacy enhancement. Conversely, UNC10062 increased DA potency by ~4-fold but increased the maximum efficacy (Emax) of DA by up to 200%. We tested both UNC9815 and UNC10062 in attempts to identify the D1R binding site of this scaffold using molecular modeling, receptor chimeras, and site-directed mutagenesis experiments. Collectively, our modeling and mutagenesis data suggest that UNC9815 and UNC10062 bind to an allosteric site formed by residues in the TM1and TM7 regions of the D1R. We have further attempted to obtain cryo-EM structures of the D1R in complex with our D1 PAM scaffolds to delineate and validate this proposed allosteric binding pocket. Initial cryo-EM data suggests that our PAMs associate with a binding pocket formed by TM1 and TM7 of the D1R, which we are currently making efforts to confirm. Ultimately, fully delineating this allosteric binding pocket will aid in the synthesis of more potent and efficacious PAMs using structure-guided analog design.

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Late-Breaking Poster

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Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.18/LBP131

Topic: C.03. Parkinson's Disease

Title: Transcranial temporal interference stimulation modulates spike timing of subthalamic nucleus neurons in a computational neuron model

Authors: *K. MALDONADO, D. B. DORMAN;
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Abstract: The current established treatment for Parkinson's disease is deep brain stimulation (DBS), an effective but invasive procedure requiring surgical implantation of electrodes. Transcranial temporal interference stimulation (tTIS) is a novel technique with potential to target deep brain regions without invasive intervention. This method uses scalp electrodes to apply two

high frequency currents with a low frequency offset, which causes a low beat frequency that may modulate neuronal activity where the two waves overlap in targeted deep brain regions. The subthalamic nucleus (STN) is the favored site for DBS to treat advanced Parkinson's disease. Currently, studies have broadly investigated the effects of tTIS on human subjects and animal models. Computational studies have modeled tTIS with generic neuron models. However, there is no current work focused on studying the effects of tTIS on optimized biophysical models of STN neurons. We sought to simulate tTIS on STN neurons to identify optimal parameters for effective STN modulation. We utilized NEURON to modify a recently optimized STN neuron model that is both anatomically and biophysically realistic. We designed a tTIS model with optimized parameters for frequency, amplitude, and gradient. Two sinusoidal electric fields with slightly offset high frequencies were applied across the STN neuron morphology using NEURON's extracellular mechanism, producing a low-frequency envelope. The gradient was optimized to accurately depict the distribution of current reaching STN neurons from scalp electrodes and its variation across neuronal compartments. The STN neuron analysis reflects expected patterns, where tTIS entrained and enhanced the firing activity, with a noticeable phase shift in spike timing. Therefore, our tTIS model successfully depicts STN neuron behavior, serving as a foundation for further optimization. These results indicate that tTIS can noninvasively influence activity in deep brain regions, specifically of STN neurons. With continued refinement to incorporate more realistic parameters, this modeling approach may guide noninvasive neuromodulation strategies targeting the STN. Ultimately, this work supports the potential of tTIS as a noninvasive therapeutic tool for treating Parkinson's disease by selectively modulating pathological activity in deep brain regions.

Disclosures: K. Maldonado: None. **D.B. Dorman:** None.

Late-Breaking Poster

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Topic: C.03. Parkinson's Disease

Support: NIH 5UG3NS105703-02

Title: Development of microfluid organ-chip models to study young onset Parkinson's disease

Authors: *Z. MYERS[1], M. G. OTERO[2], S. BELL[3], Z. SHU[4], N. T. MAIDMENT[5], C. N. SVENDSEN[6];
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Abstract: Parkinson's Disease (PD) is the second most common neurodegenerative diseases worldwide, affecting nearly one million people in the United States alone. PD results from a loss of dopaminergic neurons in the substantia nigra, disrupting the nigro-striatal pathway leading to both motor and nonmotor symptoms. In recent years, large strides have been made to optimize *in vitro* models of PD, using more advanced systems such as organoids and microfluidic organ-on-a-chip systems. We previously generated a dopamine neuron-chip (Otero et at. 2023) that incorporated induced pluripotent stem cells (iPSCs) that were differentiated into a homogeneous, functional and mature culture of dopaminergic neurons. Here we apply this model to a set of iPSC-derived dopaminergic neurons from patients with young onset Parkinsons Disease (YOPD) to recapitulate the dopamine loss seen in patients. In addition, we wanted to use the dual channel organ-chip to culture both mesencephalic dopamine neurons and striatal Darrp-32-positive medium spiny neurons for a more complete nigro-striatal system. Using this organ-chip model, we have developed a dopaminergic neuron-chip that contains tyrosine hydroxylase (TH)-positive dopaminergic neurons in one of the channels. There was significant loss of TH-positive neurons in the dopamine chips from YOPD iPSC lines compared with controls, demonstrated by immunostaining and western blotting. There was also reduced dopamine release measured via HPLC, demonstrating a decrease in the functionality of these cells. These disease phenotypes were observed in as little as 28 days in culture, without any need to add additional stressors. This model of YOPD better recapitulates phenotypes seen in the substantia nigra of patients, making it a powerful tool to study the disease. As this model shows a loss of dopamine neurons, we are now aiming to increase the model's complexity by adding Darpp-32 positive medium spiny neurons into the second channel to make these chips a more complete model of the nigro-striatal pathway. The nigro-striatal chip contains both the pre- and post-synaptic components of this pathway, making them a powerful patient-based *in vitro* model that can be used to explore this disease and ultimately as a screen for drug development.

Disclosures: Z. Myers: None. **M.G. Otero:** None. **S. Bell:** None. **Z. Shu:** None. **N.T. Maidment:** None. **C.N. Svendsen:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Emulate.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.20/LBP133

Topic: C.03. Parkinson's Disease

Title: Ubiquitinomics-Based In Vivo PK/PD Model Enabled Profiling of USP30 Inhibitors for Mitophagy enhancement

Authors: D. MENSCHING[1], M. PEDERCINI[2], T. GAITANOS[3], ***L. CABERLOTTO**[2], C. ALBRECHT[4], J. CARR[5], D. WALTER[5], M. GEMKOW[4];
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Abstract: Mitochondrial dysfunction is closely linked to the development of Parkinson's disease (PD), and enhancing mitophagy - particularly through the PINK1/Parkin pathway -presents a promising therapeutic approach to restore mitochondrial health. USP30, a mitochondrial deubiquitinase, counteracts this pathway by removing ubiquitin from mitochondrial proteins, thereby limiting mitophagy. Our studies utilize a state-of-the-art ubiquitinomics platform to profile mitochondrial protein ubiquitination and assess the efficacy of USP30 inhibitors in vivo, overcoming previous limitations in sensitivity encountered with immunoassay-based methods in complex tissues such as the central nervous system (CNS). Ubiquitinomics Platform and In Vivo PK/PD Model Development We developed cellular and in vivo pharmacokinetic/pharmacodynamic (PK/PD) models using BAM15 to induce mitochondrial damage. The ubiquitinomics platform enabled precise quantification of mitochondrial ubiquitination, with ub-TOMM20 validated as a surrogate marker for mitophagy. Utilizing this model, USP30 inhibitors were shown to significantly enhance mitophagy, demonstrating their potential therapeutic impact. Genetic Validation and In Vivo Application Genetic knockout studies confirmed USP30's role in suppressing mitophagy, supporting mitochondrial ubiquitination as a reliable in vivo biomarker for mitophagy monitoring. The mechanistic insights from these models translated effectively to a Parkinson's disease-relevant paraquat model, where USP30 inhibition produced both acute and sustained mitophagy enhancement over a three-week period. Conclusions and Therapeutic Implications Our studies demonstrate that a ubiquitinomics platform can robustly monitor mitophagy across cellular, genetic, and in vivo models with and without USP30 inhibition. The validation of ub-TOMM20 as a functional biomarker and confirmation of mitophagy induction via Mito-QC highlight the platform's effectiveness. The development of a mechanistic PK/PD model facilitated rapid translation of cellular findings to the CNS, and subsequent validation in a Parkinson's disease model revealed sustained mitophagy enhancement. Collectively, these results endorse USP30 as a promising therapeutic target for restoring mitochondrial function by resolving mitochondrial dysfunction in neurodegenerative diseases.

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Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

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Program #/Poster #: LBP072.21/LBP134

Topic: C.03. Parkinson's Disease

Support: 2017YFA0104301)
ZKX17016)

Title: Precision Magnetogenetic Regulation of Iron Homeostasis with clMagR-MSCs Improves Parkinson's Outcomes

Authors: *Q. YE;
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Abstract: Current treatments for Parkinson's disease (PD)—including drugs and deep brain stimulation (DBS)—do not regenerate dopaminergic neurons or restore function in damaged circuits. Repetitive transcranial magnetic stimulation (rTMS) can partially improve function but lacks precise targeting. Stem-cell replacement in the striatum is promising, but graft survival and neuronal regeneration remain major challenges. This study explores whether magneto-responsive MSC^{clMagR} cells can enhance graft survival, promote regeneration, and restore motor function in PD. Human umbilical cord mesenchymal stem cells were engineered to overexpress the magnetoreceptor clMagR (MSC^{clMagR}). In vitro, we assessed iron uptake, intracellular iron-oxide cluster formation, and oxidative stress reduction, with magnetic stimulation (10 Hz, 50 mT) to enhance paracrine factor secretion and synapse growth. In vivo, PD model male mice (6-8 weeks) were randomly assigned to one of four groups: MSC^{clMagR} with magnetic stimulation, MSC^{clMagR} alone, control MSCs with magnetic stimulation, and control MSCs alone. Motor function was assessed using the rotarod test and open-field assay. Histology and biomolecular analyses were performed to measure neuronal regeneration. Statistical analyses included two-way ANOVA and t-tests. MSC^{clMagR} cells sequestered excess iron and formed iron oxide clusters, reducing oxidative stress. Magnetic stimulation increased paracrine secretion and synapse growth in vitro. In PD mice, MSC^{clMagR} with magnetic stimulation led to greater motor recovery ($p < 0.01$) and higher neuronal growth in the striatum compared to controls. Striatal neuronal density and synaptic protein expression were significantly higher in the MSC^{clMagR} + magnetic
stimulation group ($p < 0.05$). In conclusion, MSC^{clMagR} combined with magnetic stimulation significantly improves motor recovery and neuronal regeneration in PD mice. This approach addresses critical challenges in PD stem-cell therapy and suggests a minimally invasive, field-controllable strategy with potential clinical applications for neurodegenerative diseases.Key word Parkinson's disease; clMagR; magnetic stimulation; iron overload; stem cells

Disclosures: Q. Ye: None.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

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Program #/Poster #: LBP072.22/LBP135

Topic: C.03. Parkinson's Disease

Support: NIH Grant 1R01NS131405-01

Title: REM sleep is associated with reduced pathophysiological daytime basal ganglia-cortical circuit activity and connectivity in Parkinson's disease

Authors: *J. ZHANG, C. SMYTH, H. HAYAT, M. ANJUM, A. KRYSTAL, P. A. STARR, S. LITTLE;
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Abstract: Sleep disturbances have been shown to be intimately and bidirectionally related to disease progression across a wide range of neurodegenerative disorders including Parkinson's disease (PD) and Alzheimer's disease (AD). However, the precise neurophysiological mechanisms relating abnormal sleep to aberrant daytime network activity that accelerates disease progression has yet to be determined. We recorded chronic, multi-night (*n*=39, recording hours=410.3), intracranial cortico-basal recordings during sleep from four patients with PD along with paired external polysomnography and morning self-report. This revealed that longer duration (and shorter latency) of rapid eye movement (REM) sleep predicted reduced daytime resting beta (13-30 Hz) activity and cortico-basal functional and effective connectivity (Figure 1C), features established to be pathophysiological in PD. Within REM sleep, stronger cortical delta activity specifically predicted reduced pathophysiological cortico-basal neural features (Figure 1D). The anti-correlation between delta activity and morning pathophysiological neural features was found to be primarily driven by the amplitude of delta waves rather than their occurrence rate. As the percentage of REM sleep increased in later hours during sleep, its protective effects also increased, suggesting a timing effect. Additionally, REM delta power significantly predicted greater self-reported morning alertness. These findings highlight a potentially protective role of REM sleep in cortico-basal network health in PD and daytime subjective experience, representing a potential target for closed loop neuromodulation therapies in neurodegenerative diseases to impact disease progression.

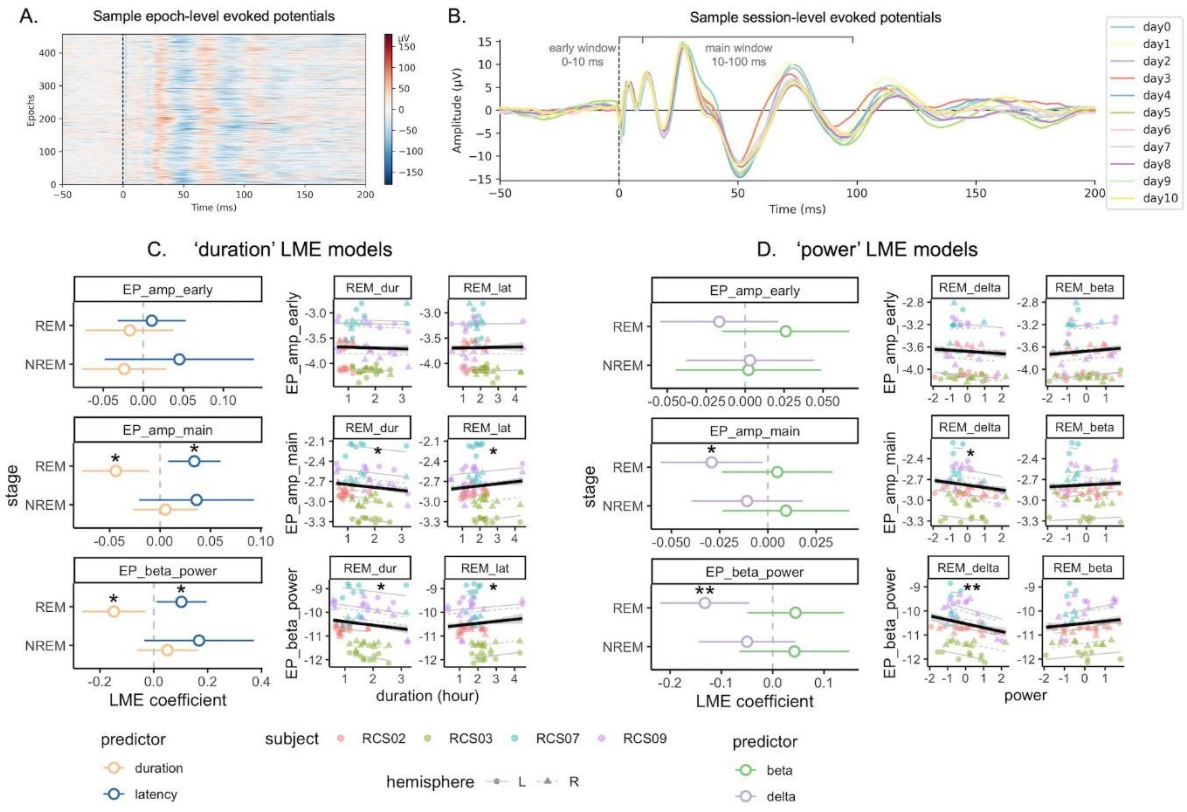

Figure 1. REM sleep predicts next-morning BG-to-cortical effective connectivity, indexed by evoked potentials (EP). (A) Trial-level cortical EP data of an example morning session. Each epoch spans from -50ms to 200 ms. (B) Session-level averaged waveform of cortical EP of an example participant. At the trial level, we calculated the peak-to-trough amplitudes in an early window (0–10 ms) and a main window (10–100 ms), and the beta power in the entire window (10–200 ms) and then averaged across epochs. (C) The results of linear mixed-effect (LME) models of sleep duration predictors (duration and latency) in prediction of EP metrics. (D) The results of LME models of sleep power predictors (cortical beta and delta) in prediction of BG-cortex EP metrics. In (C) and (D), the left panels show the LME coefficients with 95% confidence intervals and the right panels show the scatterplots of outcome variables against REM predictors with model predictions. ep_amp_ealry: peak-to-trough amplitude of EP in the early window; ep_amp_main: peak-to-trough amplitude of EP in the main window; ep_beta_power: beta power of the EP in the whole window; REM_dur: REM duration; REM_lat: REM latency. Asterisks indicate statistical significance in LME models: * = p<.05, ** = p< .01.

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Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.23/LBP136

Topic: C.03. Parkinson's Disease

Title: Detection of prodromal Parkinson's Disease with a neural network

Authors: M. ZUBAIR[1], M. FERRANTE[2], ***C. DEL GRATTA**[3], N. TOSCHI[2];
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prevention, University of Rome Tor Vergata, Rome, Italy; [3]Neuroscience Imaging and Clinical Sciences, Gabriele D'Annunzio University of Chieti and Pescara, Italy, Chieti, Italy

Abstract: Parkinson's Disease (PD) is a progressive neurodegenerative disorder affecting motor and cognitive functions. Early detection, particularly during the prodromal phase, is essential for slowing disease progression. However, current diagnostic methods struggle to identify PD in its early stages due to subtle symptoms. This study introduces a Depth-wise Separable 3D Convolutional Neural Network (DS-3DCNN) model to classify brain MRI scans into three categories: healthy control, prodromal PD, and diagnosed PD, aiming to provide a computationally efficient and accurate method for early PD detection. MRI scans from the Parkinson Progression Markers Initiative (PPMI) dataset, comprising 426 scans from 426 subjects (184 females, 242 males), were used for training and testing. The scans were categorized into healthy control, prodromal PD, and diagnosed PD groups. Preprocessing steps included image registration with the MNI template and conversion to NIFTI format for deep learning analysis. The DS-3DCNN model utilized depth-wise separable convolutions to reduce the model computational complexity without compromising performance. The study used 5-fold cross-validation to ensure replicability and assess the model robustness across subsets of the dataset. The analysis was performed with adequate sample sizes, and the study maintained rigorous control by comparing the three groups. The model was evaluated using performance metrics, achieving an average accuracy of 90.15% +/- 3.0%, with a peak accuracy of 95.29% in one-fold. Additional metrics, including precision, recall, F1-score, and ROC-AUC, demonstrated robust performance across all categories. The model accurately classified the prodromal stage, with no misclassifications in the best-performing fold. Age and sex differences were considered, with 184 females and 242 males, aged 30 years and older, included in the analysis. The DS-3DCNN model offers an efficient, scalable solution for early PD detection, particularly for identifying the prodromal phase. Its potential for clinical application is further enhanced using Grad-CAM for interpretability, providing valuable insights into the brain regions most influential for classification decisions, thereby improving the model clinical relevance and trustworthiness.

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Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

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Program #/Poster #: LBP072.24/LBP137

Topic: C.03. Parkinson's Disease

Support: NIH Grant R15NS087447
NSF Grant 1806056

Title: The elliptical nature of hand tremor: how peripheral neuromusculoskeletal dynamics shape hand tremor

Authors: L. BEUTLER[1], I. SYNDERGAARD[1], D. FARINA[2], ***S. K. CHARLES**[3];
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Abstract: Tremor is the most prevalent movement disorder, yet the influence of the peripheral neuromusculoskeletal system in modulating tremor remains incompletely characterized. Understanding how tremor-inducing muscle activity travels through this system to manifest as hand tremor is important for evaluating and enhancing tremor-suppression interventions. We introduce the first comprehensive model of tremor propagation through the upper limb, mapping the pathway from tremorogenic muscle activation to observable hand tremor. This linear, time-invariant multi-input multi-output model simulates hand tremor generated by all 50 upper-limb muscles (excluding intrinsic hand muscles), both individually and in combination, across seven postures representative of everyday function and clinical evaluation. To ensure reliability, we conducted extensive Monte Carlo simulations across a wide range of input and model parameters. Our modeling demonstrates, for the first time, that to the extent that the neuromusculoskeletal system of the upper limb can be approximated as linear and time-invariant during postural tremor, steady-state single-frequency tremorogenic activity causes the hand to trace a (two-dimensional) ellipse in three-dimensional space. Each muscle contributes a distinct tremor ellipse, defined by its direction and amplitude. Muscles influencing the same degrees of freedom—whether synergistic or antagonistic—tended to produce tremor in similar directions. While tremor direction varied notably with posture, the ensemble of individual ellipses consistently formed a relatively flat ellipsoid, with its dominant plane nearly orthogonal to the long axis of the forearm and hand. Across postures, distal muscles—especially those at the wrist—exhibited the highest potential to drive hand tremor. These results underscore the pivotal role of peripheral biomechanics in shaping hand tremor. The consistent flatness of the composite ellipsoid and the prominence of distal muscle contributions offer practical insights for the development of mechanical tremor-suppression devices and targeted therapeutic strategies.

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Title: Silicon Dioxide (SiO_2) Matrix Induces Dopaminergic Differentiation of SH-SY5Y Cells: A Potential Neuroregenerative Strategy for Parkinson's Disease

Authors: *P. VERGARA-ARAGON[1], M. SILVA-LUCERO[2], A. J. ESPADAS-ALVAREZ, Sr.[3], L. TEXCO[4], M. GÓMEZ-CHAVARÍN[5];
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Abstract: Background: Parkinson's disease (PD) is a neurodegenerative disorder characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta, leading to striatal dopamine depletion. This results in severe motor impairments and non-motor symptoms. Current therapies provide symptomatic relief but fail to restore dopaminergic neurons or halt disease progression. The development of biomaterials that promote neuronal differentiation represents a promising strategy for regenerative medicine in PD.**Materials and Methods:**A bioactive silicon dioxide (SiO_2) matrix was designed and incubated with SH-SY5Y neuroblastoma cells under controlled culture conditions. Morphological changes were assessed by microscopy, while dopaminergic differentiation was confirmed by immunocytochemistry and Western blot analysis of tyrosine hydroxylase and dopamine transporter expression.**Results:**SH-SY5Y cells cultured with the SiO_2 matrix exhibited significant neurite outgrowth and the formation of interconnected neuronal networks. Quantitative analysis revealed increased expression of dopaminergic markers, including tyrosine hydroxylase and dopamine transporter, confirming the acquisition of a mature dopaminergic phenotype. The SiO_2 matrix also enhanced cell viability and provided a favorable microenvironment for neuronal growth.**Conclusions:**The SiO_2 matrix effectively promotes dopaminergic differentiation of SH-SY5Y cells in vitro, suggesting its potential as a neuroregenerative platform for the treatment of PD. These findings open perspectives for future translational studies aimed at restoring dopaminergic function in neurodegenerative disorders.

Disclosures: P. Vergara-Aragon: None. **M. Silva-Lucero:** None. **A.J. Espadas-Alvarez:** None. **L. Texco:** None. **M. Gómez-Chavarín:** None.

Late-Breaking Poster

LBP072: C.03. Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP072.26/LBP139

Topic: C.03. Parkinson's Disease

Support: NIGMS Grant R35GM142368
CDMRP PD240020

Title: Adaptive immunodeficiency, following mild traumatic brain injury, is neuroprotective for dopaminergic neurons but exacerbates Lewy body accumulation through alpha synuclein spread in a parkinsonian preclinical model

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Abstract: Traumatic brain injury (TBI) is a known risk factor for Parkinson's disease (PD) development. A previous study examining veterans who experienced a mild TBI (mTBI) during combat found they had a 56% increased risk of developing PD later in life. Despite knowing this relationship, not much is understood about the mechanisms connecting them; specifically, little research has examined the increased neuroinflammatory response connecting both mTBI and PD, and how it may exacerbate the degeneration of dopaminergic (DA) neurons in the substantia nigra (SN) or the accumulation of Lewy bodies (LBs). In this study, we utilized a preclinical mouse model for PD involving intrastriatal alpha-synuclein (α-syn) preformed fibril (PFF) injections to examine the impact of mTBI on PFF-associated pathologies. We found that mice that received mTBI prior to PFF injections increased DA cell death within the SN compared to PFF-only and sham control mice (n = 6-8 male mice for each experimental group). We then explored the impact of adaptive immunity on our mTBI + PFF group, utilizing genetically immunodeficient Rag2 knockout (KO) mice (n = 6-8 male mice for each experimental group). These results indicated that immunodeficiency positively impacted DA neurons' survival. From these experiments, we explored α-syn spread to the cortex and found, in wildtype mice, the mTBI + PFF model increased α-syn positive aggregates in the ipsilateral cortex compared to mice who only received PFFs, suggesting increased LB accumulation (n = 5-6 male mice for each experimental group, $p < 0.05$). RNAseq analysis of DA neurons from RiboDat transgenic mice showed multiple genes associated with LB formation, neuroinflammation, and cell survival were dysregulated in mice that received mTBI prior to PFFs compared to mice who received PFFs alone. The Rag2 KO mouse model in the mTBI + PFF cohort displayed increased LB formation in the ipsilateral cortex compared to our PFF only mice but not compared to our mTBI + PFF model (n = 5-6 male mice for each experimental group). These results suggest mTBI exacerbates α-syn accumulation and spread throughout the brain. Furthermore, adaptive immunity plays a role in neuronal protection but does not affect LB formation in cortical regions. Examining the impact of neuroinflammation on DA cell survival and α-syn spread may be critical in novel therapeutic PD treatment and risk reduction.

Disclosures: J.P. Milner: None. **C. Kelly:** None. **B.A. Lester:** None. **A.M. Pickrell:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.01/LBP140

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: CHDI

Title: Elucidating Cell Type-Specific Determinants of Epigenetic and DNA Damage Response Dysregulation in Huntington's Disease

Authors: *I. M. ILYASHOV[1], M. BAFFUTO[2], S. GARDNER[3], C. PRESSL[2], N. HEINTZ[3]; [1]Laboratory of Molecular Biology, The Rockefeller University, NY, NY; [2]Laboratory of Molecular Biology, The Rockefeller University, New York, NY; [3]Laboratory of Molecular Biology, Rockefeller University, New York, NY

Abstract: In Huntington's Disease (HD), one inherited allele of the huntingtin (HTT) gene contains an expanded polyQ (CAG) tract in exon 1 that expands further over the lifetime of a patient. Past a threshold of 40 CAGs, HTT becomes toxic, resulting in selective neurodegeneration of medium spiny neurons (MSNs) in the striatum and layer 5a neurons of the cortex. However, the presence of CAG-expanding yet resilient neurons such as cortex layer 6a/b suggests that there are distinct cell-specific determinants for expansion and vulnerability in HD. While the exact cause of cell-specific vulnerability is less defined, genome wide association studies (GWAS) point to mismatch repair (MMR) proteins as the largest modifiers disease onset. Our previously published data shows that GWAS-identified disease-onset-hastening MMR proteins MSH2 and MSH3 (of the MutSβ complex) exhibit elevated expression in human MSNs compared to glial subtypes, indicating that the mechanism of CAG expansion is driven by highly cell type-specific molecular and epigenetic variables. To explore other cell type-specific determinants of expansion, Fluorescence-activated nuclei sorting and subsequent CUT&RUN-seq (FANS-CUT&RUN-seq) was carried out on NeuN+ neuronal nuclei and OLIG2+ oligodendrocyte nuclei of postmortem human donor striatum and cerebellum using multiple histone post translational modification (PTM) targets, leveraging our donor-matched ATACseq and RNAseq datasets for contextualization of gene regulation. The distribution of open-chromatin (H3K4me3 and H3K27ac) and closed-chromatin (H3K27me3, H3K9me3) histone PTMs, integrated with accessibility and transcriptional data, reveals selective enhancer de-repression in HD, in addition to human- and MSN-specific MSH3 and MSH2 intronic super enhancers. To assess relative global MMR recruitment rates, DNA repair-associated histone PTMs were also assayed via FANS-CUT&RUN-seq, including H3K56ac which is known to inhibit recruitment of MutSβ to sites of damage, and γH2AX, an indicator of local repair factor transduction at DNA damage events. H3K56ac exhibited a stronger H3K27ac enhancer overlap (including at HTT exon 1) in neuronal subtypes compared to glia, suggesting that basal MutSβ-driven repair events may be attenuated around neuronal enhancers. This work presents a valuable characterization of the epigenetic landscape that modulates the expression and activity of the largest modifiers of somatic HTT CAG expansion within a human postmortem context, adding a new dimension to established models of MMR dynamics in MSNs.

Disclosures: I.M. Ilyashov: None. **M. Baffuto:** None. **S. Gardner:** None. **C. Pressl:** None. **N. Heintz:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.02/LBP141

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NS111202

Title: APEX2-sequencing to determine RNA-huntingtin interactions

Authors: *D. AMINEVA, M. PELES, G. CANNESTRO, T. SAROVICH, J. WEI;
Biomedical Science, Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL

Abstract: Huntington's disease (HD) is a progressive neurodegenerative disorder caused by CAG repeat expansion in the HTT gene. Defining the molecular functions of wild-type and mutant huntingtin (mHTT) is essential for understanding HD pathogenesis and identifying therapeutic targets. While HTT is best known for its interactions with protein partners, recent studies suggest that HTT can also engage with RNA. We previously developed an APEX2-HTT proximity labeling platform to map HTT protein interactomes in living cells. Here, we adapted this strategy to RNA (APEX2-Seq) to identify HTT-proximal transcripts. Human SH-SY5Y cells stably expressing APEX2-HTT with either normal (23Q) or expanded (145Q) polyglutamine tracts were subjected to biotin-phenol/H_2O_2 APEX2 labeling, followed by streptavidin enrichment and RNA sequencing. Optimization confirmed efficient RNA biotinylation by APEX2-HTT, with HTT145Q producing the strongest signal. At the gene level, 6 enriched transcripts were detected in HTT23Q samples and 44 in HTT145Q samples (log_2FoldChange >1, padj <0.05). Notably, 88.6% of HTT145Q-proximal RNAs were noncoding. Pathway analysis revealed significant enrichment in RNA processing, with strongest association to U2 snRNP (padj = 1.33e-11) and nucleoprotein complexes (padj = 1.55e-05). At the transcript-variant level, 259 isoforms were enriched in HTT23Q and 202 in HTT145Q, with 17 shared. Protein-coding isoforms were most abundant in both groups, though HTT145Q showed higher proportions of lncRNA and nonsense-mediated decay (NMD) isoforms. Isoform-level enrichment further implicated synaptic compartments, suggesting a role of HTT in regulating local protein translation. Together, these findings establish APEX2-Seq as a powerful tool to resolve HTT-proximal RNAs in living cells. By uncovering and comparing normal HTT and muHTT-binding RNAs, our work provides new insights into RNA-centric mechanisms underlying HD pathogenesis.

Disclosures: D. Amineva: None. **M. Peles:** None. **G. Cannestro:** None. **T. Sarovich:** None. **J. Wei:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.03/LBP142

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NINDS R21NS119671
NIH R21NS124936
ABCD Charitable Trust
Karen Toffler Charitable Trust
The Charles and Mary Latham Fund
DC-CFAR Pilot Fund

Title: Effect of loss of junctophilin-3 on medium spiny neuron physiology

Authors: *X. ZHAN[1], R. L. MARGOLIS[2];
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Abstract: Junctophilin3 (JPH3) facilitates the formation of a junctional membrane complex between the plasma membrane and the endoplasmic reticulum, playing a vital role in Cav1-RyR2-KCa3 complexes and the regulation of intracellular calcium microdomains. This regulation is essential for neuronal excitability, spike patterns, and synaptic transmission. The modulation of calcium homeostasis by JPH3 is of potential significance in Huntington's Disease Like-2 (HDL2), an autosomal dominant neurodegenerative disorder with striking clinical, pathological, and genetic similarities to Huntingtons' disease, including early and prominent striatal atrophy. The CAG/CTG trinucleotide repeat expansion mutation that causes HDL2 is located within a variable spliced exon of *JPH3.* The expansion leads to decreased levels of JPH3 in multiple brain regions, implicating JPH3 loss in the pathophysiology of HDL2. In HD, both D1R and D2R striatal medium spiny neurons (MSNs) are affected and contribute to the disease phenotype. The effect of loss of JPH3 on MSNs is unknown. To preliminarily address the impact of loss of JPH3 on MSN function, we focused on D2R MSNs, which have a prominent inhibitory role and are lost early in HD. D2-EGFP mice were crossed with *Jph3* KO mice, generating mice with normal, hemizygote, or homozygote loss of JPH3 and labelled D2R-MSNs. Slice preparations from 3-month-old mice were used for patch clamping experiments. Experiments demonstrated that partial or complete loss of JPH3 resulted in elevated action potential thresholds, faster spiking rates, impaired accommodation of spiking activity, but had no effect on rheobase currents. Initial experiments at one month, including slice preps from *Jph3* KO mice crossed with D1-tDTomato to label D1R-MSNs, suggest that early functional changes may include elevated action potential thresholds and loss of accommodation in D2R-MSNs but not D1R-MSNs. Taken together, these data demonstrate that loss of JPH3 alters D2R-MSN physiology in mature mice, with preliminary suggestions that the effect of JPH3 loss may begin as early as 1 month and that JPH3 loss may differentially effect D1R and D2R MSNs.

Disclosures: X. Zhan: None. **R.L. Margolis:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.04/LBP143

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: SLS-Qidong Innovation Fund (C.L.)

Title: Self-inactivating AAV-CRISPR at different ages enables sustained amelioration of Huntington's disease deficits in BAC226Q mice

Authors: *Z. ABUDUJIELILI, Y. DAI;
Peking University, Beijing, China

Abstract: Huntington’s disease (HD) is a monogenic autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion in the first exon of the HTT gene, yielding a gain-of-toxic-function mutant Huntingtin protein mHTT. CRISPR/Cas9 is a potentially powerful therapeutic tool for treating HD by eliminating mutant HTT gene (mHTT) gene. We developed a specific SaCas9 guide RNA to target human mHTT, and a self-inactivating gene editing system that abolishes SaCas9 after a short transient expression for high gene editing efficiency and maximal safety to prevent off-target effects. Both conventional and the new self-inactivating gene editing systems achieved successful elimination of mHTT gene, 60-90% mHTT protein and 90% of mHTT aggregation in BAC226Q HD mouse brains, which resulted in significant long-term rescue of neural pathology, motor deficits, weight loss and shortened lifespan. These beneficial effects were observed when gene editing was applied before, at and well after the on-set of pathological and behavioral abnormalities. These proof-of-concept data demonstrate that gene editing can be a highly effective therapeutic approach for HD and other inherited neurodegenerative diseases.

Disclosures: Z. Abudujielili: None. **Y. Dai:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.05/LBP144

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: CHDI Foundation. Project A-18015

Title: Preclinical assessment of di-siRNA therapy on motor deficits and avolition in the Q175 mouse model of Huntington's disease

Authors: *C. F. CARDOZO HERNANDEZ[1], F. MORGADO[2], E. MCDONNELL[2], I. GILDISH[2], J. F. CHEER[2];
[1]Department of Neurobiology, University of Maryland, Baltimore., Baltimore, MD; [2]Department of Anatomy and Neurobiology, University of Maryland School of Medicine, Baltimore, MD

Abstract: Huntington's disease (HD) is a neurodegenerative disorder produced by an expansion of the CAG repeat in the huntingtin (HTT) gene, leading to the production of mutant huntingtin (mHTT). This results in progressive degeneration of the striatum that is manifest in motor deficits such as chorea and psychiatric symptoms including avolition. A novel therapeutic approach using a divalent small interfering RNA (di-siRNA) has been developed to reduce HTT expression in the brain. The aim of this study is to evaluate whether intracerebroventricular (ICV) di-siRNA treatment mitigates the progression of motivational and motor impairments in Q175 mice. Wild-type (WT) and Q175 animals of both sexes were treated at six month of age with either di-siRNA or a non-targeting control (NTC), generating four experimental groups (WT-NTC, WT-di-siRNA, Q175-NTC, Q175-di-siRNA). One cohort of mice underwent open field (OF) testing as well as 5 mm beam examination (5mmBT) to assess anxiety-like behavior and locomotor performance, respectively evaluated at 6, 7, 8 and 9 months of age. A second cohort, expressing the dopamine sensor GrabDA with an optical fiber implanted in the Nucleus Accumbens (NAc), was trained in a progressive ratio (PR) operant task to measure dopamine release dynamics and motivational breakpoints. Current results indicate that Q175 mice, either treated with di-siRNA or NTC, traveled shorter distances in the OF, made more foot faults in the 5mmBT and exhibited longer latencies to traverse in the 5mmBT compared to WT mice independently of the treatment. In the PR task, treated Q175 mice displayed a lower number of rewards, lower maximum effort (breakpoints) and smaller cue-evoked dopamine release compared to WT mice. Collectively, these findings confirm a genotypic difference with Q175 mice performing worse in the motor and motivational evaluation compared to WT mice. However, di-siRNA treatment at 6 months old directed to HTT lowering in the brain does not have a significant effect in avolition or motor performance parameters in Q175 mice under the current experimental conditions.

Disclosures: C.F. Cardozo Hernandez: None. **F. Morgado:** None. **E. McDonnell:** None. **I. Gildish:** None. **J.F. Cheer:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.06/LBP145

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Title: CRISPR/Cas9 based DNA editing and CRISPR/Cas13d mediated RNA targeting strategy in the treatment of Huntington's disease mouse model BAC226Q

Authors: *Y. DING;
Peking University, Beijing, China

Abstract: Accelerated global aging has increased the incidence of neurodegenerative diseases, posing a major challenge and burden to public health worldwide.Huntington’s disease, an autosomal dominant neurodegenerative disorder, results from expansion of CAG repeats within exon 1 of the *huntingtin* gene on chromosome 4. This expansion confers a toxic gain-of -function to mutant huntingtin protein. Current HD therapies primarily alleviate motor and psychiatric symptoms, with no disease-modifying treatments clinically available. The CRISPR/Cas9 system, a gene-editing tool enabling specific mutation knockout, has been widely explored for genetic disorders while inducing irreversible genomic alterations with potential safety concerns.However, CRISPR/Cas13d, an RNA-targeting system, specifically cleaves pathogenic transcripts to reduce toxic proteins offering recoverable off-target effects. This study utilized BAC226Q HD mouse model constructed by our laboratory, which expresses full-length human *HTT* with 226 CAG repeats and recapitulates HD pathology. We first constructed and AAV9-packaged CRISPR/SaCas9 system targeting the *HTT* N17sequence. AAV delivery to BAC226Q mice at disease-relevant stages: presymptomatic(1 month), hyperkinetic onset (4 months) and hypokinetic progression (7 months),achieved mHTT reduction of >90%, ~90% and ~50%, respectively. While late intervention at the age of 7 months failed to rescue severe motor deficits, it significantly improved survival rates. These results indicated the critical importance of early pre-symptomatic intervention for optimal efficacy. Subsequent anterior cingulate cortex-targeting delivery demonstrated that mHTT aggregates clearance in the ACC area ameliorated anxiety and depression-like behaviors in open filed, novelty suppressed feeding and tail suspension tests. Next we established a high fidelity Cas13d-mediated strategy. *In vitro* validation in HEK293T cells expression hHTT-exon1-EGFP showed above 50% fluorescence reduction. Stereotactic injection to 4-month-old HD mice striatum and cortex achieved >80% reduction in mHTT aggregates. Longitudinal therapeutic efficacy and safety evaluation are ongoing. In summary, AAV-SaCas9 and AAV-hfCas13d systems enable efficient HTT gene editing and transcript knockdown with significant pathological rescue, establishing a therapeutic framework with clinical potential for Huntington’s disease.

Disclosures: Y. Ding: None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.07/LBP146

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: NINDS R01NS1124084
R01NS127344

Title: Enhancing AQP4-mediated glymphatic clearance as a therapeutic strategy for Huntington's disease

Authors: ***H. LIU**[1], Y. OUYANG[2], X. CHONG[3], Y. XU[2], Y. LI[2], J. HUA[2], J. XU[2], W. DUAN[4]; [1]Johns Hopkins Medical Institutions, Baltimore, MD; [2]Johns Hopkins school of Medicine, Baltimore, MD; [3]Johns Hopkins University, Baltimore, MD; [4]Psychiatry, Neuroscience, Johns Hopkins University, Baltimore, MD

Abstract: Huntington's disease (HD) remains without effective disease-modifying therapies, highlighting the need for novel strategies targeting pathogenic mechanisms. The central nervous system lacks conventional lymphatic vessels within the parenchyma and instead relies on the glymphatic system, a glial-dependent perivascular network that mediates cerebrospinal fluid (CSF)- interstitial fluid (ISF) exchange, as well as meningeal lymphatic vessels for waste clearance and immune trafficking. We have previously demonstrated impaired glymphatic influx and clearance in HD, associated with reduced aquaporin-4 (AQP4) levels and loss of perivascular polarization in both HD patients and mouse models. In this study, We investigated whether restoring AQP4 expression and polarization could enhance glymphatic-lymphatic clearance and improve neuropathology in HD. zQ175 HD mice received systemic delivery of AAV9-PHP.EB vectors encoding either mouse Aqp4 or the Aqp4 anchoring protein alpha-1 syntrophin (Snta1) under the Gfap promoter. The glymphatic function was assessed by intra-cisterna magna injection of fluorescent tracer BSA-647, followed by analysis of tracer distribution and drainage to deep cervical lymph nodes. Longitudinal studies evaluated brain atrophy, body weight, and mutant huntingtin (mHTT) aggregation. Aqp4 overexpression significantly improved glymphatic influx in zQ175 mice relative to untreated HD controls. Tracer clearance to cervical lymph nodes was also enhanced, indicating improved glymphatic-lymphatic drainage. In contrast, Snta1only overexpression did not rescue influx deficits. Importantly, longitudinal analyses revealed that Aqp4 overexpression attenuated striatal atrophy, preserved body weight, and reduced mHTT aggregates. These findings suggest that targeting the glymphatic-lymphatic system via Aqp4 modulation represents a promising therapeutic strategy for HD.

Disclosures: H. Liu: None. **Y. Ouyang:** None. **X. Chong:** None. **Y. Xu:** None. **Y. Li:** None. **J. Hua:** None. **J. xu:** None. **W. Duan:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.08/LBP147

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: Bev Hartig Huntington's Disease Foundation
NIH RO1 NS127344
NIH RO1 NS124084

Title: Non-invasive focused ultrasound delivery of engineered U1 snRNA strategy for targeted suppression of CAG repeat expanded HTT in an HD mouse model

Authors: *Q. WU[1], H. SLIKA[1], S. K. YADAV[2], S. SURASINGHE[3], D. GEROCHI[4], A. KAKAZU[5], M.-F. VIDAVER[2], A. SMARGON[6], S. HATCH[7], G. YEO[8], B. TYLER[2], W. DUAN[9];
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Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by a CAG repeat expansion in exon 1 of the Huntingtin (HTT) gene, resulting in production of the toxic mutant huntingtin protein (mHTT). Misfolded RNA molecules may acquire abnormal structures that alter its physiological functions. Engineered U1 snRNAs are highly expressed endogenously, have a small genetic payload (~600bp), and lack catalytic activity. As single-component constructs derived from the endogenous U1 snRNA locus with modified guide sequences may have low immunogenicity. In our cell-based screening, an engineered U1 snRNA dramatically reduced CAG repeat expanded RNA and poly-glutamine product. In mHTT knock-in mice, intra-striatal injection of this U1 snRNA selectively suppressed mHTT expression. HD pathology extends beyond the striatum, necessitating broader brain delivery and less invasive approaches than intracranial injection. To address this issue, we employed MRI-guided focused ultrasound (FUS) to transiently open the blood-brain barrier (BBB) and enable intravenous (i.v.) delivery of AAV9-engineered U1 snRNA. Optimization of FUS parameters, combined with low-intensity FUS and microbubbles, facilitated broader brain delivery of AAV9-engineered U1 snRNAs, resulting in targeted expression and effective mHTT suppression. CAG-targeting constructs, particularly one with 40-nucleotide guide sequence targeting CAG repeats, achieved significant mHTT reduction. MRI and biochemical analyses confirmed efficient brain transduction and mHTT reduction. These findings demonstrate that FUS-mediated AAV delivery enhances therapeutic distribution across the BBB. Together, this strategy offers a promising platform for advancing targeted RNA-based therapies in HD.

Disclosures: Q. Wu: None. **H. Slika:** None. **S.K. Yadav:** None. **S. Surasinghe:** None. **D. Gerochi:** None. **A. Kakazu:** None. **M. Vidaver:** None. **A. Smargon:** None. **S. Hatch:** None. **G. Yeo:** None. **B. Tyler:** None. **W. Duan:** None.

Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.09/LBP148

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Title: Next-generation CNS genome editing for Huntington's disease, ALS and SCA2

Authors: *M. CONCEICAO, C. SMITH, L. MENENDEZ BERLANA, E. KYRIAKOPOULOU, D. CARTER, C. DANIEL, R. SLOVAK, P. PARSI, D. LONERGAN, P. HORROCKS, R. TAWAR, A. EVANS, K. KAUR, R. GAVIN, M. SINGH;
Evox Therapeutics, Oxford, United Kingdom

Abstract: Huntington’s disease (HD), amyotrophic lateral sclerosis (ALS), and spinocerebellar ataxia type 2 (SCA2) have no curative therapies. Our programmes target two genetic disease modifiers, MSH3 (HD) and ATXN2 (ALS/SCA2), utilising our proprietary technology consisting of a fast-acting, rapidly degraded CRISPR/Cas ribonucleoprotein (RNP) delivered to the CNS via a natural, non-viral delivery system based on extracellular vesicles (EVs). Guide RNAs (gRNAs) were first screened at scale in Huh7 cells (>150) to identify high-activity candidates; for the top guides, further assessments were performed in Huh7 and cross-validated in human iPSC-derived neurons. Primary outcomes were on-target editing by amplicon NGS or ICE, and target-protein reduction by immunocytochemistry (ICC) and capillary Western (Jess). Lead EV-RNPs demonstrated near-saturating editing efficiency with approximately 1000-fold improved EC50 values compared to liposomal RNP delivery in Huh7 cells, for both DNA editing and protein knockdown. In iPSC-derived neurons, editing levels close to 100% were achieved, accompanied by up to 80% protein knockdown. To establish in vivo proof-of-concept for CNS editing, adult wild-type C57BL/6 mice received EVs by intracerebroventricular (ICV) injection, and editing at a proxy locus in the brain was quantified 9-days later by amplicon NGS or ICE. Results demonstrate that EVs achieved genetic editing in up to 40% of cells within the cortex and hippocampus of treated mice. In non-human primates (Macaca fascicularis; 2-4 years; n/route = 2; males; non-randomised/unblinded), radiolabelled EVs enabled PET/MRI biodistribution mapping 1-72 h after intraparenchymal (IP), intracerebroventricular (ICV), or intracisternal magna (ICM) administration. Preliminary data indicates that intra-striatal dosing achieved complete coverage of the target brain region, although we are currently waiting for more detailed quantitative analyses, as well as evaluating alternative routes of administration; these data will guide selection of the lead program and route for primate proof-of-mechanism (PoM). Off-target risk was triaged in silico with both our drug candidates targeting ATXN2 and MSH3 showing a favourable preliminary specificity profile. Together, this staged workflow, from high-throughput gRNA discovery to neuronal validation, murine CNS proof-of-concept at a proxy locus, and primate biodistribution, supports our non-viral CNS editing approach for MSH3 and ATXN2 and underpins planned NHP PK/PD studies in support of a future first-in-human clinical trial.

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Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.10/LBP149

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Title: Evaluating the cognitive deficits in spinocerebellar ataxia type 12 (SCA12) patients in India

Authors: N. MISHRA[1], ***K. RAMACHANDRAN**[1], B. DONGAONKAR[2], S. CHOUDHURY[3], H. KUMAR[4], S. CHATTARJI[1];
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Abstract: Spinocerebellar ataxia type 12 (SCA12) is a neurodegenerative movement disorder and one of the most prevalent SCAs in India. As SCA12 is primarily a motor disorder, less is known about the nature and severity of the associated cognitive impairment. The aim of our study was to characterize cognitive impairment in SCA12 and determine which domains are impaired versus preserved. We designed a cross-sectional study with genetically confirmed SCA12 patients, recruited from the Institute of Neurosciences Kolkata Hospital (IN-K). The patients had a mean CAG repeat length of 52.13±1.22 and the ataxia severity score of 11.35±1.38. Their mean age at disease onset was 54.32±1.41 years and disease duration was 8.48±0.92 years. We also recruited age, sex, education, and community-matched healthy controls. After recording demographic information, medical history, and ataxia severity, we administered a battery of cognitive tests. We collected data from 25 SCA12 patients (12 males, 13 females) and 26 healthy controls (9 males and 16 females). Global cognitive function, measured by the Montreal Cognitive Assessment (MoCA), was significantly impaired in SCA12 patients. Patients also performed worse in tests of executive function including the Trail Making Test (TMT), Digit Span Test, and Frontal Assessment Battery. Additionally, SCA12 patients showed slower learning in the Verbal Learning Test. Specifically, the patients recalled fewer number of the words in trial 1 and 2 but were able to recall a similar number of words by trial 3 as compared to controls. Importantly, while delayed recall continued to be poorer in SCA12 patients, delayed recognition was not affected, suggesting a problem with retrieval and not encoding. Similarly, the recall of visuospatial memory, assessed using the Geriatric Complex Figure task, was also affected in SCA12 patients. They performed similar to controls while copying the figure, but worse during delayed recall. In summary, we found that SCA12 patients have cognitive impairments in several domains, which is in line with neuroimaging literature indicating cortical atrophy in this patient group (Ganaraja et al., 2022). Comprehensive whole-

brain imaging, coupled with correlations to ataxia severity, may provide critical insights into the trajectory of motor and cognitive impairments in SCA12, while also revealing points of convergence and divergence with other spinocerebellar ataxias.

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Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.11/LBP150

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

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Admera Health & Complete Genomics Spatial Biology Stereo-seq Grant 24302-05-R0
The Company of Biologists Grant DMMTF24101625
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Title: Multi-omics analysis of mouse cortices with CAG repeat expansion in the PPP2R2B gene reveals dysregulated lipid metabolism

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Abstract: Spinocerebellar ataxia type 12 (SCA12) is an autosomal dominant, progressive neurodegenerative disorder for which no disease-modifying treatment exists, and its underlying pathogenesis remains poorly understood. SCA12 is caused by a CAG repeat expansion in the *PPP2R2B* gene, which encodes a brain-specific regulatory subunit of phosphatase 2A expressed in both neurons and astrocytes. Clinically, patients usually present with tremor, gait abnormalities, neuropsychiatric symptoms, and cortical and cerebellar atrophy. To investigate SCA12 pathogenesis in vivo, we generated a humanized knock-in (KI) mouse model using CRISPR/Cas9. In this model, mouse *PPP2R2B* exon 2 was replaced with human exon 7 carrying either 10 or 150 CAG repeats, generating homozygous KI-10/10 control mice and heterozygous KI-150/10 SCA12 mice. The SCA12 mice exhibited significant motor abnormalities compared with controls, consistent with symptoms observed in patients. To identify a transcriptomic signature of SCA12, we performed bulk RNA-seq on cortical tissues from 9-month-old male SCA12 and control mice. This analysis revealed 178 differentially expressed genes (DEGs), including 74 upregulated and 104 downregulated genes. RT-qPCR validation confirmed altered expression of several key DEGs, including *PLIN4*, *LDLR*, *HMGCR*, and *DHCR7*. Notably, *PLIN4* and *LDLR* are involved in lipid transport, while *HMGCR* and *DHCR7* regulate cholesterol biosynthesis. Enrichment analysis of the DEGs highlighted significant disruptions in lipid

biosynthesis and metabolic pathways, including those of cholesterol. To confirm if cortical lipid metabolic alterations exist in SCA12 mouse cortices, we conducted comprehensive lipidomics on cortical tissues from 12-month-old male SCA12 and control mice. Across 820 detected and quantified lipids, 39 were differentially expressed, with 19 upregulated and 20 downregulated in SCA12 cortices compared with controls. Consistent with our bulk RNA-seq findings, functional analysis of these differentially expressed lipids, including cholesterol, confirmed the disruptions in lipid biosynthesis and metabolic pathways. By integrating transcriptomic and lipidomic analyses, our study provides new insights into the molecular basis of SCA12, particularly its link to cortical lipid metabolism. Ongoing work includes spatial single-cell transcriptomics (Stereo-seq) and proteomics to resolve cell-type-specific transcriptomic changes and corresponding protein-level alterations. Ultimately, this work seeks to bridge mechanistic insights with translational potential, laying the foundation for mechanism-based interventions in SCA12.

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Late-Breaking Poster

LBP073: C.04. Movement Disorders Other Than Parkinson's Disease

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP073.12/LBP151

Topic: C.04. Movement Disorders Other Than Parkinson's Disease

Support: BMBF 01GM1905B
BMBF 01GM2209B

Title: Establishing a patient-derived in vitro model for SPG11 and SPG15-related hereditary spastic paraplegia for drug testing

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Abstract: Motor neuron diseases are characterized on a cellular level by the dying-back of axons from upper- or lower motor neurons. In hereditary spastic paraplegias, a rare group of disorders, the upper motor neurons are predominantly affected, leading to a clinical course that progresses from paraparesis and spasticity to paraplegia of the lower limbs. The SPG11 and SPG15-related hereditary spastic paraplegia share additional clinical features of intellectual disability and morphological features of a thin corpus callosum. On the cellular level, SPG11 and SPG15-encoded proteins play a crucial role in lysosomal biogenesis. Spatacsin (SPG11) and spastizin (SPG15) function together within a complex to regulate lysosomal regeneration through autophagic lysosome reformation. We used fibroblasts from controls and patients to demonstrate

those lysosomal defects in patient-derived fibroblasts. We generated hiPSC from those fibroblasts and differentiated them into cortical progenitors and neurons from six healthy controls, five SPG11 patients, and three SPG15 patients. In a drug screening approach, we identified compounds to rescue the lysosomal function and neuronal resilience.

Disclosures: T. Börstler: None. **K. Metzner:** None. **C. James:** None. **M. Regensburger:** None. **J. Winkler:** None. **B. Winner:** None.

Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP074.01/LBP152

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: The Intramural Research Program of the National Institutes of Health (NIH)

Title: The use of mesh MEA to illuminate how loss and corruption of prion protein roles contribute to human prion disease pathogenesis.

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Abstract: In mice, cellular prion protein (PrPC) has been shown to regulate neuronal network communication and protect neurons from oxidative stress damage. These roles are lost or corrupted when PrPC is misfolded into the pathogenic isoforms (prions) in prion disease. It remains unknown if PrPC plays similar roles in the human brain. Furthermore, prion protein structure is altered to some degree by an E200K mutation (PrPE200K) within its core residues. This autosomal dominant mutation predisposes carriers to developing genetic Creutzfeldt-Jakob Disease, the most common human genetic prion disease. Whether the mutation causes a loss or corruption of prion protein roles, leading to the disease, has not yet been determined. Here, we utilized a novel technology, a mesh multi-electrode array (MEA; MultiChannel Systems, Germany), to evaluate neuronal network function in human cerebral organoids (COs) expressing prion protein with and without the E200K mutation, or lacking prion protein. COs were generated from human induced pluripotent stem cells, cultured for at least 5 months, and adhered to the mesh MEA using a Polyethyleneimine solution and laminin. They were then cultured in BrainPhys media (StemCell) for at least a month, while monitoring the neuronal network activity. We found that a complete loss of PrPC increased neuronal activity due to a lack of excitation regulation, which predisposed organoids to damage under oxidative stress. COs heterozygous for PrPE200K showed less neuronal firing and connectivity with enhanced susceptibility to oxidative stress damage. This suggests that the PrPE200K was either neurotoxic or it corrupted the normal function of its co-expressed PrPC. Importantly, similar phenotypes were observed in COs homozygous for PrPE200K, suggesting that the mutation was toxic and

enhanced the vulnerability of COs to oxidative stress damage. Furthermore, proteomic and metabolomic analyses revealed that PrPE200K reduced neural motor transport, depleted GABA, and increased acetylcholine. Together, mesh MEA long-term monitoring of network activity in live COs, coupled with biochemical analyses, suggests that PrPE200K causes neuronal network breakdown associated with oxidative stress, vesicle transport, and neurotransmitter trafficking and usage that is distinct from PrPC loss of function.

Disclosures: **S. Foliaki:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Multi Channel Systems. **B.R. Groveman:** None. **K. Williams:** None. **Y. zhang:** None. **B. Schwarz:** None. **C. Haigh:** None.

Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP074.02/LBP153

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: p75NTR Modulation Restores Synaptic Plasticity in Tauopathy by Normalizing Activity-Dependent Gene Networks and Microglia-Mediated Synapse Remodeling

Authors: ***A. LATIF-HERNANDEZ**, P. MORAN LOSADA, J. FERNANDEZ DA PONTE, R. R. BUTLER III, T. YANG, T. WYSS-CORAY, F. M. LONGO;
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Abstract: Introduction: Synaptic dysfunction is an early hallmark of Alzheimer's disease and related dementias (ADRD), characterized by impaired long-term potentiation (LTP) and disrupted excitatory/inhibitory balance. Dysregulated neuron-glia interactions, including aberrant astrocyte-interneuron communication and excessive microglial synaptic engulfment, likely contribute to these deficits. We previously showed that modulating p75 neurotrophin receptor (p75NTR) signaling with the small molecule LM11A-31 (C31) restores LTP in the PS19 tauopathy model. Here, we extend these findings to test whether C31 can normalize transcriptomic signatures and attenuate pathological microglial synapse pruning. Methodology: 22 wild-type (WT) and 24 Tau.P301S (PS19) mice were treated once daily by oral gavage with vehicle or C31 for 3 months starting at 6 months of age, when tau pathology is well established. Hippocampi were harvested 24 hours after the last dose of the drug, and LTP was induced in acute hippocampal slices using theta burst stimulation (3xTBS). Bulk RNA sequencing and weighted gene co-expression network analysis were performed on stimulated and unstimulated slices, with cell-type enrichment analyses. To assess astrocyte contributions and microglial synaptic pruning, we used GFAP/VGAT immunofluorescence and Iba1/CD68/PSD95 triple immunostaining in LTP-stimulated slices. Results: PS19 mice exhibited impaired LTP and dysregulated activity-dependent gene expression, with 16 co-expression modules downregulated (9 interneuron/neuron-enriched) and 8 upregulated (3 glial/neuroinflammatory). C31 treatment restored many altered transcriptional modules toward WT patterns, overlapping with human AD-

relevant transcriptomic networks. At the cellular level, LTP-stimulated PS19 slices showed elevated astrocyte-GABAergic interneuron colocalization (GFAP/VGAT) and microglial synaptic phagocytosis (Iba1/CD68/PSD95 colocalization), consistent with disrupted neuron-glia interactions and pathological synapse loss. In vivo C31 treatment restored astrocyte-interneuron interactions and reduced microglial engulfment of synapses, suggesting restoration of a healthier, less inflammatory glial state. Conclusions: The p75NTR modulator C31 restores synaptic plasticity in tauopathy in association with rebalanced neuron-glia interactions at transcriptional and cellular levels, linking molecular resilience programs to preserved synaptic function. These results highlight p75NTR modulation as a promising therapeutic avenue to restore human AD-relevant transcriptional networks.

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Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP074.03/LBP154

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH Grant AG065925
NIH Grant NS130256

Title: ApoE4 promotes human tau release at Drosophila larval neuromuscular junctions

Authors: R. UDDIN, ***D. LEE**;
Ohio University, Athens, OH

Abstract: Intracellular neurofibrillary tangles (NFTs) are a pathological hallmark of Alzheimer's disease (AD) and related tauopathies. NFTs consist of hyperphosphorylated and aggregated tau, and their spatial and temporal progression correlates closely with disease severity. A prion-like model of tau propagation has emerged, in which pathogenic tau spreads between synaptically connected neurons to seed further pathology. Apolipoprotein E4 (ApoE4), the strongest genetic risk factor for late-onset AD, has been shown to enhance tau spreading, but the underlying mechanism remains unclear. Our central question is whether ApoE4 promotes tau release from neurons, thereby driving propagation of tau pathology. Using the Drosophila larval neuromuscular junction (NMJ), we investigated how ApoE isoforms regulate tau release and phosphorylation. Human tau (2N4R) was expressed with ApoE3 or ApoE4 in glutamatergic motor neurons. Released tau was collected from third instar larval hemolymph and quantified by western blot and ELISA under spontaneous and optogenetically evoked conditions. Phosphorylation state was assessed with site-specific antibodies (e.g., AT8, PHF-1), and tau-

ApoE interactions were examined by co-immunoprecipitation. ApoE4 significantly increased spontaneous tau release compared to ApoE3, and this effect was independent of neuronal activity. Tau phosphorylation was not required for ApoE4-mediated release, as phosphorylation-deficient AP tau (14 serine/threonine sites mutated to alanine) was still elevated in the presence of ApoE4. However, phosphorylation further amplified release, since phospho-mimetic tau (E14) was secreted at significantly higher levels. Notably, tau released with ApoE4 was enriched in AT180- and PHF-1-positive species, indicating that this isoform regulates not only the quantity but also the phosphorylation profile of secreted tau. We also observed that ApoE4 itself is released from neurons, and co-immunoprecipitation assays revealed strong tau-ApoE4 interactions. These findings suggest that ApoE4-dependent tau release occurs, at least in part, through co-trafficking of ApoE4 and tau as interacting partners. Our findings identify ApoE4 as a key regulator of tau release and phosphorylation state, providing new mechanistic insight into how genetic risk factors accelerate tau propagation in AD and related tauopathies.

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Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

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Program #/Poster #: LBP074.04/LBP155

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NINDS U01NS093334
NINDS R21NS140565
Alzheimer's Association 25A1001012698

Title: Third Ventricle Shape Complexity as a Marker of Cognitive Decline in Former American Football Players

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Abstract: Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease linked to repetitive head impacts (RHI) and marked by cognitive, emotional, and behavioral disturbances. Ventricular enlargement is a well-recognized feature of neurodegeneration and has been commonly reported in postmortem CTE, yet the potential role of ventricular shape as a biomarker remains unexplored. Shape-based metrics, such as Shannon entropy, provide a novel approach to quantifying subtle morphological irregularities that may reflect altered cerebrospinal fluid dynamics, periventricular white matter disruption, and adjacent tau pathology. In this study, we tested whether ventricular shape entropy can detect neuroanatomical changes associated with RHI exposure and cognitive impairment. We applied a novel shape entropy metric to quantify the three-dimensional complexity of the lateral, third, and fourth ventricles. T1-weighted MRI scans from the DIAGNOSE-CTE Research Project (170 former American football players, 54 asymptomatic unexposed controls) were processed to generate triangular surface meshes of each ventricle. For each structure, a three-dimensional centroid was defined, and radial distances from each mesh vertex to the centroid were calculated. The resulting distance distributions were used to compute Shannon entropy, yielding a robust, quantitative measure of ventricular shape complexity. Using a general least squares regression model controlling for age, race, education, body mass index, APOE ε4 status, and scanner site, we observed a significant overall effect (adjusted $R^2 = 0.30$) in the third ventricle ($F(7,215) = 12.04$, $p < 0.0001$). Follow-up pairwise comparison showed that former football players had significantly lower shape entropy than controls ($p = 0.020$). No significant group differences were detected in the lateral or fourth ventricles (all p's > 0.1). Within the player group, K-means clustering based on cognitive performance (Ascertain Dementia 8-Item questionnaire, Montreal Cognitive Assessment, Trail Making Test Part A and Part B) revealed that individuals with worse cognition also had significantly lower third ventricle entropy compared to those with better cognition ($p = 0.026$). No other ventricles showed cognitive associations. These findings suggest that exposure to RHI is associated with reduced morphological variability (lower entropy) of the third ventricle, and that this reduction relates to cognitive impairment. Lower entropy may reflect a shift toward more ordered, hydrocephalus-like expansion, offering a potential novel morphometric biomarker of RHI in former American football players.

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Bouix: None. **H. Arciniega:** 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.; NINDS U01NS093334, NINDS R21NS140565, Alzheimer's Association 25A1001012698.

Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

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Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NINDS U01NS093334
NINDS R21NS140565 (HA)
Alzheimer's Association 25A1001012698

Title: Radiological indices reveal ventricular enlargement in former american football players exposed to repetitive head impacts

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Abstract: Chronic traumatic encephalopathy (CTE) is a progressive neurodegenerative disease linked to repetitive head impacts (RHI). Ventricular enlargement is frequently described in CTE pathology, but its expression in living individuals, at high risk for CTE, remains poorly characterized. In this study, we address this gap by applying radiological indices, validated in hydrocephalus and other neurological conditions, to structural MRI scans of former American football players. This approach provides a clinically relevant framework for assessing ventricular dilation in individuals with an extensive history of RHI.We analyzed structural MRI data from 170 former American football players in the DIAGNOSE CTE Research Project. T1-weighted images were analyzed in 3D Slicer to extract ventricular dimensions. Five radiological indices were applied to assess ventricular dilation: the Evans Index (EI) (abnormal >0.30, borderline 0.25-0.30); the z-Evans Index (zEI) (abnormal >0.42); the Callosal Angle (CA) (<90° abnormal); the Brain Ventricle Ratio (BVR) (<1.0 abnormal at the anterior level and <1.5 at the posterior level); and the Anteroposterior Lateral Ventricle Index (ALV) (>0.5 abnormal). Each measure was compared to the established thresholds to determine abnormal ventricular size. Ventricular enlargement was highly prevalent among former players. A notable proportion of former football players exceeded established thresholds for ventricular enlargement. Abnormal EI values were observed in 20% of participants (n = 34/170), with an additional 4.1% (n = 7/170) falling in the borderline range. In contrast, abnormalities on the zEI were rare, identified in only 0.6% (n = 1/170). CA values <90° were observed in 1.2% (n = 2/170) at the posterior level, with no abnormalities at the anterior level. For the BVR, thresholds were exceeded in 2.4% (n = 4/170) at the posterior level and 4.7% (n = 8/170) at the anterior level. Finally, abnormalities on the ALVI were detected in 6.5% of participants (n = 11/170).In this cohort of former American football players, ventricular enlargement was most commonly detected using the Evans Index, while abnormalities on other indices were relatively rare. These findings suggest that reliance on a single measure may overestimate ventricular abnormalities in individuals with a history of RHI. Applying multiple radiological indices provides a more nuanced characterization of ventricular morphology in vivo and may help refine imaging markers relevant to CTE and related neurodegenerative processes.

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Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

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Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: AARG-NTF-22-926555
R01-AG-076434

Title: Detection of tau seeding activities in archived human brain tissue

Authors: *H. XU[1], V. M. LEE[2], R. CHEN[3], D. M. MOZIER, Jr.[4];
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Abstract: Alzheimer's disease (AD) is pathologically defined by the presence of misfolded tau and Amyloid β pathologies. Misfolded tau has the bioactivity of seeding physiological tau monomers, and the development of seeding amplification assays (SAA) has provided a highly sensitive platform to evaluate this activity at the femtomolar (fM) level. The accessibility and convenience of archival brain tissues make them a valuable resource for large-scale studies. To improve the accessibility of tau seeds, we adapted a well-characterized SAA to reliably measure tau seeding activities from archived human brain tissues.We tested 15 cases of pathologically confirmed AD and non-disease controls. To ensure the amount of seeds was comparable, we used adjacent tissue slides to quantify tau pathology with immunohistological p-tau staining (PHF1) for AD cases and matched total protein load for control cases. For different tissue types and processing approaches, we used both ethanol and formalin-fixed tissues, with and without rehydration, and compared five different antigen retrieval methods.Our results show consistent and robust seeding activity in AD cases with both ethanol and formalin-fixed tissues, which was significantly faster than in control reactions. The sensitivity of the SAA was comparable to assays using fresh brain lysates. When coupled with laser dissection microscopy, the SAA shows the ability to detect tau seeds at the single-cell level. We found that different antigen retrieval approaches did not significantly affect the separation between AD and control cases. Our findings confirm that AD-tau seeding activity can be sensitively and consistently measured from fixed human brain tissues. This new method greatly expands our ability to survey tau seeding activities in large, archived tissue banks with a high level of convenience and accessibility, which will be crucial for future retrospective studies on the natural history of AD cases.

Disclosures: H. Xu: None. **V.M. Lee:** None. **R. Chen:** None. **D.M. Mozier:** None.

Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP074.07/LBP158

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: NIH-NIA Grant 1K01AG092910
NIH-NIA NINDS Grant 5R01NS120488
NIH-NIA NINDS Grant 5R01NS077239
NIH-NIA Grant 5R01AG032611

Title: Differential effects of two familial tauopathy mutations on human neuronal function

Authors: *C. JI, E. M. SIGURDSSON;
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Abstract: Emerging evidence reveals that certain neuronal subtypes are selectively vulnerable to tauopathy, yet how it causes neuronal dysfunction and degeneration remains understudied. Further exploration of the functional consequences of tauopathy on neural circuits is warranted. In iPSC-derived human cortical neurons from familial tauopathy patients, we previously showed that pathological tau alters the ratio and firing modes of excitatory (E) vs inhibitory (I) neuronal subtypes, resulting in an E/I imbalance. Here, we investigated the impact of two different pathological tau mutations on neuronal function and network activity, which has not been previously studied together in detail. Analyzing these parameters in a mixed E/I population is more physiological than studying only E neurons generated with accelerated one month differentiation protocols. Towards this aim, we performed microelectrode array (MEA) recordings on four-month-old human cortical neurons composed of both E and I subtypes that had a mature electrophysiological profile based on patch clamp recordings. In these mature neurons, P301L tau significantly increased spontaneous neuronal spiking frequency, whereas R406W tau did not alter it, compared to their isogenic controls. In addition, both tau mutations increased network bursting frequency but P301L tau increased network bursting duration, whereas R406W tau decreased it, compared to isogenic controls. During high-frequency electrical stimulation, P301L vs R406W tau led to firing of more vs less evoked spikes, and longer vs shorter evoked network bursts, respectively, but both with shorter first spike latency, compared to isogenic controls. These results indicate that P301L tau induces robust network hyperactivity, whereas R406W tau has a substantial but more complex effects on network activity and lesser effects than P301L tau at the neuronal level. Overall, MEA recordings revealed clearly distinct electrophysiological profiles between control and tauopathy human cortical neurons, which varied depending on the specific familial tau mutation. Further studies are ongoing on the molecular mechanisms underlying these differential functional changes at the neuronal and network levels. Functional readouts in human neurons derived from patients as described here are necessary to clarify tau pathogenesis and should ideally be implemented in all therapeutic studies designed to alleviate tauopathy.

Disclosures: C. Ji: None. **E.M. Sigurdsson:** None.

Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP074.08/LBP159

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: R01 AG062359
R01 AG082141

U54 NS100717
A.P. Gianni Foundation Postdoctoral Fellowship

Title: Multi-omic phenotyping of iPSC-derived neurons harboring the MAPT V337M mutation reveals tau hypophosphorylation and perturbed axon morphology pathways

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Abstract: Tau aggregation is a hallmark of several neurodegenerative diseases, including Alzheimer's disease and frontotemporal dementia. There are disease-causing variants of the tau-encoding gene, *MAPT*, and the presence of tau aggregates is highly correlated with disease progression. However, the molecular mechanisms linking pathological tau to neuronal dysfunction are not well understood. This is in part due to an incomplete understanding of the normal functions of tau in development and aging, and how the associated molecular and cellular processes change in the context of causal disease variants of tau. To address these questions in an unbiased manner, we conducted multi-omic characterization of iPSC-derived neurons harboring the *MAPT* V337M mutation or *MAPT* knockdown. RNA-seq and phosphoproteomics revealed that both V337M mutation and tau knockdown perturbed levels of transcripts and phosphorylation of proteins related to axonogenesis or axon morphology. Surprisingly, we found that neurons with V337M tau had much lower tau phosphorylation than neurons with WT tau. Functional genomics screens uncovered regulators of tau phosphorylation in neurons and found that factors involved in axonogenesis modified tau phosphorylation in both *MAPT* WT and *MAPT* V337M neurons. Intriguingly, the p38 MAPK pathway specifically modified tau phosphorylation in *MAPT* V337M neurons. We propose that V337M tau perturbs tau phosphorylation and axon morphology pathways that are relevant to the normal function of tau, which could contribute to previously reported cognitive changes in preclinical *MAPT* variant carriers.

Disclosures: G. Dixon: None. **G. Mohl:** None. **D. Swaney:** None. **M. Kampmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Montara Therapeutics, Inventor on US Patent 11,254,933 related to CRISPRi and CRISPRa screening, and on a US Patent application on in vivo screening methods.. F. Consulting Fees (e.g., advisory boards); Engine Biosciences, Casma Therapeutics, Cajal Neuroscience, Alector, Montara Therapeutics, Modulo Bio, Recursion Therapeutics.

Late-Breaking Poster

LBP074: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP074.09/LBP160

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Title: Evidence for a distinct dominant prion strain in Norwegian reindeer compared to North American chronic wasting disease

Authors: *S. E. GOEROLD;
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Abstract: Chronic wasting disease (CWD) is a fatal prion disease affecting cervids globally. While CWD has been well documented in North American cervids since 1967, it was first detected in Norwegian reindeer in 2016. Our group and others have demonstrated that the prions comprising the index case are distinct from the CWD prions in North America. Due to the importance of reindeer to Norwegian ecosystems and culture, the government culled thousands of reindeer in two valleys surrounding the Nordfjella region. More recently, the Norwegian wildlife agencies discovered a case of CWD in reindeer in an adjacent valley, illustrating that this disease is still prevalent in this region. Because the reemergence of CWD after the culling event indicates that this disease is not contained, there is a need to further understand the properties of prions in reindeer and their risk to sympatric species and the Norwegian ecosystem. To investigate CWD in a laboratory setting, our group has developed gene-targeted (Gt) mice that encode the cervid prion protein (PrP) and recapitulates key features of pathogenesis. We assessed the strain properties of several Norwegian reindeer (R-NO) CWD isolates from before and after the cull and contrasted these experiments with CWD isolates from North America. Transmissions of all R-NO CWD prions to Gt mice revealed similar disease kinetic profiles, which were starkly different from those of North American CWD. While Norwegian reindeer CWD produced disease in only a portion of Gt mice for observation periods exceeding 600 days, immunohistochemistry (IHC) and Real-Time Quaking Induced Conversion (RT-QuIC) analyses revealed that the majority of mice harbored subclinical prion replication in the brain and spleen. These data suggest that reindeer could be shedding CWD prions into the Norwegian ecosystem before the onset of disease. Taken together with further IHC analyses of prion deposition in the brain, these data bolster our group's previous findings that R-NO and North American CWD prions are distinct and suggest that there is a dominant strain circulating in Norwegian reindeer. These findings have critical implications for the zoonotic potential of R-NO CWD prions, transmissibility among and between species, and protecting vulnerable reindeer populations.

Disclosures: S.E. Goerold: None.

Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.01/LBP161

Topic: C.06. Neuromuscular Diseases

Support: DP1 NS137219
NSF 1828993

Title: Elucidate the functional role of RNA localization in neurodegenerative disease using in vitro & in vivo models

Authors: ***M. FU**[1,2], Y. SITU[2], M. HAN[3], B. DENG[4], Y. ZENG[5], A. D. GITLER[5], S. WANG[4], S. QI[2];
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Abstract: RNA molecules are essential for neuronal function, playing a key role in coordinating gene expression across different subcellular locations. Various RNAs, including messenger RNA (mRNA), microRNA (miRNA), and long non-coded RNA (lncRNA), respond to environmental cues and synaptic activity, supporting dynamic processes such as axonal growth, synaptic plasticity, and long-term memory formation. The spatial organization of RNAs within neurons enables localized protein synthesis at synapses, spanning distances from millimeters to meters, and is vital for nerve repair. However, how specific mRNA's spatial organization causes neuronal activities remains understudied. Prior studies have shown that mis-localization of mRNA may result in neurodegenerative diseases, including spinal muscular atrophy (SMA), amyotrophic lateral sclerosis (ALS) and frontal temporal dementia (FTD). To study the neuronal function of RNA organization within the cell, we have developed a novel technology, termed CRISPR-mediated transcriptome organization (CRISPR-TO), which can perturb endogenous RNA localization in various cell types including primary neurons. Building on this, we develop CRISPR-TO for both in vitro and in vivo applications for studying neurodegenerative disease. In vitro, we apply CRISPR-TO to human-induced pluripotent stem cell (hiPSC)-derived induced neurons (iNs) to study the role of RNA localization on neurodegenerative processes. In vivo, we deliver the system into the mouse retina to study the role of axonal RNA localization in retinal regeneration. We foresee both in vivo and in vitro CRISPR-TO systems will serve as powerful tools for identifying novel RNA localization function in the nervous system, which may provide a potential therapeutic strategy for enhancing neuronal regeneration in neurodegenerative diseases.

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Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.02/LBP162

Topic: C.06. Neuromuscular Diseases

Title: Quantitative cell free assessment of TDP-43 aggregation and analysis of arsenite-induced cryptic exon inclusion in human neuronal cell models

Authors: *D. KORUMILLI[1,2], S. ARYA[3], V. MATHUR[4], M. KOKES[5], V. SEAWRIGHT[2]; [1]Acelot, San francisco, CA; [2]Acelot Inc., South San Francisco, CA; [3]Acelot, South San Francisco, CA; [4]R&D, Acelot Inc., South San Francisco, CA; [5]Acelot, Inc, Burlingame, CA

Abstract: The significance of RNA-binding protein TDP-43 is well established in the pathology of Amyotrophic Lateral Sclerosis (ALS), a motor neuron disease afflicting >200,000 patients worldwide with no known cure. In >97% of ALS patients, the normally nuclear TDP-43 in motor neurons mislocalizes to the cellular cytoplasm where it forms aggregates. Despite the clear and prevalent link between TDP-43 aggregates and ALS, our understanding of how these aggregates play a role remains incomplete partially due to the challenge of working with TDP-43 aggregates in vitro and inducing their formation in cells. Here, we describe a platform using in vitro cell-free methods to characterize TDP-43 aggregation and assess the role of arsenite-induced aggregation on loss-of-function phenotypes in cells. Here, we describe a platform based on in vitro cell-free methods to characterize TDP-43 aggregation. We characterize the aggregation of three forms of TDP-43: a short minimal amyloidogenic TDP-43 peptide, the low-complexity C-terminal domain (LCD), and the full length protein. We find that aggregates from all three forms have characteristics of amyloid aggregates, including Thioflavin-T reactivity, insolubility, and partial sarkosyl-resistance. Additionally, peptide and LCD aggregates are reactive with an amyloid marker congo red. LCD aggregate formation was further confirmed using molecular weight cut-off filters. To characterize a cellular model of TDP-43 aggregation, we evaluated how varying concentrations of sodium arsenite - an oxidative stressor which can induce TDP-43 aggregates - at different time points result in the inclusion of cryptic exons in TDP-43-regulated neuronal mRNAs, specifically STMN2 and UNC13A, in both neuron-like SH-SY5Y cells and human induced pluripotent stem cell (iPSC)-derived motor neurons. Our findings highlight the utility of cell-free assays for dissecting TDP-43 aggregation dynamics and demonstrate that arsenite treatment can impair TDP-43-dependent splicing regulation in human neuronal models.

Disclosures: D. Korumilli: A. Employment/Salary (full or part-time); Full-time Employee at Acelot. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); I have stock options at Acelot. **S. Arya:** A. Employment/Salary (full or part-time); Full-time Employee at Acelot. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Have stock options at Acelot. **V. Mathur:** A. Employment/Salary (full or part-time); Full-time Employee at Acelot. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Have stock options at Acelot. **M. Kokes:** A. Employment/Salary (full or part-time); Full-time Employee at Acelot. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Have stock options at Acelot. **V. Seawright:** A. Employment/Salary (full or part-time); Full-time Employee at Acelot. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Have stock options at Acelot.

Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.03/LBP163

Topic: C.06. Neuromuscular Diseases

Support: Project ALS
NIH Grant 1RF1MH132653-01

Title: Continuous Home Cage Monitoring for Identifying Novel Behavioral Signatures of ALS

Authors: *E. DAVIS[1], T. HAN[2], M. SHAIKH[3], N. NONO[3], L. MAREE[3], B. NIELSEN[4], N. ANDREWS[3], E. AZIM[5], T. D. PEREIRA[6];
[1]Salk Institute for Biological Studies, San Diego, CA; [2]TPEREI, Salk Institute for Biological Studies, Brunswick, ME; [3]Salk Institute for Biological Studies, La Jolla, CA; [4]Bio Compute, Salk Institute, La Jolla, CA; [5]MNL-E, Salk Institute, La Jolla, CA; [6]TPEREI, Salk Institute for Biological Studies, La Jolla, CA

Abstract: Understanding the progression of neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS) and Alzheimer's disease requires sensitive measures of behavior across naturalistic conditions. Traditional assays—including the rotarod test, wire hang test, and Morris water maze—have been instrumental in establishing timelines of disease progression, but these constrained tasks fail to capture the full complexity of spontaneous, ecologically relevant behaviors. In contrast, continuous home-cage monitoring can reveal subtle, previously unrecognized phenotypes. Because mice are social animals, capturing these behaviors requires methods that support multi-animal tracking in group-housed settings. Here we present a scalable behavioral phenotyping pipeline that integrates long-term home-cage monitoring, pose estimation with SLEAP, and a novel multi-object tracker (MOT) designed to minimize identity swaps across extended recordings. This framework enables independent tracking of multiple animals over weeks to months. We then apply supervised and unsupervised machine learning approaches to segment behavioral syllables and characterize locomotor dynamics. Using this approach, we have begun to uncover novel locomotor signatures of disease progression in ALS mouse models. Importantly, these insights could only be revealed through continuous, 24/7 monitoring in naturalistic group-housed conditions—patterns that would have been missed by conventional, task-based paradigms. This pipeline provides a generalizable framework for continuous behavioral monitoring and opens the door to identifying previously hidden phenotypes of neurodegenerative disease progression.

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Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.04/LBP164

Topic: C.06. Neuromuscular Diseases

Support: RF1AG076493
R01AG078788

Title: Early social isolation stress drives endogenous retrovirus expression and exacerbates neurodegeneration and intercellular spread of pathology in a Drosophila TDP-43 model

Authors: S. MURTHYGOWDA[1], K. HUYGHUE[1], B. CASTILLO[2], F. GUGALA[2], W. LI[2], *J. DUBNAU[1];
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Abstract: A key pathophysiological hallmark of Amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) is loss of nuclear localization and abnormal cytoplasmic aggregation of TAR DNA-binding protein 43 (TDP-43). The functional roles of TDP-43 include transcriptional regulation, mRNA splicing, mRNA transport and repression of retrotransposons (RTEs) and endogenous retroviruses (ERVs). Previous studies in *Drosophila*, in human postmortem cortical tissues and in cell culture, reveals that TDP-43 pathology activates expression of RTEs and ERVs. RTEs and ERVs are mobile genetic elements that replicate through an RNA intermediate to insert cDNA copies at de novo chromosome locations. We have previously reported that TDP-43 aggregation causes dysfunctional RTE/ERV overexpression and that ERV expression triggers TDP-43 pathology. This feedback amplification between TDP-43 pathology and ERV expression also contributes to toxic signaling from glia-to-neurons, leading to both cell intrinsic and non-autonomous cell death. But the upstream triggers that initiate or drive this phenomenology are not identified. Although dominant mutations in TDP-43 explain a small fraction of cases, the majority of ALS and FTD cases are sporadic, with no known genetic causes. Thus, most cases exhibit aggregation pathology of TDP-43 protein that contains wild type amino acid sequence. Although the environmental factors that influence onset and progression of disease are largely unexplored, epidemiological studies suggests that anxiety, depression and loneliness are associated with increased risks of neurodegenerative disease. We examined the impacts of several of ethologically relevant behavioral stressors in *Drosophila*. We report that early life social isolation is sufficient to exacerbate effects of subsequent induction of pathological levels of TDP-43 in glial cells. Social isolation stress drives more rapid activation of mdg4-ERVs, more aggressive propagation of TDP-43 protein pathology from surface glial cells to nearby neurons and shortened life span ensues. We demonstrate that flies require a holistically complete social interaction to prevent these effects of social isolation. Our findings have implications for the association between psychological stressors such as loneliness and risk of neurodegenerative diseases in humans.

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Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.05/LBP165

Topic: C.06. Neuromuscular Diseases

Support: Duke University Biology, Trinity College of Arts and Sciences

Title: A spastin CRIMIC allele reveals broad Spastin expression across tissues but not a loss of function phenotype at the Drosophila NMJ

Authors: *T. LEE[1], N. T. SHERWOOD[2];
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Abstract: Autosomal Dominant Hereditary Spastic Paraplegia (AD-HSP) is most often caused by mutations in the SPAST gene, which encodes the microtubule-severing protein Spastin. Although complete knockouts of spastin in Drosophila produce severe defects in neuronal cell biology, morphology, and function, the mechanism by which this occurs is still unclear. Here, we have utilized a CRIMIC (CRISPR-Mediated Integration Cassette) insertion in the first coding intron of Drosophila Spastin, to examine 1) the tissue-specificity of Spastin expression, and 2) consequences of spastin loss of function caused by the CRIMIC insertion. Using the GAL4 insertion contained within the CRIMIC to drive expression of nuclear-localized mCherry, we find that Spastin is expressed in a wide range of cell types in addition to neurons, including glial and muscle cells. This result supports the possibility that multiple cell types contribute to the mechanism underlying neuronal dysfunction when spastin is mutated. The CRIMIC insertion is also predicted to truncate spastin transcription following exon 1, removing key domains including that encoding the AAA ATPase catalytic region essential for microtubule remodeling. We hypothesized that CRIMIC mutants would yield a strong loss-of-function phenotype, but surprisingly, detected no defects in neuromuscular junction (NMJ) synaptic branching, which is prolific in spastin homozyous null animals. These results suggest that either exon 1 alone is sufficient for aspects of NMJ development, which would challenge conclusions from prior knockout studies, or that CRIMIC lines can be leaky in their loss-of-function capacity, an important consideration when utilizing them for such studies.

Disclosures: T. Lee: None. **N.T. Sherwood:** A. Employment/Salary (full or part-time); Duke University.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP075.06/LBP166

Topic: C.06. Neuromuscular Diseases

Support: This study was funded by Woolsey Pharmaceuticals, Inc. (New York, NY, USA).

Title: Non-monotonic pharmacodynamic effects of an oral Rho kinase inhibitor, fasudil, on neurofilament light chain and CNS target engagement: an open-label phase 2a study to assess safety and biomarker changes in patients with amyotrophic lateral sclerosis

Authors: C. PENA[1], C. BARKER[1], A. GROSSBERG[1], I. MIAN[2], T. MACALLISTER[2], ***D. A. LINSEMAN**[3,1];
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Abstract: Background and Study Design: Animal models and mechanistic data indicate that fasudil may have a non-monotonic dose response in amyotrophic lateral sclerosis (ALS). In this open-label phase 2a clinical trial, patients diagnosed with definite, probable, or probable laboratory-supported ALS received WP-0512 (oral fasudil) 60 mg or 100 mg TID for 24 weeks for total daily doses of 180 mg or 300 mg. The primary outcome measures were safety and tolerability. Serum neurofilament light chain (NfL) concentrations were measured at baseline, 12, and 24 weeks and neuron-derived and CSF-derived extracellular vesicle phospho-AKT to total AKT (pAKT/tAKT) ratios were measured at baseline and 24 weeks as an indirect assessment of CNS target engagement. Results: A total of 31 patients were enrolled into each dosing cohort; 25 patients completed 24 weeks of treatment in the 180 mg cohort and 22 completed in the 300 mg cohort. Fasudil was generally well tolerated. Both mixed model for repeated measures and non-modeled analyses demonstrated an approximate 15% reduction in serum NfL at 24 weeks in the 180 mg group ($p < 0.001$ for both), whereas no significant change was observed in the 300 mg group. Reductions in NfL in the 180 mg group were inversely correlated with the rate of decline in ALSFRS-R [Spearman = -0.45 ($p=0.028$)]; there was no correlation in the 300 mg group. Both neuron-derived and CSF-derived extracellular vesicle pAKT/tAKT ratios were significantly increased in the 180 mg group after 24 weeks of fasudil treatment indicating probable CNS target engagement. Conclusions: These data indicate that oral fasudil is safe and well-tolerated among patients with ALS. The statistically significant reduction in NfL, which was negatively correlated with ALSFRS-R, and demonstration of CNS target engagement in the 180 mg group warrants advancing oral fasudil in a larger double-bind placebo-controlled study. The lack of dose response between the 180 mg group and the 300 mg group is consistent with animal models and indicates that the appropriate dose for further study is 180 mg per day.

Disclosures: C. Pena: None. **C. Barker:** None. **A. Grossberg:** None. **I. Mian:** A. Employment/Salary (full or part-time); Woolsey Pharma. **T. MacAllister:** A. Employment/Salary (full or part-time); Woolsey Pharma. **D.A. Linseman:** 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.; Woolsey Pharmaceuticals. F. Consulting Fees (e.g., advisory boards); Woolsey Pharmaceuticals.

Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.07/LBP167

Topic: C.06. Neuromuscular Diseases

Support: Dominium Foundation Career Development Award (Clarkson)
Generous donation from Susan Olde

Title: Cellular regulation, interferon signaling, and neuroinflammation in ALS and neurodegenerative diseases

Authors: *I. GARLAND, K. LOIDOLT, E. FRAZIER, B. D. S. CLARKSON;
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Abstract: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that primarily affects motor neurons in the brain and spinal cord, where transactive response DNA-binding protein 43 (TDP43) mislocalization has been implicated as a major hallmark. Loss of TDP43 function or TDP43 mislocalization disrupts nucleic acid sequestration and has been suggested to drive activation of cytosolic DNA and RNA sensors including the cyclic GMP-AMP synthase-stimulator of interferon genes (cGAS-STING) pathway, leading to the expression of interferon-stimulated genes (ISGs). We have found evidence that ISG15, a ubiquitin-like protein, contributes to neuron loss; thus, we aim to determine the involvement of interferon (IFN) signaling and ISG15 in TDP43 related pathology. Using adeno-associated viral (AAV) vectors in primary murine cortical neurons transduced with fluorescent IFN reporters AAV1.ISRE-EGFP, which drives green fluorescent protein (eGFP) expression under the interferon stimulated response element (ISRE) promoter, and M1RED transgenic neurons, we report the impact of TDP43 knockdown and mislocalization on neuronal IFN signaling and ISG15 expression using live cell imaging. We further assessed the impact of driving IFNγ, IFNα, or stimulator of interferon genes (STING) activation in neurons in the context of TDP43 mislocalization. Comparisons are made with neurons transduced with AAVs driving expression of Taup301L (Alzheimer's), HTT exon 1 (Huntington's), TDP43ΔNLS (nuclear localization signal, ALS), and hnRNPA1ΔNLS (multiple sclerosis). We report evidence that cytoplasmic TDP43 and hnRNPA1 drive accelerated IFN signaling in these cultures prior to neuron loss. At the end point, we conducted immunofluorescence (IF) of ISG15 in cells co-treated with

neurodegenerative AAV and IFN signals; to which we found colocalization of ISG15 and ISRE with increased expression in cells co-treated with a neurodegenerative AAV and IFNγ, whereas morphology of the neurons treated with CMA, a STING agonist, and IFNα were altered. Using an AAV-C9orf72 $(G_4C_2)_{149}$ somatic transgenesis mouse model (intracranial injection at postnatal day 2) that induces TDP43 proteinopathy and models ALS pathology, we further report ISG15-dependent effects on cGAS-STING signaling (p-STING), astrogliosis (glial fibrillary acidic protein, GFAP), microgliosis (ionized calcium-binding adapter molecule, Iba1), neuron loss (neuronal nuclei, NeuN), aggresome formation/autophagy impairment (p62/sequestosome 1, SQSTM1), and dipeptide deposition (poly glycine-arginine, pGR) in wild-type mice compared to global and conditional ISG15 knockout mice using IF.

Disclosures: I. Garland: None. **K. Loidolt:** None. **E. Frazier:** None. **B.D.S. Clarkson:** None.

Late-Breaking Poster

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Program #/Poster #: LBP075.08/LBP168

Topic: C.06. Neuromuscular Diseases

Support: ATTR-ASPIRE

Title: TTR interaction with ECM components promotes toxicity in ATTR-PN

Authors: *T. RYAN[1], S. D. RYAN[2];
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Abstract: Background: Transthyretin amyloidosis with polyneuropathy (ATTR-PN) is a progressive, often hereditary disorder in which misfolded transthyretin (TTR) protein forms amyloid deposits that damage peripheral nerves. Thus, determining the biophysical mechanisms that regulate TTR fibrillogenesis may offer insight into disease pathogenesis. While tetrameric TTR protein undergoes an intermediate monomerization event prior to fibril nucleation, the triggers of pathogenic phenoconversion from structured monomer to beta-sheet-enriched fibrils are poorly understood. Goal: To combine biophysical characterization recombinant TTR fibrilization and cellular models of TTR sequestration to characterize how TTR monomers lead to fibril deposition in tissue. Approach: We have developed recombinant TTR expression and purification approaches to generate both WT-TTR and mutant TTR (resistant to tetramer formation, monomeric). We then used Real-time quaking-induced conversion (RT-QuIC) combined with thioflavin T (ThT) incorporation to track the effect of buffer constituents and pathological seed material on fibrilization kinetics. We also tracked changes in secondary structure of TTR through circular dichroism spectroscopy, and differences in its hydrodynamic radius (R_H) through dynamic light scattering (DLS). Transmission electron microscopy (TEM) helped to visualize the formation of fibrils under each condition. Finally, we assessed whether

the extracellular matrix (ECM) of hiPSC-derived tissues differentially sequester TTR tetramers and monomers. Results: TTR fibrilization is dependent on and requires, 1) the presence of monomeric protein and 2) the presence of heparin. In a physiological setting, we found that ECM sequesters TTR monomer, suggesting that heparan sulfate might nucleate seed formation in a disease setting. Conclusion: This work informs on the mechanism of TTR fibrillation and how the extracellular matrix may lead to tissue-specific deposition.

Disclosures: T. Ryan: None. **S.D. Ryan:** None.

Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.09/LBP169

Topic: C.06. Neuromuscular Diseases

Support: NIHR01NS123023
NIHR01NS069726
NIHR01NS094539

Title: A sensory and motor neuropathy caused by a genetic variant of *NAMPT*

Authors: *S. DING;
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Abstract: Nicotinamide phosphoribosyl transferase (NAMPT) is the rate-limiting enzyme in the salvage pathway for NAD^+ biosynthesis in mammalian cells and is essential for survival. Here, we report on a novel axonal sensory and motor neuropathy likely caused by a homozygous genetic variant of missense mutation (c.472G>C, p.P158A) in *NAMPT* gene. Two affected siblings presented with a range of clinical features including impaired motor coordination, muscle atrophy, foot deformities, and positive Babinski sign. Using different preparations including recombinant human and mouse NAMPT proteins, patient fibroblasts (FBs) and mouse model, we showed that the p.P158A mutation decreased NAMPT enzyme activity, leading to disrupted cellular bioenergetics, metabolic derangements, and increased oxidative stress. Moreover, the p.P158A mutation could cause synaptic dysfunction and motor neuron degeneration in the mouse model. This Mutation in NAMPT Axonopathy (MINA) syndrome is the first human hereditary neurological disease linking to a NAMPT variant. Our study has significant clinical implications.

Disclosures: S. Ding: None.

Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.10/LBP170

Topic: C.06. Neuromuscular Diseases

Title: LNP-CRISPR-Cas9 editing of muscle satellite cells to resist muscle injury

Authors: *T. MOCHIDA[1], N. FUJIMOTO[2], M. A[3], S. ASANO[4], S. ARAKI[5], N. INUKAI[6], A. HOTTA[2];
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Abstract: Background and Aim: Satellite cells are skeletal muscle-resident stem cells that function as donors of myonuclei, providing regenerative ability to muscles. Duchenne muscular dystrophy (DMD) is a progressive muscle-wasting disease caused by loss-of-function mutations in the dystrophin gene. Satellite cells are an attractive therapeutic target for genome editing therapy in DMD. Currently, efficient delivery of genetic components to *in vivo* satellite cells is a major challenge. We have developed a promising lipid nanoparticle encapsulating Cas9 mRNA and sgRNAs targeting human DMD exon 45 (LNP-CRISPR) to induce in-frame dystrophin expression by exon skipping. However, it is unknown whether or not LNP-CRISPR is able to edit satellite cells. In this study, we investigated the effect of intramuscularly (i.m.) injected LNP-CRISPR on satellite cells using humanized mouse models of DMD. **Results:** LNP-CRISPR induced exon skipping in satellite cells isolated from mice treated with the i.m. injection, achieving higher efficiency than CRISPR-encoded adeno-associated virus (AAV) vectors. Pre-incubated LNP-CRISPR with ApoE3 protein induced higher exon skipping activity when compared to non-precoated LNP-CRISPR in isolated satellite cells, suggesting that the efficient editing in satellite cells with LNP is, at least in part, mediated by the binding of ApoE to LNP. Regarding the functional contribution of satellite cells, skeletal muscle tissue genome-edited by LNP-CRISPR showed greater resistance to injury compared to AAV-CRISPR. Furthermore, after the implantation of satellite cells isolated from reporter mouse models into the muscles of immuno-deficient mice, the satellite cells showed a proliferative response to injury. This response was greater when implanting full-length dystrophin^{+} satellite cells compared to dystrophin^{-} satellite cells. The satellite cells isolated from mice treated with LNP-CRISPR differentiated into dystrophin^{+} myotubes *in vitro*. **Conclusion:** LNP-CRISPR effectively edited satellite cells via i.m. injection. The genome-edited satellite cells would contribute to the recovery of genome editing effects in skeletal muscle tissue after injury. Our results demonstrate the promise of LNP-based delivery for future *in vivo* non-viral genome editing therapy for DMD.

Disclosures: T. Mochida: A. Employment/Salary (full or part-time); Takeda Pharmaceutical Company Limited. **N. Fujimoto:** A. Employment/Salary (full or part-time); Center for iPS Cell

Research and Application. **M. A:** A. Employment/Salary (full or part-time); Takeda Pharmaceutical Company Limited. **S. Asano:** A. Employment/Salary (full or part-time); Axcelead Drug Discovery Partners, Inc. **S. Araki:** A. Employment/Salary (full or part-time); Takeda Pharmaceutical Company. **N. Inukai:** A. Employment/Salary (full or part-time); Takeda Pharmaceutical Company Limited. **A. Hotta:** A. Employment/Salary (full or part-time); Center for iPS Cell Research and Application.

Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.11/LBP171

Topic: C.06. Neuromuscular Diseases

Support: European Union's Horizon 2020 Framework Programme for Research and Innovation 'Brain Involvement in Dystrophinopathies' (BIND) (847826)

Title: Identification of novel dystrophin interactors and their role in Duchenne muscular dystrophy brain deficiency

Authors: *K. TETOROU[1,2], S. MA[2], T. E. GILEADI[2], P. SPITALI[3], L. ZHANG[4], J. MORGAN[2], F. MONTANARO[2], L. MUNTONI[2];
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Abstract: Duchenne muscular dystrophy (DMD) is a severe neuromuscular disorder caused by mutations in the X-linked DMD gene, resulting in the disruption of functional dystrophin protein production. DMD patients exhibit progressive muscle weakness and are at a heightened risk of respiratory and cardiac failure. Notably, a significant proportion of DMD patients also experience intellectual disability and/or neurobehavioral complications, such as autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and anxiety, which have been linked to deficiency of different isoforms in the brain. The presence of at least seven alternative promoters, two polyA addition sites and multiple alternative splicing sites results in several dystrophin isoforms with different expression patterns and putative roles. The variability in DMD isoform deficiency, determined by the location of the gene mutation, is associated with varying degrees of brain comorbidities among affected individuals. DMD mouse models that carry a mutation affecting Dp427 dystrophin isoforms, display an enhanced fear response and increased anxiety- and depressive-like behaviours. We hypothesised that the various dystrophin brain isoforms interact with different protein complexes in the brain. The aim of this study was to identify potential candidate dystrophin protein interactors in the mouse brain, to better understand DMD brain co-morbidities. In this study, mdx5cv mice lacking Dp427, mdx52 mice lacking both Dp427 and Dp140 and DMD-null mice lacking Dp427, Dp140 and Dp71 were

used. Different brain regions (cortex, hippocampus, cerebellum, midbrain and olfactory bulbs) were used for immunoprecipitation followed by mass spectrometry analysis to identify dystrophin's protein interactors in the brain followed by trancriptomics analysis. The proteins were further validated with immunohistochemistry and western blot analysis. Our results revealed that different proteins interact differently with Dp427, Dp140 and Dp71 in the different brain regions. Various proteins involved in ion channels activity, synaptic GABAergic transmission, neurodegeneration and neurodevelopemnt were found to interact differently with dystrophin isoforms across brain regions. This study provides insights into dystrophin's role in the molecular networks underlying emotional and cognitive comorbidities in DMD, offering potential targets for therapeutic intervention.

Disclosures: K. Tetorou: None. **S. Ma:** None. **T.E. Gileadi:** None. **P. Spitali:** None. **L. Zhang:** None. **J. Morgan:** None. **F. Montanaro:** None. **L. Muntoni:** 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.; As COI, F. Muntoni is an investigator in Sarepta, Genethon, Roche clinical trials. He has participated to advisory boards and/or symposia for Sarepta, Roche, Dyne therapeutics, Wave and Entrada..

Late-Breaking Poster

LBP075: C.06. Neuromuscular Diseases

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 8:00 AM - 12:00 PM

Program #/Poster #: LBP075.12/LBP172

Topic: C.06. Neuromuscular Diseases

Support: NINDS
CIRM
FARA
Uplifting Athletes

Title: Single infusion of FXN-Edited HSPCs (mPPL-001) Ameliorates Motor Dysfunction and Neuroinflammatory Signatures in Friedreich's Ataxia Mice

Authors: *S. ARUMUGAM[1], A. SIVAKUMAR[2], A. CORL[1], R. BADELL-GRAU[3], S. CHERQUI[2];
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Abstract: Friedreich's ataxia (FRDA) is a multi-systemic, autosomal recessive neurodegenerative disorder that manifests with ataxia, areflexia, sensory loss and muscle weakness, with cardiomyopathy being the leading cause of mortality. FRDA is caused by a homozygous GAA repeat expansion in intron 1 of the frataxin gene (FXN), leading to reduced production of FXN protein, a mitochondrial protein critical for cellular homeostasis. Currently

there are no effective treatments for FRDA. We previously showed that a single, systemic infusion of wild-type (WT) hematopoietic stem and progenitor cells (HSPCs) completely rescue neurologic, muscular, and cardiac complications in the YG8sR FRDA mouse model via FXN transfer from the engrafted HSPC-derived microglia/macrophages to neurons/myocytes. We next developed an ex vivo CRISPR/Cas9 gene editing approach that excises the GAA expansion in FRDA patients' CD34+ HSPCs (PPL-001) as a potential autologous transplantation therapy. This study evaluates the efficacy of mPPL-001 in YG8s(GAA)>800 mice (YG8JR) carrying the human FXN (hFXN) with >800 GAA repeats. Myeloablated YG8JR mice (2.0-2.5 months old) were transplanted with either ex vivo gene edited Sca1+ HSPCs (mPPL-001) or mock HSPCs and analyzed 6 months later. With a mean editing efficiency of 19.67%, mPPL-001-derived cells were detected in the hematopoietic tissues and primary organs affected by FRDA. mPPL-001 improved motor functions by normalizing left hind swing speed, duty cycle and step sequence to WT levels, compared to untreated or mock HSPC transplanted YG8JR mice. Mechanistically, mPPL-001 transplantation preserved cerebellar granular neurons and dendritic arbors of the molecular layer. These changes were mediated by increased FXN expression and normalization of transcriptomic signatures in the cerebellum of mPPL-001 transplanted mice compared to untreated or mock mice. RNA sequencing revealed normalization of disease-associated microglial and inflammatory genes along with enrichment of mitochondrial, autophagy, phagocytosis and immune regulatory pathways in mPPL-001 transplanted mice. Consistently, Sholl analysis of cerebellar Iba1+ microglia demonstrated that transplantation of mPPL-001 restored microglial morphology from an activated to a homeostatic state, validating the inflammation transcriptomic profile. Together, these findings demonstrate that a single infusion of FXN gene edited HSPCs confers long-term engraftment with tissue-wide distribution, functional rescue of gait and balance, and reversal of pathogenic pathways for cerebellar tissue preservation in YG8JR mice, supporting its clinical translation for FRDA.

Disclosures: S. Arumugam: None. **A. Sivakumar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Papillon Therapeutics. **A. Corl:** None. **R. Badell-Grau:** None. **S. Cherqui:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Papillon Therapeutics. F. Consulting Fees (e.g., advisory boards); Cystinosis Research Foundation.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.01/LBP001

Topic: E.01. Somatosensation – Pain and Itch

Title: Pharmacological interaction of chlorpheniramine and diclofenac on nociception and inflammation in rats

Authors: *M. ORTIZ RAMIREZ;
Univ. Aut. Estado de Hidalgo, Pachuca, Mexico

Abstract: The nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic and anti-inflammatory effects. However, gastrointestinal adverse reactions are common with these drugs. The combination of NSAIDs with antihistaminic drugs, which have analgesic and anti-inflammatory effects, may increase their beneficial effects and limit the side effects of the NSAIDs. In this study, the effects of an interaction between the antihistaminic drug chlorpheniramine and the NSAID, diclofenac, on nociception (formalin test) and inflammation (paw inflammation by carrageenan) in Wistar rats were assessed. The Institutional Animal Care and Use Committee (CINVESTAV. IPN, Mexico) approved the study protocol with registration number 0169-15. The rats were treated in accordance with the Guiding Principle on Ethical Standards for Animal Research. Diclofenac (30-560 µg/paw in local administration and 10-56 mg/kg in systemic administration), chlorpheniramine (10-300 µg/paw in local administration and 1-30 mg/kg in systemic administration), or diclofenac-chlorpheniramine (32.7-261.4 µg/paw in local administration and 3.0-24.4 mg/kg in systemic administration) combinations produced antinociceptive effects in rat ($p<0.05$). Likewise, diclofenac (3-30 mg/kg in systemic administration), chlorpheniramine (5.6-56 mg/kg in systemic administration), or diclofenac-chlorpheniramine (3.6-28.9 mg/kg in systemic administration) combinations produced anti-inflammatory effects in rats ($p<0.05$). Effective dose (ED_{40}) values were determined for each individual drug and analysed isobolographically. The theoretical ED_{40} values for the local peripheral antinociceptive (261.4 µg/paw in local administration) and systemic anti-inflammatory (28.8 mg/kg in systemic administration) effects differed significantly ($p<0.05$) from the experimental ED_{40} values (83.3 µg/paw in antinociception and 5.7 mg/kg in anti-inflammation), demonstrating synergistic interaction in local peripheral antinociceptive and systemic anti-inflammation. However, the theoretical ED_{40} value for the systemic antinociceptive (24.4 mg/kg in systemic administration) effect did not differ ($p>0.05$) from the experimental ED_{40} value (16.2 mg/kg in systemic administration), demonstrating an additive interaction in systemic antinociception. It is concluded that the interactions between diclofenac and chlorpheniramine are synergistic and additive. These data suggest that the diclofenac-chlorpheniramine combinations can interact to produce minor adverse effects, thereby offering a safer therapeutic alternative for the clinical management of inflammation and/or inflammatory pain.

Disclosures: M. Ortiz Ramirez: None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.02/LBP002

Topic: E.01. Somatosensation – Pain and Itch

Title: A vagal skin-lung sensory circuit suppresses type 2 lung inflammation

Authors: *R. SHIBUYA[1], K. SONG[1], Z. WANG[1], H. IRIKI[2], A. IIJIMA[1], N. D. ROSSEN[1], N. P. BISCOLA[1], K. ANTHONY[1], B. KIM[1];
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Abstract: Vagal sensory neurons regulate immune responses in visceral organs, but whether cutaneous inputs acting through vagal afferents influence distal inflammation is unclear. Here, we define a skin-lung neuroimmune pathway in which TRPV1-expressing vagal afferents innervating the auricular skin suppress allergic lung inflammation. Although these afferent fibers express nociceptor-associated markers, ablation of $TRPV1^+$ neurons in the vagal ganglion did not alter capsaicin-induced nocifensive behavior on the ear. By contrast, chemogenetic and optogenetic activation of auricular $TRPV1^+$ vagal afferents increased airway CGRPβ and attenuated ILC2-mediated type 2 responses. Loss-of-function experiments confirmed their necessity in regulating type 2 allergic inflammation. These data offer a possible mechanistic insight for anti-inflammatory effects of auricular transcutaneous vagus nerve stimulation and argue that peripherally accessible vagal afferents can modulate pulmonary immunity with CGRPβ possibly acting downstream in the airway. Our findings extend the lung-brain axis to include a cutaneous-visceral reflex and suggest the auricular skin as a potential portal for targeted peripheral neuromodulation in allergic lung diseases.

Disclosures: R. Shibuya: None. **K. Song:** None. **Z. Wang:** None. **H. Iriki:** None. **A. Iijima:** None. **N.D. Rossen:** None. **N.P. Biscola:** None. **K. Anthony:** None. **B. Kim:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Allen Discovery Center, Doris Duke Charitable Foundation, NIAMS Grant AR070116, NIAMS Grant AR077007, NIAID Grant AI167933, NIAID Grant AI176660, NIDDK Grant DK141106. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); ABRAX Japan, Alys Pharmaceuticals, Attovia Therapeutics, Locus Biosciences, Neurommune Therapeutics, Recens Medical, Triveni Bio, Patent for the use of JAK1 inhibitors for chronic pruritus. F. Consulting Fees (e.g., advisory boards); ABRAX Japan, AbbVie, Amgen, Attovia Therapeutics, Clexio Biosciences, Eli Lilly and Company, Escient Pharmaceuticals, Evommune, Galderma, LEO Pharma, Micreos, Novartis, Pfizer, Recens Medical, Regeneron Pharmaceuticals, Sanofi, Septerna, Triveni Therapeutics, Triveni Bio.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.03/LBP003

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant #1R01NS113189-01
National Academy of Science of Ukraine grant 0124U001557
National Academy of Science of Ukraine grant 0125U001123

Title: C5a-induced increase in intrinsic excitability of dorsal horn neurons in intact murine spinal cord

Authors: S. V. ROMANENKO[1], V. V. KROTOV[1], O. HALAIDYCH[1], I. BLASHCHAK[1], A. KEYES[2], B. V. SAFRONOV[3], ***N. V. VOITENKO**[4], Y. M. USACHEV[2], P. V. BELAN[1];
[1]Biophysics of Sensory Signalling, Bogomoletz Institute of Physiology, Kyiv, Ukraine; [2]Neuroscience and Pharmacology, University of Iowa, Iowa City, IA; [3]Neuronal Networks, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal; [4]Dobrobut Academy Medical School, Kyiv, Ukraine

Abstract: Emerging research indicates that C5a, a key molecule in the complement system, strongly influences neuroimmune activity and nociceptive processing in the spinal cord. Here, we have further elucidated C5a-dependent spinal mechanisms that may contribute to the development of neuropathic pain. In dorsal horn (DH) neurons, a prolonged C5a application led to an increase in the number of action potentials (APs) evoked by the dorsal root stimulation , while the primary sensory inputs to these neurons were mostly unaffected. A C5a-induced increase in spontaneous AP firing was also observed. These results implied that C5a altered intrinsic neuronal properties rather than enhanced primary synaptic drive in the DH network. The analysis of APs showed that the upregulated AP firing following C5a application was associated with a decreased AP generation threshold. To further investigate the intrinsic mechanisms underlying this AP threshold change, we used the voltage ramp protocol, which revealed transmembrane current dynamics and enabled qualitative evaluation of intrinsic membrane mechanisms. Applying the ramp protocol to the DH neurons typically produced a rapid AP train superimposed on a subthreshold current response. Postprocessing of these current responses allowed us to extract the ramp-response parameters, including the maximum inward current and corresponding voltage, and slope of the ramp-driven current. A comparison of these parameters before and 30 minutes after C5a application showed that maximum inward current and corresponding voltage were affected, with a leftward shift observed. This result aligned with the decrease in the AP generation threshold. Furthermore, the slope of the ramp-driven current, calculated from the range prior to inward current activation, remained stable in C5a, while being decreased in the vehicle. It suggested a C5a-induced increase in membrane resistance and, consequently, enhanced cellular excitability. We conclude that C5a/C5aR1 signaling results in an increased AP activity of dorsal horn neurons due to enhancement of their intrinsic excitability that may contribute to neuropathic pain development.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.04/LBP004

Topic: E.01. Somatosensation – Pain and Itch

Support: Lilly Research Labs

Title: Intrathecal administration of siRNA for Nav1.8 reduces neuropathic pain and evoked responses of nociceptive dorsal horn neurons

Authors: X. ZHANG[1], V. VIATCHENKO-KARPINSKI[1], S. G. KHASABOV[1], I. KHASABOVA[1], C.-C. J. HUANG[2], T. JESSOP[3], K. S. RATLIFF[4], J. S. MCDERMOTT[5], ***D. A. SIMONE**[1];
[1]University of Minnesota, Minneapolis, MN; [2]Eli Lilly, Boston, MA; [3]Lilly Research Labs, Zionsville, IN; [4]Eli Lilly and Company, CARMEL, IN; [5]Eli Lilly & Co., Indianapolis, IN

Abstract: The voltage-gated sodium channel Nav1.8 is selectively expressed in nociceptors and modulates neuronal excitability. Earlier studies have shown that Nav1.8 contributes to acute and chronic inflammatory and neuropathic pain, and it is therefore currently being pursued as a therapeutic target. Here we determined the effects of a rodent tool siRNA targeting the Scn10a transcript (termed Nav1.8 siRNA) on hyperalgesia and evoked responses of nociceptive spinal neurons in a model of neuropathic pain. Adult male and female Sprague-Dawley rats underwent spinal nerve ligation (SNL) followed by intrathecal (i.t.) administration of Nav1.8 siRNA (20 µL of a 30.0 mg/mL stock solution for a final dose of 600 ug) (N=10) or an equal volume of PBS (N=9) two weeks after the surgery. Electrophysiological studies were conducted 4 weeks after siRNA or PBS administration. Behavioral measures of mechanical hyperalgesia, defined as a decrease in paw withdrawal threshold (PWT), were determined weekly prior to electrophysiology. PWT decreased after SNL and this was partially reversed by the Nav1.8 siRNA. In electrophysiological studies, recordings were made from a total of 225 single wide dynamic range neurons (Nav1.8 siRNA=116; PBS=109) at 4 weeks after i.t. administration of siRNA or PBS. Mechanical response thresholds were elevated and the number of impulses evoked by a suprathreshold stimulus (15 g for 5 sec) were lower in the Nav1.8 siRNA group. Responses evoked by heat (50°C for 5 sec) and cold (0°C for 5 sec) were also reduced as compared to the PBS group. These studies demonstrate that a single i.t. administration of Nav1.8 siRNA may be an effective approach to reduce neuropathic pain produced by peripheral nerve injury.

Disclosures: X. Zhang: None. **V. Viatchenko-Karpinski:** None. **S.G. Khasabov:** None. **I. Khasabova:** None. **C.J. Huang:** A. Employment/Salary (full or part-time); Lilly Research Labs. 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.; None. C. Other Research Support

(receipt of drugs, supplies, equipment or other in-kind support); None. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); None. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); None. F. Consulting Fees (e.g., advisory boards); None. Other; None. **T. Jessop:** A. Employment/Salary (full or part-time); Lilly Research Labs. **K.S. Ratliff:** A. Employment/Salary (full or part-time); Lilly Research Labs. **J.S. McDermott:** A. Employment/Salary (full or part-time); Lilly Research Labs. **D.A. Simone:** A. Employment/Salary (full or part-time); University of Minnesota. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Lilly Research Labs. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Lilly Research Labs. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); None. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); None. F. Consulting Fees (e.g., advisory boards); None. Other; None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.05/LBP005

Topic: E.01. Somatosensation – Pain and Itch

Support: Swiss National Science Foundation (SFN) funding

Title: Characterization of translatomic changes in spinal cells after peripheral nerve injury

Authors: *C. BECCARINI[1], A. CHOUDHURY[2], H. WILDNER[3], H. U. ZEILHOFER[4]; [1]Pharmacology and Toxicology (IPT), University of Zurich (UZH), Zurich, Switzerland; [2]Department of Mathematics, ETH Zürich, Zürich, Switzerland; [3]University of Zurich, Zurich, Switzerland; [4]Institute of Pharmacology, University of Zurich, Zurich, Switzerland

Abstract: Background – One in three patients with peripheral nerve injury develop neuropathic pain, a chronic condition marked by spontaneous pain and pathologically amplified responses to stimuli. Evidence suggests this arises from altered spinal dorsal horn circuits, including enhanced excitability and reduced inhibition, yet the neuron-type-specific mechanisms remain unclear.**Methods** – To model neuropathic pain, spared nerve injury (SNI) surgery was performed in mice. Bulk RNA-seq and Translating Ribosome Affinity Purification (TRAP-seq) were used to identify SNI-induced transcriptional and translational changes. We analyzed the translatomes of spinal inhibitory (vGatcre;nuTRAP) and excitatory (vGlut2cre;nuTRAP, CCKcre;nuTRAP) neurons in both sexes at 2 and 7 days post-PNI to assess transient versus sustained effects.**Results** – In naïve mice, 3320 genes were enriched in the transcriptome and 3544 in the translatome. However, when analysing PNI-induced changes, a robust correlation between

transcriptome and translatome was found, indicating that most injury-induced transcripts were translated. Sex differences were limited. In cell-type-specific analyses, 528 SNI-responsive genes were identified across CCK^{cre}, $vGlut2^{cre,}$ and $vGat^{cre}$ neurons and grouped into 11 temporal expression profiles. Pathway analysis revealed key alterations: CCK neurons showed early downregulation of neurotransmitter signaling (day 2), followed by upregulation of stress and injury genes (day 7). vGlut2 neurons exhibited persistent upregulation of growth and proliferation pathways across both timepoints. vGat neurons displayed early downregulation of amino acid/ion transporters (day 2) and later downregulation of intracellular and second messenger signaling (day 7).**Conclusions** – Our investigation has demonstrated that SNI condition in mice induces transcriptional changes in the spinal cord, the majority of which are carried on to the translatome. To test whether more differential gene expression changes can be uncovered after PNI, we further characterized the translatome changes occurring in 3 distinct spinal subpopulations of neurons: CCK^{cre}, $vGlut2^{cre,}$ and $vGat^{cre}$. Expression pattern analysis classified the SNI-responsive genes in 11 profiles, and Ingenuity Pathway analysis provides insights into the molecular pathways driving neuropathic pain. Taken together, our study uncovers novel mechanisms of specific spinal cell populations after PNI and highlights translatome differences during maladaptive plasticity, emphasizing the importance of considering spinal-cell type specific translating mRNAs to identify new therapeutics targets.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.06/LBP006

Topic: E.01. Somatosensation – Pain and Itch

Support: R01DA044481
New York Stem Cell Foundation

Title: A functional atlas of μ-opioid receptor-expressing spinal cord neuron types

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Abstract: The spinal cord integrates nociceptive signals from sensory neurons and relays them to the brain, and is a critical site of action for opioid analgesics that act on the μ-opioid receptor (MOR). Classically, these functions are thought to be executed by neurons localized in the dorsal horn of the spinal cord, whereas activity in ventral horn neural circuits generates movements. Here, we combined spinal cord snRNA-sequencing, mouse genetics, light-sheet microscopy,

slice electrophysiology, chemogenetics, and behavioral approaches to map MOR expression and function across spinal neuron types. In the dorsal horn, we found that MOR mediates the analgesic effects of clinically used opioids via a spino-parabrachial pathway. In the ventral horn, we found that MOR is notably expressed in V2a and V1 premotoneurons. Unexpectedly, we reveal that V1 neurons, previously linked exclusively to locomotion, form reciprocal connections with the dorsal horn and directly contribute to mechanical pain modulation. Conditional MOR deletion in V1 neurons completely blocked pain recovery following peripheral inflammation, while activating MOR+ V1 neurons is necessary and sufficient to control mechanical pain. Furthermore, this function is specific to V1 neurons, as we show that V2a neurons do not project dorsally but exclusively ventrally, and mediate opioid-mediated muscle rigidity, a major side effect of opioids. Collectively, our results highlight the importance of sensorimotor integration in pain processing, challenge the dorso-ventral segregation of spinal neuron functions, and elucidate both the logic of opioid actions in the spinal cord and unconventional neural mechanisms of pain threshold adjustment.

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Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP076.07/LBP007

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Title: SBI-810, an Arrestin-Biased Allosteric Modulator of Neurotensin Receptor 1, Relieves Acute and Chronic Pain and Attenuates Addiction-Related Responses

Authors: *R. GUO[1], O. CHEN[3], Y. ZHOU[3], S. BANG[4], S. CHANDRA[3], Y. LI[3], W. HE[7], J. XU[5], K. PERSON[8], A. ALWIN[9], M. JACKSON[11], S. OLSON[11], M. G. CARON[12], L. M. SLOSKY[10], W. C. WETSEL[6], L. BARAK[13], **R.-R. JI**[2];
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of Minnesota, Apple Valley, MN; [10]Pharmacol., Univ. of Minnesota, Minneapolis, MN; [11]Sanford Burnham Prebys Med. Discovery Inst., La Jolla, CA; [12]Departments of Cell Biology, Neurobiology, Med., Med. Ctr., Durham, NC; [13]Dept. of Cell Biol., Duke Univ. Med. Center,, Durham,, NC

Abstract: G-protein biased agonists have been shown to enhance opioid analgesia by circumventing β-arrestin-2 (βarr2) signaling. We previously reported that SBI-553, a neurotensin receptor 1 (NTSR1) positive allosteric modulator biased toward βarr2 signaling, attenuates psychostimulant effects in mice. Here, we demonstrate that its analog, SBI-810, exhibits potent antinociceptive properties in rodent models of postoperative pain, inflammatory pain, and neuropathic pain via systemic and local administration. SBI-810's analgesic effects require NTSR1 and βarr2 but not NTSR2 or βarr1. Mechanistically, SBI-810 suppresses excitatory synaptic transmission, inhibits NMDA receptor and ERK signaling in spinal cord nociceptive neurons, reduces Nav1.7 surface expression and action potential firing in primary sensory neurons, and dampens C-fiber responses. Behaviorally, it reduces opioid-induced conditioned place preference, alleviates constipation, and mitigates chronic opioid withdrawal symptoms. These findings highlight NTSR1-biased allosteric modulators as a promising, non-addictive therapeutic strategy for acute and chronic pain management, acting through both peripheral and central mechanisms.
PUBLICATIONS: 1. Guo, R., Chen, O., Zhou, Y., Bang, S., Chandra, S., Li, Y., Chen, G., Xie, R.G., He, W., Xu, J., et al. (2025). Arrestin-biased allosteric modulator of neurotensin receptor 1 alleviates acute and chronic pain. Cell 188, 4332-4349.e4321. 10.1016/j.cell.2025.04.038. 2. Pottie, E., Steinmüller, S.A.M., and Decker, M. (2025). Pain management beyond opioids: a β-arrestin2-biased allosteric GPCR modulator opens new avenues for drug development. Signal Transduct Target Ther *10*, 264. 10.1038/s41392-025-02361-1. 3. Didenko, O., and Wood, J.N. (2025). Arrestins and opioid-independent analgesia. Cell *188*, 4175-4177. 10.1016/j.cell.2025.07.008. 4. Crunkhorn, S. (2025). Neurotensin receptor modulator safely tackles pain. Nat Rev Drug Discov *24*, 586. 10.1038/d41573-025-00109-8.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

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Topic: E.01. Somatosensation – Pain and Itch

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Title: Astrocytic GPR37L1 regulates astrogliosis and synaptic transmission in the spinal cord dorsal horn and protects against neuropathic pain

Authors: *J. XU[1], Z. YAN[1], S. BANG[2], D. VELMESHEV[3], R.-R. JI[4];
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Abstract: Summary: Astrocytes in the spinal cord dorsal horn (SDH) play an important role in synaptic transmission and neuropathic pain. Astrocyte reactivity and astrogliosis have long been implicated in the pathogenesis of neuropathic pain. However, the classification of SDH astrocytes in health and disease remains unclear, and their protective role in neuropathic pain is not well defined. Using single-nucleus RNA sequencing, we identified *Gpr37l1* as a selective GPCR marker for spinal cord astrocytes. In naïve animals, knockdown of GPR37L1 in SDH astrocytes induced astrogliosis, increased excitatory postsynaptic currents (EPSCs), and caused pain hypersensitivity. Moreover, *Gpr37l1* knockout mice exhibited reactive astrocyte phenotypes and exacerbated neuropathic pain following peripheral nerve injury. In contrast, treatment with maresin-1 (MaR1), an endogenous ligand of GPR37L1, enhanced astrocytic GLT-1 activity, reduced spinal EPSCs, and alleviated neuropathic pain. Finally, selective overexpression of *Gpr37l1* in SDH astrocytes rescued neuropathic pain and mitigated enhanced excitatory synaptic transmission and astrogliosis after nerve injury. Taken together, our findings highlight astrocytic GPR37L1 as a key negative regulator of spinal pain signaling and highlight it as a promising therapeutic target for neuropathic pain. **ACKNOWLEDGMENTS:** This study was supported by Duke University Anesthesiology Research Funds, NIH R01 grant 1NS13181201A1, DoD grants W81XWH2110885 and W81XWH2110756 to R.R.J. This study was also supported by Duke University Neurobiology Research Funds and NIH R00 grant 5R00MH121534 to D.V.
PUBLICATIONS: 1. Xu, J., Yan, Z., Bang, S., Velmeshev, D., and Ji, R.R. (2025). GPR37L1 identifies spinal cord astrocytes and protects neuropathic pain after nerve injury. Neuron. 10.1016/j.neuron.2025.01.012. 2. Kohro, Y., and Tsuda, M. (2025). Astrocytic GPR37L1: A new guardian against the onset and chronicity of neuropathic pain. Neuron *113*, 1121-1123. 10.1016/j.neuron.2025.03.013. 3. Ji, R.R., Donnelly, C.R., and Nedergaard, M. (2019). Astrocytes in chronic pain and itch. Nat Rev Neurosci *20*, 667-685. 10.1038/s41583-019-0218-1.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

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Program #/Poster #: LBP076.09/LBP009

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant No. R37 MH076136

Title: Common and distinct neural correlates of nociception and pain

Authors: *L.-B. ZHANG[1], B. PETRE[1], T. D. WAGER[2];
[1]Dartmouth College, Hanover, NH; [2]Psychological and Brain Sciences, Dartmouth College, Hanover, NH

Abstract: Common and distinct neural correlates of nociception and pain
AuthorsLI-BO ZHANG[1], BOGDAN PETRE[1], TOR D. WAGER[1]1Department of Psychological and Brain Sciences, Dartmouth College, Hanover, NH**DisclosuresLi-Bo Zhang**: None. **Bogdan Petre**: None. **Tor D. Wager**: None.
AbstractPain is a subjective experience distinct from nociception, which refers to the neural processing of noxious stimuli. It is widely accepted that pain cannot be inferred from nociception alone, but neural correlates of nociceptive stimulus intensity have been assumed to be similar to those of subjective pain intensity. It thus remains unclear to what extent neural correlates of nociception and pain differ. To reveal common and distinct neural representations of nociception and pain, we used a large fMRI database (N = 338) curated from 10 published studies, in which healthy participants received contact heat pain stimuli of various temperatures and reported subjective pain ratings. A Bayes factor-based system identification approach was adopted to isolate brain regions that encoded nociception (i.e., nociceptive stimulus intensity), pain (i.e., subjective pain ratings), both, or neither. We observed that brain areas responding to stimulus intensity overlapped with those encoding pain ratings when the correlation between nociception and pain (mean r = 0.59) was not considered. However, when this correlation was controlled for, both overlapping and distinct brain regions emerged for nociception and pain. Specifically, while areas such as the midcingulate cortex and insula encoded both nociception and pain, other regions were specific to nociception (e.g., lateral rostral thalamus) or pain (e.g., ventral medial prefrontal cortex). Further analyses demonstrated no substantial impact of multicollinearity when intercorrelated stimulus intensity and pain ratings were both included in our regression models. Altogether, these findings suggest that different brain systems are recruited to transform nociception into pain, providing potential targets for neuromodulation to alleviate pain.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

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Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.10/LBP010

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R01NS129059

Title: Altered Theta-Band Connectivity Underlying Pain Processing in Chronic Pain Patients: A Magnetoencephalography Study

Authors: M. CANNISTRA[1], V. SACCA[2], S. P. AHLFORS[3], W. LI[4], ***J. KONG**[5]; [1]Massachusets General Hospital, Charlestown, MA; [2]Psychiatry, Massachusetts General Hospital, Boston, MA; [3]Radiology, Massachusetts General Hospital, Charlestown, MA; [4]Department of Psychiatry, UTHealth Houston, Houston, TX; [5]Psychiatry, Massachusetts General Hospital, Charlestown, MA

Abstract: Purpose: Chronic pain is debilitating, with unclear mechanisms that hinder treatment development. Neural biomarkers may provide targets, but MEG studies in chronic low back pain (cLBP) are limited. This study used MEG to compare pain processing in cLBP patients and healthy controls during rest, no-pain pressure, and tonic pain. **Methods** Structural MRI (3T Siemens) and MEG (MEGIN TRIUX) data were collected. Six-minute MEG scans were acquired during tonic pressure pain (individualized VAS 4/10) and no-pain pressure, applied to the right leg in random order, with resting-state MEG recorded first. Source reconstruction was based on FreeSurfer parcellation. Left paracentral cortex connectivity was analyzed using imaginary coherence across frequency bands (theta, alpha, beta, gamma). Group differences across conditions (rest, no pain, pain, rest vs. no pain, rest vs. pain, no pain vs. pain) were tested using linear mixed-effects models (LMEM). The significant LMEM results were then used as input features for a Machine Learning (Support Vector Machine) model to predict group (controls vs. patients). Permutation test assessed AUC significance. MEG analysis was performed with MNE-python. **Results:** In the theta band, the LMEM revealed increased left paracentral-bilateral DLPFC connectivity ($p=0.015$) and decreased left paracentral-left rostral anterior cingulate cortex (rACC) ($p=0.018$) in cLBP patients during resting, compared to control, but not during no-pain pressure. Decreased paracentral-DLPFC ($p=0.004$) and increased paracentral-rACC ($p=0.035$) connectivity was observed in cLBP during pain pressure compared to controls. In addition, we detected a significant condition × group interaction in left paracentral-bilateral DLPFC ($p=0.003$) connectivity when comparing resting vs. pain and no pain vs. pain conditions ($p=0.012$), but not when comparing resting vs. no pain. The left paracentral - left rACC showed significant condition x group interaction when comparing resting vs pain ($p=0.008$), and no significant results for no pain vs pain and resting vs no pain. Machine learning analysis showed that resting vs. pain connectivity deltas predicted group status with an AUC of 0.77 ($p < 0.001$), and pain-pressure connectivity predicted group status with an AUC of 0.71 ($p = 0.002$). No other connectivity features significantly distinguished cLBP patients from pain-free controls. **Conclusion:** Our findings highlight altered theta-band connectivity in cLBP patients, reflecting disrupted network dynamics during pain processing. Theta-band connectivity alterations may serve as potential biomarkers for understanding the pathophysiology of chronic pain.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.11/LBP011

Topic: E.01. Somatosensation – Pain and Itch

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Title: Bayesian modelling of ON- and OFF-cells in the rostral ventromedial medulla explains dynamics across multiple concurrent timescales

Authors: C. ASHWORTH[1], Z. SHI[2], C. DE PRETER[3], *M. M. HEINRICHER[3], F. MANCINI[4];
[1]Engineering, University of Cambridge, Cambridge, United Kingdom; [2]Oregon Health & science university, Beaverton, OR; [3]Oregon Health & Science University, portland, OR; [4]University of Cambridge, Cambridge, United Kingdom

Abstract: The rostral ventromedial medulla (RVM) is a critical control hub of the brainstem pain-modulatory system, exerting both inhibitory and excitatory control over nociceptive processing in the dorsal horn. RVM neurons are traditionally classified by their responses to noxious input, giving three distinct classes: ON-cells, which are activated during nocifensive responses; OFF-cells, which pause firing; and NEUTRAL-cells, which show no change in firing. While this stimulus-driven classification is foundational, the mechanisms of RVM control also depend on ongoing dynamics, which are not understood. Furthermore, how ON- and OFF-cell activity recovers over extended timescales following nocifensive responses—potentially reflecting hysteretic properties of RVM control—remains unclear, despite its importance for understanding how pain-modulating circuits sustain or reset their influence beyond immediate responses. Here, using single-electrode recordings, we monitored the activity of 166 single units in the RVM during noxious stimulation in lightly-anesthetized male Sprague-Dawley rats. After classifying neurons by their withdrawal-related responses, we trained a latent Gaussian process machine learning model coupled with a generalised Poisson likelihood to predict, at the single neuron level, both the ongoing dynamics and variance of quasi-periodic ongoing activity in each RVM subpopulation. ON- and OFF-cells ($N_{ON} = N_{OFF} = 25$) showed quasi-periodic activity with a period of approx. 5 minutes (μ_{ON}: 296.63 s, SD_{ON}: 22.39 s, μ_{OFF}: 303.52 s, SD_{OFF}: 27.18 s). Model predictions successfully generalized to 300 s of held-out test (future) data. In contrast, the population of NEUTRAL-cells ($N_{Neutral} = 32$) showed no evidence of periodicity. Bayesian model comparisons further revealed that ON- and OFF-cell responses to noxious stimulation unfold over multiple concurrent time scales, indicating distinct underlying processes. Piecewise

modelling of neuronal activity identified the timing of peak and nadir activity: OFF-cells exhibited a depression in firing post paw withdrawal, reaching their nadir 2.23 s (97% HDI: 1.53, 3.00) after the withdrawal, whilst ON-cells peaked 0.18 s (97% HDI: -0.25, -0.10) seconds prior to the withdrawal. These findings show that RVM neurons display quasi-periodic ongoing dynamics and distinct post-withdrawal adaptations. By applying probabilistic modeling, these findings reveal new principles of how brainstem circuits organize nociceptive control across multiple timescales.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.12/LBP012

Topic: E.01. Somatosensation – Pain and Itch

Title: Impact of Virtual Reality on Procedural Pain and Anxiety in Chronic Low Back Pain Patients: A quasi-experimental study

Authors: *K. S. AL GHAMDI[1], A. BAKHURJI[2], S. FALLATAH[2], M. ALHARIRI[2]; [1]Physiology, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; [2]Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia

Abstract: Introduction One of the most common types of pain that people experience worldwide is chronic low back pain (CLBP). Chronic pain patients often turn to procedural pain management despite using all pharmaceutical pain relief options. The impact of non-immersive VR on pain and anxiety reduction is controversial. Some studies indicate that using non-immersive VR significantly reduces these symptoms when compared to regular sedatives. Thus, this study aimed to assess and compare the effects of VR distraction technologies versus Midazolam-based sedation among patients with CLBP undergoing painful intervention on pain and anxiety levels**Methods**This quasi-experimental study design was conducted at the Intervention Unit of King Fahad University Hospital in Khobar. In the period (May 2022 to May 2023), 30 chronic low back pain (CLBP) patients who met the inclusion criteria were involved in the study. All patients were randomly allocated to either sedation or virtual groups. Patients in the sedation group (SD) received sedative medication (Midazolam) while the others applied VR glasses. Pain, anxiety, comfort, and satisfaction scores were measured using the NPS, STAI scale, and comfort and satisfaction scale. Moreover, hemodynamic measurements were monitored in all groups.**Results**Both intervention (VR and SD) groups demonstrated significantly reduced post-intervention pain intensity and anxiety scores, compared to the baseline values. Notably, the VR group exhibited a significant decrease in intra-operative scores compared to baseline values with p-value=0.00. When we compared the overall effects between both interventions (VR and SD), the results showed non-significant differences in pain and

anxiety levels, suggesting similar effects of both interventions against pain and anxiety. Hemodynamic parameters did not differ significantly except systolic blood pressure, which showed a significant reduction when we compared the basal reading with the second and third reading in the VR and SD groups respectively.
ConclusionBoth interventions (VR and SD) demonstrated significantly reduced post-intervention pain intensity and anxiety scores in distracting patients and reducing chronic low back pain when compared to the baseline values. When we compared the overall effects between VR and SD groups, the results showed non-significant differences in pain and anxiety levels, suggesting similar effects of both interventions agonist pain and anxiety. Virtual reality should be further adapted and researched to benefit patients in appropriate clinical settings.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

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Program #/Poster #: LBP076.13/LBP013

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant R01

Title: Defining mouse trigeminal neuropathic pain behaviors using manual and automated high-speed video analysis

Authors: *D. MOHSENIN[1], R. COLÓN[1], B. O. AHANONU[2], A. I. BASBAUM[2], X. YU[1]; [1]Anesthesia, University of California: San Francisco, San Francisco, CA; [2]Anatomy, University of California, San Francisco, San Francisco, CA

Abstract: Trigeminal neuralgia (TN) is one of the most devastating neuropathic pain conditions that profoundly impact human well-being physically and psychologically. Without universally effective treatment, managing TN remains an unmet clinical challenge. To address this knowledge gap, several preclinical trigeminal neuropathic pain models have been developed to mimic chronic compression of the trigeminal nerve observed in classical TN. However, it is often challenging to reliably recapitulate facial pain phenotype characteristic of patients with TN due to unreliable behavioral measures and operator's subjective bias. Here, we aimed to define facial pain behavioral metrics using the customized platform to record both spontaneous and von Frey-evoked behavior of freely moving mice. In contrast to naïve uninjured mice, we recorded a remarkable increase of injury-induced asymmetric grooming favoring ipsilateral, injured side that persisted for several months. Notably, this spontaneous asymmetric grooming was effectively suppressed by non-sedating dose of carbamazepine (CBZ), the first-line pharmacologic treatment for TN. We conclude that the asymmetric grooming is a spontaneous behavior of trigeminal neuropathic pain. As evoked pain is a mandatory criterion for diagnosing

TN, we subsequently applied soft von Frey filament to the affected V2 region, and the evoked behavior was assessed frame-by-frame. We recorded an increase in facial rubbings which include both groomings and ipsilateral wipings. Importantly, the number of evoked rubbings was significantly reduced by non-sedating dose of either CBZ or **α**2 agonist PS75, a novel non-opioid analgesic. Aiming to increase throughput of behavioral assay and reduce human bias, we further used Deeplabcut tracking to capture kinematic information including total distance, acceleration, and velocity upon facial stimulation across each frame. We demonstrated that the head movement immediately following von Frey stimulation is a behavioral metric of trigeminal neuropathic pain. Notably, the injury-induced movement increase remained to be detected through a 5-month study; and was readily reversed by either CBZ or PS75. Furthermore, emotional stress that occurred after nerve injury was also recorded in the elevated Plus Maze test. Taken together, we have developed improved facial pain assessment by defining mouse trigeminal neuropathic pain behavioral metrics through manual and automated analysis. Our finding will pave the way toward better mechanistic study of TN and effective development of novel therapies.

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Late-Breaking Poster

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Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.14/LBP014

Topic: E.01. Somatosensation – Pain and Itch

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Title: Exploring Suzetrigine in the Preclinical Screening Platform for Pain (PSPP) Program

Authors: C. CONRAD, S. A. WOLLER, S. SHARMA, *S. IYENGAR;
NINDS/NIH, Rockville, MD

Abstract: The urgency to address the national opioid epidemic led to the NIH Helping to End Addiction Long-term® (HEAL) Initiative to help address this crisis. The PSPP program, within the NIH Heal Initiative, was developed to accelerate the discovery and development of potential non-opioid, non-addictive, small-molecule, biologic, natural-product, or device-based pain therapeutics. Evaluation within the PSPP workflow includes in vitro assessments of safety and abuse liability and protein binding, and in vivo assessments of pharmacokinetics, side effect profile, efficacy in pain-related models, and/or abuse liability in Sprague Dawley male and female rats (Envigo). As part of the program's efforts to validate clinically used drugs, the PSPP

is investigating the preclinical assessment of Suzetrigine, a novel non-opioid analgesic recently approved by the US FDA for the treatment of moderate-to-severe acute painin adults. This approval has been met with cautious optimism due to its selective inhibition of the Nav1.8 sodium channel in peripheral sensory neurons, offering pain relief without the addictive properties and CNS effects associated with opioids. In preparation for in vivo model testing in validated pain models within the PSPP program, we have evaluated suzetrigine in panels of in vitro abuse liability and off-target safety with 47 human recombinant targets, protein binding (PB), and pharmacokinetics (PK). Suzetrigine exhibited high levels of binding to plasma (97.6%) and moderate binding to brain (86.2%). Suzetrigine potentiated the EC20 response for the three opioid receptors in vitro above 30% when tested in positive allosteric modulation (PAM) mode: delta opioid receptor (OPRD1: EC50=unable to calculate; Emax@100μM=64%), kappa opioid receptor (OPRK1: EC50=17μM; Emax@100μM=61%), and mu opioid receptor (OPRM1: EC50=24μM; Amax@100μM=52%). Additional recombinant targets have been evaluated for off-target activity, and PK experiments are in progress to determine exposure profiles. In summary, these new data will enable more extensive evaluation of the effects of Suzetrigine in vivo, within the PSPP program.The data generated in the program will be added to the public-facing PSPP database, which includes clinically used drugs and negative controls, with more data to be added as it is collected.

Disclosures: C. Conrad: None. **S.A. Woller:** None. **S. Sharma:** None. **S. Iyengar:** A. Employment/Salary (full or part-time); National Institute of Neurological Disorders and Stroke, NIH, USA. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Retiree, Eli Lilly and Company.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.15/LBP015

Topic: E.01. Somatosensation – Pain and Itch

Title: Translational Human DRG Model Reveals Selective Efficacy of Nav1.8 Inhibitor Against Inflammatory Pain Responses

Authors: *Y. MIRON, F. CHEN, J. LIAW, J.-M. PACLEB, A. FERRAIUOLO, G. BAUTISTA, Z. GUZMAN, K. CARLIN;
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Abstract: Voltage-gated sodium channels are essential components of the nervous system and among them, Nav1.8 has emerged as a critical player in pain signaling. Predominantly expressed in peripheral sensory neurons of the dorsal root ganglia (DRG), Nav1.8 is distinguished by its ability to sustain repetitive neuronal firing, particularly under conditions of inflammatory pain. Experimental and clinical evidence demonstrates that upregulation or hyperactivity of Nav1.8 contributes to hypersensitivity, allodynia, and chronic pain states, making it a central mediator of

pathological nociception. Moreover, selective inhibition of Nav1.8 has shown promising analgesic effects in both preclinical models and clinical studies, which have led to the recent FDA approval of Suzetrigine. Understanding the role of Nav1.8 not only sheds light on fundamental mechanisms of pain transmission but also provides a targeted avenue for developing safer, more effective treatments for diverse pain disorders. Using a human ex-vivo model of dorsal root ganglion primary culture, we investigated the effects of sodium channel blockers on an inflammation response induced by bradykinin and PGE2 generated spontaneous activity detected in calcium imaging. Using this method, we can show the efficacy of Nav 1.8 blockers like Suzetrigine and LTGO-33 in reducing an inflammation response. Contrarily, selective Nav 1.7 blockers like PF 05089771 do not show efficacy in reducing the inflammation response, but non-selective sodium channel blockers like TTX, Tetracaine or Lidocaine do. We believe that this platform can be used to screen sodium channel blocker efficacy against an inflammatory pain model as well as other ion channel modulators. Moreover, the use of primary human culture offers a large translational advantage over the traditional rodent models in achieving relevant insights into human biology.

Disclosures: **Y. Miron:** A. Employment/Salary (full or part-time); AnaBios Corporation. **F. Chen:** A. Employment/Salary (full or part-time); AnaBios Corporation. **J. Liaw:** A. Employment/Salary (full or part-time); AnaBios Corporation. **J. Pacleb:** A. Employment/Salary (full or part-time); AnaBios Corporation. **A. Ferraiuolo:** A. Employment/Salary (full or part-time); AnaBios Corporation. **G. Bautista:** A. Employment/Salary (full or part-time); AnaBios Corporation. **Z. Guzman:** A. Employment/Salary (full or part-time); AnaBios Corporation. **K. Carlin:** A. Employment/Salary (full or part-time); AnaBios Corporation.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.16/LBP016

Topic: E.01. Somatosensation – Pain and Itch

Support: DFG KFO5001

Title: The pathomechanism of neuropathic pain caused by anti-CASPR2 autoantibodies

Authors: ***M. HABIB**[1], A.-L. WIESSLER[1], P. FISCHER[2], K. DOPPLER[2], C. VILLMANN[1]; [1]Institute for Clinical Neurobiology, Wuerzburg, Würzburg, Germany; [2]Department of Neurology, University Hospital Wuerzburg, Würzburg, Germany

Abstract: Contactin-associated protein-like 2 (CASPR2) autoantibodies (aAbs) are associated to various neurological disorders, e.g. encephalitis, epilepsy, and neuropathic pain. Most patients harbor aAbs of the IgG4 subclass. A distinct group of patients carries additional IgG subtypes (IgG1, IgG2, and/or IgG3) but IgG4 can also be the only subclass of CASPR2 aAbs. A correlation between the present IgG subclasses and clinical symptoms has not been discovered

and the precise pathomechanism remains unknown. Focusing on pain as the only or major symptom in patients, we unraveled parts of the pathology of CASPR2 aAbs. We utilized dorsal root ganglion (DRG) neurons, which possess a crucial function in pain transmission from the periphery to the central nervous system. DRG neurons express the voltage-gated potassium channel (VGKC) complex, which contains voltage-gated potassium channels (Kv) and CASPR2. Due to their close proximity, we hypothesized the main source of pathogenicity to be caused through an alteration of neuronal excitability by impaired function of the CASPR2-associated Kv channels. We investigated structural and functional alterations of the VGKC complex caused by CASPR2 aAbs. Categorizing patient' sera regarding to their pain symptom and IgG subclasses to four groups: no pain/ IgG4, no pain/ IgGX (IgG4 and other subclasses), pain/ IgG4, and pain/ IgGX. To discover structural alterations, we used microfluidic chambers which separate somata from axons. The cultured DRG neurons were treated with the sera groups, stained for Kv1.2 and CASPR2, and imaged the samples with high-resolution lattice SIM^2 microscopy. The distance between the two proteins was determined as well as their expression level. As a result, CASPR2 aAbs from patients with pain altered the distance of CASPR2 to Kv1.2 and also decreased the expression of CASPR2 in the axons. Functional consequences of CASPR2 aAb presence were analyzed through calcium imaging and whole cell patch-clamp recordings. Interestingly, excitability was increased upon treatment with aAbs associated to pain. Potassium currents were reduced the most after treatment with IgG4 aAbs. Experiments after withdrawal of the aAbs showed persisting hyperexcitability of the DRG neurons while potassium currents recovered. These findings suggest the involvement of different pathways that lead to hyperexcitability of the cells even after a washout of the aAbs. In sum, CASPR2 aAb alter the structure of the VGKC complex, and cause hyperexcitability of DRGs. The significance of aAbs of the IgG4 subclass has been substantiated by patch-clamp recordings. *This work is supported by the Deutsche Forschungsgemeinschaft KFO5001.*

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.17/LBP017

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH/NINDS Grant Number # NS045594
NIH/NINDS Grant Number # NS135157

Title: Surgical menopause exacerbates neuropathic spontaneous pain but does not affect acute stress-induced pain enhancement

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Abstract: Neuropathic spontaneous pain, which is characterized by non-evoked burning, shooting, or electric shock-like sensations in the affected limb, is the most reported and often limiting symptom of neuropathic pain conditions; however, it is vastly understudied. Additionally, research indicates there is a higher prevalence of peripheral neuropathy disorders in women who have undergone bilateral oophorectomy or menopause compared to age-matched controls. This suggests that postmenopausal status may be a risk factor for neuropathy in women. To investigate this, we performed bilateral ovariectomy (OVX) as a model of surgical menopause, 2, 4, and 10 weeks prior to spared-nerve injury (SNI). Spontaneous pain behaviors were recorded for 1 hour on post-operative day (POD) 21 and 28, and then ipsilateral hindpaw flinches and shakes were counted. Results show that OVX mice that underwent OVX 2 and 4 weeks prior to SNI had an increased number of flinches and shakes compared to their Sham OVX mice, signifying more spontaneous pain. Surprisingly, OVX mice that underwent OVX surgery 10 weeks prior to SNI did not have a significantly higher number of flinches or shakes compared to Sham OVX mice. Together, these results suggest that the effect of menopause on spontaneous pain may be partially dependent on the length of time a woman has been in the postmenopausal period. Furthermore, menopause significantly impacts how women respond to stress, both of which, on their own, exacerbate chronic pain. To test this interaction with neuropathic spontaneous pain, we performed bilateral OVX 4 weeks prior to SNI. On SNI POD21, the mice were restrained for 10 minutes to serve as an acute stressor, then spontaneous pain behaviors were recorded for 30 minutes. Here, an increase in spontaneous pain scores in the Sham OVX mice was seen, as well as an increase in licking of the injured hindpaw. However, there was no change in the spontaneous pain scores or licking of the OVX mice, providing further evidence that ovarian hormones help mediate a stress-induced increase in spontaneous pain. Overall, these findings demonstrate that ovarian hormones are able to modulate mechanisms of neuropathic spontaneous pain.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.18/LBP018

Topic: E.01. Somatosensation – Pain and Itch

Support: VT Regenerative Medicine IGEP
UL1TR003015
KL2TR003016

Title: Examining the subcellular localization of the α6 nicotinic receptor subunit in the dorsal root ganglion during pain and non-pain states

Authors: A. M. MANN[1], *R. L. PARKER[2];
[1]School of Neuroscience, Virginia Tech, Blacksburg, VA; [2]VA-MD College of Veterinary Medicine, Blacksburg, VA

Abstract: In this study, we evaluated the α6 nicotinic acetylcholine receptor (nAChR) subunit in the dorsal root ganglion (DRG), the first neuron in the nociceptive pathway. The nAChR receptor is not well studied outside of the brain. Previous studies have shown this receptor is downregulated in the DRG during chronic pain states, and therefore may be a viable target for alleviating chronic pain. First, we determined the subcellular localization of the α6 nAChR during non-pain states in the DRG using transgenic mice with α6 nAChRs labelled with GFP (*Chrna6*GFP mice). Primary adult neurons, cultured from three male *Chrna6*GFP mice, were fixed and immunostained to identify α6-GFP labelled nAChRs, early endosomes, Golgi, and endoplasmic reticulum (ER) and imaged using a confocal microscope. Using the JACoP plug-in in ImageJ, each immunolabel was compared to endogenous GFP (endoGFP) to determine colocalization of the α6-GFP receptor subunits in each organelle, and the overlap coefficient (OC) was determined. For endosomes and Golgi, the OC was 0.95 and 0.78, respectively, with ER results pending. An antiGFP antibody was used to measure autofluorescence and compared to the endoGFP, OC = 0.99. Next, we investigated whether α6 nAChR locations were altered after the induction of mechanical allodynia via Spared Nerve Injury (SNI). DRG were collected from male and female *Chrna*6GFP adult mice that underwent SNI surgery. They were sliced and immunostained for GFP, early endosomes, and ER. In the SNI mice, endosomes, ER, and anti-GFP antibody had OC of 0.96, 0.90, and 0.88, respectively. Control mice had OC of 0.90, 0.86, 0.91, respectively. No sex differences were assessed. From the cell culture results, we concluded firstly that endoGFP is an appropriate way to measure α6-GFP as there is a 99% overlap between endoGFP and the GFP antibody. Second, while both organelles had a large overlap of endoGFP, there was less colocalization in the Golgi, indicating that the majority of receptors are located in the ER. Due to small sample sizes for SNI and control, no statistical testing was performed. Additional data is needed, and there are some limitations with the current study. This study will be expanded to include larger sample sizes to allow for statistical testing, as well as to examine more organelles and the receptors on the cell surface to gain a deeper understanding of α6 nAChR subcellular localization and regulation during pain states. It will also be expanded to include more models of chronic pain, including inflammatory pain models such as Complete Freud's Adjuvant, as the mechanisms of nAChR regulation may vary by the underlying source of allodynia.

Disclosures: A.M. Mann: None. **R.L. Parker:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.19/LBP019

Topic: E.01. Somatosensation – Pain and Itch

Title: Validation of MRGPRX2 as a target for the treatment of osteoarthritis pain

Authors: *A. DOMANSKYI, K. AUVINEN, W. HENNAH, R. LUND, I. PARKKINEN, E. SERKKOLA, E. POLLARI, A. VUORENPÄÄ, C. STENFORS, A.-P. KOIVISTO;
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Abstract: Mas-related G-protein coupled receptor member X2 (MRGPRX2) is a primate specific GPCR expressed in mast cells, basophiles and eosinophils. MRGPRX2 is a highly promiscuous receptor that is activated e.g. by numerous neuropeptides and exogenous drugs. It mediates IgE-independent human mast cell activation and degranulation. Interestingly, mRNA for MRGPRX2 and its agonist neurotensin are increased in mast cells from osteoarthritis patient knee tissue by 4.5- and 39-fold, respectively. We hypothesize that mediators (such as histamine, tryptase, etc.) released from mast cells after MRGPRX2-dependent degranulation can sensitive nociceptors, contributing to osteoarthritis pain. In line with this hypothesis, tryptase level is elevated in osteoarthritis and alpha-tryptasemia is genetically associated with pain. We demonstrate that mast cell mediators released upon MRGPRX2 activation increased spontaneous activity of human and rat dorsal root ganglia (DRG) neurons. Using RNAScope, we detected a subset of non-neuronal MRGPRX2 expressing cells in DRG, but not spinal cord, sections from in pain patients. MRGPRX2 positive cells were not detected in the DRG or the spinal cord in non-pain subjects. The number of mast cells tended to be increased in knee sections from rat osteoarthritis models. Our data demonstrate that small molecule MRGPRX2 antagonist has a potential for the treatment of osteoarthritis pain.

Disclosures: A. Domanskyi: A. Employment/Salary (full or part-time); Orion Corporation. **K. Auvinen:** A. Employment/Salary (full or part-time); Orion Corporation. **W. Hennah:** A. Employment/Salary (full or part-time); Orion Corporation. **R. Lund:** A. Employment/Salary (full or part-time); Orion Corporation. **I. Parkkinen:** A. Employment/Salary (full or part-time); Orion Corporation. **E. Serkkola:** A. Employment/Salary (full or part-time); Orion Corporation. **E. Pollari:** A. Employment/Salary (full or part-time); Orion Corporation. **A. Vuorenpää:** A. Employment/Salary (full or part-time); Orion Corporation. **C. Stenfors:** A. Employment/Salary (full or part-time); Orion Corporation. **A. Koivisto:** A. Employment/Salary (full or part-time); Orion Corporation.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.20/LBP020

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R01NS105715
NIH R01NS113965

Title: Selective mast cell inhibition regulates post-surgical pain-like hypersensitivity

Authors: *J. M. ROSARIO CLAUDIO[1], N. G. RAUT[2], A. O. FADAKA[3], M. C. HOFMANN[4], M. P. JANKOWSKI[5];
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Abstract: Repetitive invasive procedures in a healthcare setting is one of the main causes of neonatal injury which can have long term detrimental effects on the patient's ability to regulate painful stimuli and increases the risk of developing chronic pain later in life. Although pain development is complex, it is well acknowledged that inflammation and immune interactions contribute to its development. Our recent report has shown that macrophages (MΦs) play a crucial role in neonatal nociceptive priming, the principle where early-life injuries induce prolonged pain to re-injury later in life. Upon surgical incision during the neonatal period, MΦs undergo upregulation of neurotrophic factor receptor p75 (p75NTR or NGFR). This upregulation allows MΦs to develop a pro-inflammatory phenotype and form a cellular memory of the early life insult. Recently, mast cells (MCs) have been associated with pain regulation under various contexts as they are known to release factors that can influence nociception. Specifically, MCs are also a source of nerve growth factor (NGF), a ligand for p75 NTR expressed on MΦs. It is not known however, if MCs contribute to neonatal nociceptive priming by influencing MΦ function. We hypothesized that MCs-produce mediators promote an M1-like phenotype in trained MΦs that exacerbates pain after repeated incision. To test this, we first established a model of neonatal nociceptive priming that requires injuries at both the neonatal (P6-P8) and adolescent stage (P35-P38). MCs were inhibited using transgenic (Mcpt5Cre;DTR) and pharmacological (cromolyn sodium (CS): a MC-stabilizing agent) interventions. Pain-like behaviors were assessed through spontaneous paw guarding assays and mechanical hypersensitivity using the muscle pressure test. Afferent sensitization was evaluated using calcium imaging and confocal microscopy in our *ex vivo* hind paw muscle/tibial nerve/DRG/spinal cord preparation. Results revealed that both genetic deletion and pharmacological inhibition of MCs acutely reduced neonatal nociceptive priming at multiple levels. By using this multidisciplinary experimental approach, we expect to shed light on the role

of mast cells in neonatal nociception. Results will hopefully lead to new information or treatments for neonatal chronic post-surgical pain.

Disclosures: J.M. Rosario Claudio: None. **N.G. Raut:** None. **A.O. Fadaka:** None. **M.C. Hofmann:** None. **M.P. Jankowski:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

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Program #/Poster #: LBP076.21/LBP021

Topic: E.01. Somatosensation – Pain and Itch

Support: Klingenstein Foundation
University of Pennsylvania School of Arts and Sciences
NIH Grant F31DK131870
NSF GRFP

Title: A parabrachial hub for need-state control of enduring pain

Authors: *N. GOLDSTEIN[1,2], A. MAES[3], H. N. ALLEN[4], T. S. NELSON[5], M. KINDEL[6], A. YEUNG[2], N. K. SMITH[2], J. CARTY[7,2], B. K. TAYLOR[8], A. KENNEDY[3], J. BETLEY[2]; [1]Massachusetts Institute of Technology, Cambridge, MA; [2]University of Pennsylvania, Philadelphia, PA; [3]The Scripps Research Institute, La Jolla, CA; [4]Pharmacology & Therapeutics, University of Florida, Gainesville, FL; [5]Department of Pharmacology and Therapeutics, University of Florida, Gainesville, FL; [6]University of Pennsylvania, Philadephia, PA; [7]Icahn School of Medicine at Mount Sinai, New York, NY; [8]Department of Anesthesiology, University of Pittsburgh, Pittsburgh, PA

Abstract: Enduring pain following acute physical injury is a prominent feature of chronic pain conditions. Populations of neurons that rapidly respond to noxious stimuli or tissue damage have been identified in the spinal cord and several nuclei in the brain. Understanding the central mechanisms that signal ongoing sustained pain, including after tissue healing, remains a challenge. We used spatial transcriptomics to characterize gene expression in the parabrachial nucleus following a persistent pain stimulus and found that immediate early genes were upregulated across spatial and molecular cell types. The NPY Y1 receptor was expressed in a small subset of neurons across most neuron types. We found that Y1R-positive neurons expressed the immediate early gene Fos more frequently than Y1R-negative neurons, suggesting a unique functional role for PBN Y1R neurons in enduring pain. *In vivo*, PBN Y1R neuron activity was elevated following injury and predicted functional coping behavior. Chemogenetic activation of PBN Y1R neurons was sufficient to induce a pain-like state including allodynia, escape and anxiety-like behavior, and negative affect while inhibition suppressed persistent pain. Hunger, thirst, or predator cues suppressed sustained pain, regardless of the injury type, by

inhibiting parabrachial Y1R neurons via the release of NPY in the PBN. Together, our results demonstrate an endogenous analgesic hub at pain-responsive parabrachial Y1R neurons.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

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Program #/Poster #: LBP076.22/LBP022

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant UH3123308

Title: Intracranial EEG Reveals Insula Thalamocortical Dysrhythmia Linked to Chronic Pain Intensity

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Abstract: Background. The insula integrates sensory–discriminative and affective–motivational aspects of pain along a posterior–anterior gradient. Thalamocortical dysrhythmia (TCD) predicts regional slowing and altered alpha pacing in these circuits. We examined how insular spectral organization and connectivity vary by anatomy and how they relate to day-to-day pain fluctuations.Methods. Six patients with chronic pain underwent bilateral transinsular electrode implantation along the anterior–posterior axis as part of an FDA-approved DBS trial, enabling multi-day intracranial EEG. We quantified spectral power, peak dominant frequency (PDF), spectral slowing (θ/α ratio), and coherence across bipolar pairs. Mixed-effects models tested subregional differences and associations with daily pain intensity and unpleasantness, with study day as a covariate.Results. Spectral power showed robust TCD-consistent organization: alpha and beta were stronger anteriorly, delta was stronger posteriorly, PDF was slower posteriorly, and slowing (θ/α) was more pronounced posteriorly. In addition to this gradient, contralateral channels generally exhibited weaker alpha and gamma power than ipsilateral channels, consistent with lateralized suppression relative to the pain side. Within this framework, posterior-contralateral alpha power tracked daily pain intensity ($\beta = 0.18$, $p = 0.071$ at the subregion level; $\beta = 0.53$, $p = 2\times10^{-6}$ at the channel level) and was positive in 5 of 6 patients. At the channel level, alpha power also showed an unexpected association with unpleasantness ($\beta = 0.39$, $p = 0.0005$). Across days, posterior-contralateral alpha declined modestly (–0.53 dB/day, $p = 0.0026$) while θ/α remained stable, indicating a dynamic state marker against a persistent slowing background. Subject-level analyses showed positive alpha–intensity slopes in most patients (5/6), with variability in slope strength. Gamma coherence exhibited strong posterior > anterior ($\eta^2p =$

0.51) and ipsilateral > contralateral organization ($\eta^2p = 0.36$) but did not predict pain.Conclusions. Intracranial insular recordings reveal an anterior–posterior frequency gradient consistent with TCD. Persistent slowing emerged as a candidate trait marker of chronic pain, while posterior-contralateral alpha power functioned as a lateralized, state-dependent biomarker of pain intensity. Gamma coherence reflected anatomical organization but lacked behavioral relevance. These findings underscore the importance of distinguishing trait-like dysrhythmia from state-dependent rhythms when developing insula-based neuromodulation targets.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.23/LBP023

Topic: E.01. Somatosensation – Pain and Itch

Support: 5R01NS127901

Title: Investigating the effects of early life trauma exposure on structural brain biomarkers for chronic pain

Authors: *C. S. GUZMAN[1], M. E. TIVARUS[2], P. Y. GEHA[3,4,5,6];
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Abstract: Exposure to childhood trauma significantly elevates the risk of developing chronic pain in adulthood, yet the neural mechanisms underlying this vulnerability remain unclear. Brain structures implicated in early life stress (ELS) are also central to chronic pain, but few studies have examined their combined impact. Here, we tested the hypothesis that ELS-exposed patients with chronic pain exhibit cumulative structural alterations in limbic regions, building on prior findings of changes associated with each condition independently. We predicted chronic pain patients would exhibit thinning of limbic structures and that this "inward retraction" would be accentuated by ELS. Because volumetric and surface area measures have yielded mixed results in both ELS and chronic pain, we applied a more sensitive approach: shape analysis of limbic structures derived from high-resolution T1-weighted (T1w) images. Shape analysis captures localized deformations often overlooked by global volumetric measures, making it well suited to identify subtle morphological effects of trauma and pain. We analyzed data from the Multidisciplinary Approach to the Study of Pelvic Pain (MAPP) cohort, focusing on patients and controls who completed the Childhood Traumatic Events Scale, a validated measure of ELS. Using FSL's FIRST, we segmented limbic structures from T1w images and performed vertex-

wise shape analysis in 79 fibromyalgia (FM) patients and 67 healthy controls, generating four groups: healthy controls, trauma-exposed controls, FM, and trauma-exposed FM. We compared these groups using ANCOVA with FSL's randomise to test patient × ELS interaction, correcting for age, sex, BMI, and region SNR. Results showed a significant interaction between patient and trauma groups ($p < 0.05$, corrected). Trauma-exposed controls exhibited outward expansions in the right hippocampus and right amygdala relative to non-exposed controls. FM patients with trauma also showed expansion in these regions relative to healthy controls, but to a lesser degree compared to FM patients without trauma, with a significant interaction observed. Contrary to our initial hypothesis of cumulative plasticity, these findings suggest a potential compensatory mechanism in trauma patients with ELS. This highlights the importance of considering trauma in structural analyses, revealing a complex compensatory mechanism. Understanding how ELS interacts with chronic pain to reshape limbic circuitry provides insight into neurobiological pathways of vulnerability and resilience, with implications for identifying targets for prevention and treatment in trauma-exposed pain populations.

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Late-Breaking Poster

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Topic: E.01. Somatosensation – Pain and Itch

Support: 5R01NS129059
R01MH132209

Title: The Brain's Pain Matrix Synchronizes with Respiration to Respond to Tonic Pain

Authors: J. MASSA[1], K.-H. CHENG[1], Y. MA[1], J. BROWN[1], J. KONG[2], ***W. LI**[3];
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Abstract: Pain is a pervasive health problem in our society, amplified by its difficulty to treat. Research has evinced the role of a network of brain regions, referred to as the pain matrix, in the experience of chronic pain. With key nodes in the dorsal anterior cingulate cortex (dACC), posterior cingulate cortex (PCC), somatosensory cortex (S1/S2), thalamus, and insular cortex, the pain matrix is responsible for the sensory, emotional, and cognitive features of pain. Outside of the brain, respiration is commonly associated with pain. Pain has been shown to modulate respiratory patterns, while paced slow breathing may reduce pain. However, the direct physiological linkage between pain and respiration remains unclear. In our study, we aimed to examine the intrinsic coupling between fluctuations in the brain's pain matrix and ongoing respiration. Functional MRI (fMRI) and respiratory signals were simultaneously recorded among healthy participants (N = 45, 30 females; age = 26.5 +/- 8.5 years), who underwent a six-minute

tonic pain and a six-minute no-pain pressure via inflation of a pressure cuff on the right calf, following a 12-minute resting state. Respiration volume per time (RVT; per TR) was extracted as a time series and convolved with a canonical hemodynamic response function (HRF). This convolved RVT signal was then entered into a general linear model (GLM) as a parametric modulator regressor to model the coupling with respiration and blood-oxygen-level-dependent (BOLD) signals. We observed that during the pain (vs. no-pain pressure) condition, key nodes of the pain matrix —including the dACC, S1, PCC, and thalamus—as well as the cerebellum exhibited heightened coupling with respiration. By contrast, such coupling effects were absent when comparing no-pain pressure with the resting state. Together, these findings reveal a mechanistic brain-body interaction, through which the brain's pain matrix synchronizes with respiration to maintain homeostasis in response to a physiological threat to the organism. Future research will be pursued to elucidate how this synchronization is regulated.

Disclosures: J. Massa: None. **K. Cheng:** None. **Y. Ma:** None. **J. Brown:** None. **J. Kong:** None. **W. Li:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.25/LBP025

Topic: E.01. Somatosensation – Pain and Itch

Support: NIDCR Grant R01DEO25946

Title: Functional connectivity between amygdala and inferior frontal gyrus during a placebo-related task mediates the negative association between adverse childhood experiences and placebo analgesia

Authors: *B. RODRIGUES[1,2], L. COLLOCA[1,2];
[1]Pain and Translational Symptom Science, UMB, Baltimore, MD; [2]Placebo Beyond Opinions Center, University of Maryland Baltimore, Baltimore, MD

Abstract: Adverse childhood experiences (ACEs) may shape individual differences in placebo analgesia, particularly among those with chronic pain. In this study, 401 participants with temporomandibular disorder underwent a placebo pain-conditioning paradigm using visual cues paired with pain stimuli. Higher ACE scores were significantly associated with reduced placebo responses. This reduction was driven by lower pain ratings during high-pain expectation (red cue) trials, suggesting altered anticipatory processing. Mediation analyses showed that depressive symptoms significantly explained part of the ACE-placebo relationship. In a subsample that underwent a MRI-based pain task, greater ACE scores were associated with increased functional connectivity between the left amygdala and right inferior frontal gyrus during high-pain expectancy (vs low-pain expectancy), which in turn predicted lower placebo response. This connectivity mediated the ACE-placebo relationship, indicating a neural

mechanism linking early adversity to reduced pain modulation. Together, these findings suggest that individuals with chronic pain and high ACEs show diminished placebo analgesia due to both affective symptoms and altered brain responses to pain cues.

Disclosures: B. Rodrigues: None. **L. Colloca:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.26/LBP026

Topic: E.01. Somatosensation – Pain and Itch

Title: Piezo1 as a Molecular Basis for Microcone Disk Analgesia . Linking Brain Activity and Fascial Changes .

Authors: *S. FUKASAWA;
TOYO RESIN corporation, Fuji City, Shizuoka Prefecture, Japan

Abstract: Piezo1 as a Molecular Basis for Microcone Disk Analgesia: Linking Brain Activity and Fascial Changes
AuthorsSatoshi Fukasawa; TOYORESIN corporation
AbstractChronic pain is a persistent challenge, and non-invasive strategies are urgently needed. Our early pilot studies (2013, 2014) showed that microcone disk application increased pain thresholds in healthy volunteers. In 2018, we extended this work in a randomized, placebo-controlled trial with 42 participants. As a first report, fMRI was performed in one subject, demonstrating that disk application not only elevated pressure pain thresholds but also reduced activity in pain-related brain regions, including S1, S2, insula, and anterior cingulate cortex (ACC). Ultrasound imaging further revealed increased hydration and improved sliding of fascia, consistent with a fascial release effect. These observations parallel Hotta's basic finding that gentle skin stimulation suppresses the somatocardiac sympathetic C-reflex elicited by C-fiber excitation, indicating that innocuous tactile input modulates both nociceptive and autonomic responses. The molecular mechanism underlying these effects, however, has remained unclear. The discovery of Piezo1, a mechanosensitive ion channel, provides a unifying explanation. We propose that Piezo1 transduces gentle cutaneous stimulation into neural and anatomical outcomes, linking peripheral fascial dynamics with central pain modulation. Our results suggest that Piezo1 represents the first molecular framework that connects previous clinical and basic evidence, bridging physiology with anatomy and neuroscience with practice. This discovery highlights Piezo1 as a novel target for non-invasive neuromodulatory devices in chronic pain management.
KeywordsPiezo1, microcone disk, pain modulation

Disclosures: S. Fukasawa: None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.27/LBP027

Topic: E.01. Somatosensation – Pain and Itch

Support: R01-DA006214
T32-DA055569

Title: Orexin antagonism attenuates pain-related and opioid-withdrawal-related negative affect without altering opioid analgesic efficacy

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Abstract: Two-thirds of those who misuse opioids do so for pain management, and up to 12% go on to develop an opioid use disorder1. The negative reinforcing qualities of opioid withdrawal are one of the ways that opioid addiction is perpetuated 2. The neuropeptide orexin (OX) influences opioid withdrawal severity and pain processing, though the way that orexin influences pain and opioid withdrawal-related affect is unclear 3,4. This study aims to determine if administration of the orexin antagonist suvorexant during opioid withdrawal impacts mechanical hypersensitivity, as well as pain- and withdrawal-related negative affect, and opioid analgesia. We hypothesize that suvorexant will attenuate negative affect associated with both pain and withdrawal and will not alter nociception or disrupt analgesic efficacy of opioids. We assigned male and female Long-Evans rats to either the vehicle or suvorexant group, then tested them for mechanical hypersensitivity (von Frey), pain-related negative affect (Rat Grimace Scale), and anhedonia (saccharin preference) before and during chronic inflammatory paw pain (Complete Freund's Adjuvant) and opioid withdrawal from oxycodone as well as after a 3mg/kg dose of oxycodone. Suvorexant significantly increased paw withdrawal thresholds on the contralateral paw but did not alter nociception on the ipsilateral paw. Suvorexant also decreased the amount of pain-related facial grimacing and anhedonia without impeding opioid analgesia. These data indicate that when opioids are used to treat pain, suvorexant may be a useful adjunct therapy for attenuating negative affect and thus decreasing the risk of opioid use disorder.

1. Vowles, K. E., McEntee, M. L., Julnes, P. S., Frohe, T., Ney, J. P., & Van Der Goes, D. N. (2015). Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain, 156(4), 569-576.

2. Evans, C. J., & Cahill, C. M. (2016). Neurobiology of opioid dependence in creating addiction vulnerability. F1000Research, 5, F1000-Faculty.

3. Sharf, R., Sarhan, M., & DiLeone, R. J. (2008). Orexin mediates the expression of precipitated morphine withdrawal and concurrent activation of the nucleus accumbens shell. Biological psychiatry, 64(3), 175-183.

4. Georgescu, D., Zachariou, V., Barrot, M., Mieda, M., Willie, J. T., Eisch, A. J., ... & DiLeone, R. J. (2003). Involvement of the lateral hypothalamic peptide orexin in morphine dependence and withdrawal. Journal of Neuroscience, 23(8), 3106-3111.

Disclosures: A.S. Zumbusch: None. **K. Newman:** None. **K. Huang:** None. **G.S. Aston-Jones:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.28/Web Only

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant K25DA048179

Title: Multivariate analysis of neural network alterations, sensory processing, and cognitive function in chronic low back pain with long-term opioid therapy

Authors: *B. JARRAHI;
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Abstract: With their potent analgesic qualities, prescription opioids offer some relief in chronic pain conditions. However, the effects of long-term (<90 days) opioid treatment on brain networks, sensory processing, and cognitive function in chronic low back pain (CLBP) are still unknown. In this study, we investigated multivariate relationships between intrinsic brain network features, quantitative sensory testing (QST) measures, and cognitive performance in CLBP patients with and without chronic opioid exposure. 73 CLBP patients (30 on opioids, 43 opioid-free; 45 females; mean age ± SD 51.8 ± 15.3 years) underwent multimodal assessment, including resting-state fMRI, standardized QST, and computerized neuropsychological testing. Multivariate ANOVAs assessed the effects of opioid use on QST measures, including heat and cold pain thresholds and tolerance, as well as cognitive scores. Independent component analysis (ICA) of fMRI data identified intrinsic connectivity networks (ICNs), and multivariate analyses of covariance (MANCOVA) examined group differences in spatial map intensities (within-network connectivity) and BOLD spectral power, controlling for age and sex. QST analyses revealed no significant main effects of opioid use; however, sex significantly predicted heat pain tolerance ($F(1,69) = 13.65$, $p < 0.001$). Neuroimaging results demonstrated reduced within-network connectivity in basal ganglia, salience, subcortical, and sensorimotor networks among opioid users, alongside spectral shifts marked by increased high-frequency and reduced mid-frequency power in sensory-affective networks. CLBP patients on opioids also showed increased ventral striatum connectivity and low-to-mid frequency power in amygdalohippocampal and

sensorimotor networks with thermal pain. Cold pain tolerance in opioid users was linked to reduced mid-frequency spectral power in the frontal, dorsal attention, central executive, and thalamic brain networks. The results of cognitive testing revealed opioid-related deficits in decision-making (Cambridge Gambling Task, $p = 0.038$, partial $\eta^2 = 0.243$), spatial planning (One Touch Stockings of Cambridge, $p = 0.010$-0.020, partial $\eta^2 = 0.167$-0.179), and working memory (Spatial Working Memory, $p = 0.047$, partial $\eta^2 = 0.218$). ICA-MANCOVA results indicated reduced frontal and sensorimotor intra-network and decreased mid-frequency power in attention networks correlated with opioid-related cognitive performance deficits. These preliminary findings underscore the importance of further research on the brain and behavioral effects of chronic opioid use in pain management.

Disclosures: B. Jarrahi: None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.29/LBP028

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH R01DA052340

Title: Development of NDNB-01, an Orally Bioavailable HSP90β Inhibitor for Opioid Dose Reduction Therapy

Authors: *P. TANGUTURI[1], M. SERWETNYK[2], T. D'AMICO[2], D. BARLOW[3], B. BLAGG[2], K. HOUSEKNECHT[4], J. M. STREICHER[5];
[1]The University of Arizona, Tucson, AZ; [2]University of Notre Dame, Notre Dame, IN 46556 USA, IN; [3]Department of Pharmacology, University of New England, Portland, OR; [4]University of New England, Portland, OR; [5]Pharmacology, University of Arizona, Tucson, AZ

Abstract: In our work, we've found that Hsp90 inhibition in the spinal cord enhances the potency of opioid pain relief by 2-3-fold, while strongly reducing tolerance, rescuing already established tolerance, and without altering the potency of opioid constipation and reward. This points the way to use Hsp90 inhibitors to improve the therapeutic index of opioids. However, non-selective Hsp90 inhibitors given systemically also inhibit brain Hsp90, which leads to the loss of opioid pain relief. To surmount this difficulty, we examined the active Hsp90 isoforms in brain vs. spinal cord, finding that in the brain, Hsp90α alone regulated opioid anti-nociception. In contrast, in the spinal cord, we determined that Hsp90α, Hsp90β, and Grp94 all regulate anti-nociception. These data led to our hypothesis that systemic Hsp90β and Grp94 isoform-selective Hsp90 inhibitors will selectively block spinal cord Hsp90 activity, resulting in enhanced anti-nociception and reduced side effects. We validated this hypothesis with the Hsp90β-selective inhibitor KUNB106, which enhanced pain relief and reduced and rescued tolerance, without altering respiratory depression. However, KUNB106 is a poor clinical candidate, with weak

metabolic stability and pharmacokinetics with no oral bioavailability. We thus engaged in a medicinal chemistry effort to improve the drug-like features of KUNB106 while retaining Hsp90β isoform selectivity. We report here the creation of multiple selective HSP90β inhibitors with low nanomolar affinity/potency, high Hsp90β selectivity, and promising ADME features. Further, compounds such as NDNB-01 and NDNB-25 showed oral bioavailability in enhancing opioid anti-nociception at a 10 mg/kg dose in male and female CD-1 mice. The lead compound NDNB-01 mouse oral dose pharmacokinetic assessment confirms the target engagement of spinal cord tissue. These advances point the way to further lead development and pre-IND testing for our Hsp90β inhibitors and their eventual use as a therapy for opioid dose reduction.

Disclosures: P. Tanguturi: None. **M. Serwetnyk:** None. **T. D'Amico:** None. **D. Barlow:** None. **B. blagg:** None. **K. Houseknecht:** None. **J.M. Streicher:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.30/LBP029

Topic: E.01. Somatosensation – Pain and Itch

Support: University of Pittsburgh Medical Center, Competitive Medical Research Fund
University of Pittsburgh Health Sciences Bridge Fund

Title: Mechanistic insights into cold activation and small molecule inhibition of human TRPM8

Authors: S. WEINER, D. UREDI, ***V. B. JOURNIGAN**;
Pharmaceutical Science, University of Pittsburgh, Pittsburgh, PA

Abstract: *Background and purpose:* The mechanism of cold temperature activation of the human transient receptor potential melastatin 8 (TRPM8) ion channel is understudied, and how small molecule antagonists inhibit cold as the therapeutically relevant physiologic stimulus is unknown. We demonstrate that key residues in the S1 and S4 helices of the voltage sensor like domain (VSLD) control cold activation, and provide evidence that antagonists block cold activation within the VSLD. *Experimental approach:* We demonstrate using single point mutations that residues lining the VSLD control cold temperature activation (4ºC) of human TRPM8. Further, we show that the well-known antagonists VBJ103, TC-I 2014 and AMTB inhibit cold activation within the VSLD. *Key results:* Both mutations of N799 and R842 are insensitive to cold temperature, while mutation of Y745 gave an attenuated response to cold. Mutation of Y745 alters sensitivity to VBJ103, TC-I 2014 and AMTB inhibition. *Conclusion and implications:* This study advances our fundamental understanding of cold sensing by human TRPM8, as well as inhibition of cold activation, at the molecular and structural level. Further, these results suggest a molecular framework to enable the discovery of novel therapies to treat cold hypersensitivity associated with neuropathic pain.

Disclosures: S. Weiner: None. **D. Uredi:** None. **V.B. Journigan:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.31/LBP030

Topic: E.01. Somatosensation – Pain and Itch

Support: 5R42NS119103-03

Title: A novel, non-hepatotoxic, analgesic modulates cisplatin induced neuropathic pain using a preclinical rodent model.

Authors: *S. BHATTACHARJEE[1], B. GILES[2], S. EDWARDS[3], H. A. BAZAN[4,5], N. G. BAZAN[6];
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Abstract: Objective: Chemotherapy-induced peripheral neuropathy (CIPN) is a common and debilitating side effect of cancer treatments, like cisplatin and paclitaxel. This condition impacts quality of life and often leads to dose reduction or discontinuation of an otherwise effective therapy. Current therapeutic options include gabapentinoids such as gabapentin and pregabalin. However, these are associated with adverse events including dizziness, somnolence (drowsiness), and peripheral edema (limb swelling). Analgesics like acetaminophen and NSAIDs have toxic side effects, including hepatotoxicity and gastrointestinal- and nephro- toxicities with NSAIDs. Opioids, while effective, carry a risk of addiction and abuse. This study evaluates SRP-001, a novel, non-hepatotoxic, non-addictive analgesic, in a rodent model of CIPN, focusing on its effects on mechanical and thermal hypersensitivity. Methods: Young male and female Sprague Dawley rats (n=50; 25 male, 25 female) received intraperitoneal cisplatin at dose 2mg/kg body weight per injection, (16-20 mg/kg cumulative) to induce neuropathy, confirmed by reduced paw withdrawal thresholds. Pain sensitivity was assessed using von Frey (mechanical allodynia) and Hargreaves (thermal hyperalgesia) assays. SRP-001 was administered orally at 3, 10, 30, and 100 mg/kg. Researchers were blinded during administration and testing. Results: SRP-001 produced a dose-dependent reversal of mechanical hypersensitivity, with significant effects at 30 and 100 mg/kg. Both sexes responded similarly, though females showed slightly lower thresholds. The ED_{50} for SRP-001 was 8.502 mg/kg (0.0210 mmol/kg), indicating high potency. SRP-001 also reversed thermal hypersensitivity. Mechanistically, SRP-001 induced AM404 formation in the periaqueductal gray (PAG), activating TRPV1 and enhancing CB1/CB2-mediated endocannabinoid signaling. Single-cell multiomic analysis revealed modulation of pain-related transcription factors (SOX, SP/KLF) and ion channels (TRPV4, KCNA1, KCNT1), supporting central analgesic action. Conclusion: SRP-001 effectively reversed both cisplatin-induced mechanical and thermal hypersensitivity in rats, demonstrating

potential as a non-opioid, non-toxic analgesic for managing chemotherapy-induced peripheral neuropathy. Its dose-dependent efficacy supports clinical titration and positions SRP-001 as a promising alternative or adjunct therapy for patients who are intolerant to current therapies.

Disclosures: S. Bhattacharjee: None. **B. Giles:** None. **S. Edwards:** None. **H.A. Bazan:** None. **N.G. Bazan:** None.

Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.32/LBP031

Topic: E.01. Somatosensation – Pain and Itch

Support: NIH Grant HL173002
NSF 2334697

Title: Assessment of itch responses in mouse glabrous skin induced by different pruritogens

Authors: *S. WU[1], H. STEELE[2], K. LAWSON[1], R. STEWART[1], L. HAN[1];
[1]Georgia Institute of Technology, Atlanta, GA; [2]Georgia Institute of Technology Institute of Neuroscience, Neurotechnology, and Society, Atlanta, GA

Abstract: Itch is an unpleasant sensation that arises in the superficial layers of the skin and often leads to significant discomfort. Since most of the itch research has focused on the trunk or nape hairy skin of the mice, the behavioral characteristics of itch in the paw glabrous skin remains understudied. Here, we investigated itch responses in mice following the intradermal administration of various pruritogens into the plantar hindpaw. We found that synthetic peptide SLIGRL selectively increased licking, indicating pain sensation, whereas DCA (deoxycholic acid) primarily induced biting, indicating itch. Serotonin, 5-HT1F receptor agonist LY344864, and IL-31 induced both licking and biting behaviors. Similarly, mice exhibit both responses in a mouse allergic itch model induced by ovalbumin. To further validate that biting is a behavioral response associated with itch, we tested the responses after morphine treatment. We found that biting behaviors induced by DCA and Bam8-22 were not affected by morphine treatment. In contrast, capsaicin-induced licking were significantly reduced by morphine. Taken together, these results demonstrate that mice glabrous skin exhibits distinct itch responses to various pruritogens and provide a framework for studying itch mechanisms in this specialized skin location.

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Late-Breaking Poster

LBP076: E.01. Somatosensation – Pain and Itch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP076.33/LBP032

Topic: E.01. Somatosensation – Pain and Itch

Title: Neuropeptide Regulation of Chronic Itch

Authors: *X. LI[1], Z. WANG[1], B. KIM[2];
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Abstract: Peripheral sensory neurons derived from Substance P shape sensation and neurogenic inflammation via NK1R (also known as Tacr1) and Mrgprb2 expressed by immune cells. Increased Substance P-positive nerve fibers are found in the skin lesions obtained from pruritus patients. However, if and how Substance P interacts with immune cells to promote chronic pruritus remains largely unknown. Here, we verified that Substance P is highly expressed in the skin lesions of oxazolone (OXA)-induced mouse model and is involved in the development of chronic pruritus. Although Substance P is usually linked to itch and inflammation through activation of Mrgprb2 on mast cells, this pathway does not seem indispensable in OXA-induced chronic itch. Instead, basophils may be involved in Substance P-related chronic itch through NK1R. This work suggests a new potential mechanism for neuropeptide regulation of chronic pruritus.

Disclosures: X. Li: None. **Z. Wang:** None. **B. Kim:** None.

Late-Breaking Poster

LBP077: E.02. Somatosensation – Touch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP077.01/LBP033

Topic: E.02. Somatosensation – Touch

Support: Howard Hughes Medical Institute (HHMI)
National Institute of Neurological Disorders and Stroke (NINDS).
The Hock E. Tan and K. Lisa Yang Center for Autism Research at Harvard Medical School

Title: Constructing Tactile Receptive Fields in the Discriminative Touch Pathway

Authors: *H. KWAK[1,2], C. NOBLE[1,2], D. D. GINTY[1,2];
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Abstract: The traditional view of the ascending touch pathway suggests that rapidly adapting (Aβ RA-LTMR) and slowly adapting (Aβ SA-LTMR) low-threshold mechanoreceptor signals remain segregated as they ascend along the touch pathway hierarchy. Contrary to this belief, recent studies from our group have shown that Aβ RA-LTMR and Aβ SA-LTMR signals converge subcortically. Here, we report that mechanoreceptor signals converge in the earliest stage of the discriminative touch pathway, the spinal cord dorsal horn, to shape neuronal receptive field (RF) properties along the hierarchy. We found that spinal cord interneurons and postsynaptic dorsal column projection neurons (PSDCs) exhibit small slowly adapting (SA) RF hotspots surrounded by large rapidly adapting (RA) RFs. To determine whether these RF properties arise from differential convergence of LTMR types, we mapped optically evoked RFs of spinal cord neurons using genetically labeled dorsal root ganglion (DRG) neuron types. We found that both Aβ RA-LTMRs and Aβ SA-LTMRs converge from large skin areas onto individual spinal neurons, suggesting that differential convergence does not explain spatiotemporal RF properties in the cord. Moreover, pharmacological disinhibition of the spinal cord enlarged the mechanically evoked SA-like RFs, indicating that active inhibitory refinement might underlie the small SA-like RFs. Among the DRG types examined, Aβ SA-LTMRs were found to play a key role in shaping RF sizes through active inhibition. Specifically, Aβ SA-LTMR ablation enlarged, and Aβ SA-LTMR activation reduced the sustained RF hotspots in spinal interneurons and PSDCs. In addition, manipulation of spinal cord outputs strongly altered spatiotemporal RFs bidirectionally in the brainstem and thalamus, indicating that central RF properties along successive stages of the touch pathway hierarchy are inherited from the spinal cord. Thus, sensory subtype convergence and active RF refinement in the spinal cord shape mechanical RF properties along the discriminative touch pathway hierarchy. This work is supported by HHMI, NINDS, and K. Lisa Yang.

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Late-Breaking Poster

LBP077: E.02. Somatosensation – Touch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP077.02/LBP034

Topic: E.02. Somatosensation – Touch

Support: DoD Grant HT9425-23-1-0678

Title: Regenerative Peripheral Nerve Interfaces on the Sciatic Nerve Elicit Sensation in the Foot and Distal Leg

Authors: *J. KANETIS[1], D. M. WALLACE[2], L. CUBILLOS[2], P. CEDERNA[3], T. A. KUNG[4], C. A. CHESTEK[5], D. GATES[6];
[1]Robotics, University of Michigan, Ann Arbor, MI; [2]Robotics, University of Michigan, Ann Arbor, Ann Arbor, MI; [3]University of Michigan, Ann Arbor, MI; [4]Plastic Surgery, University of Michigan, Ann Arbor, MI; [5]Biomedical Engineering, University of Michigan, ANN ARBOR, MI; [6]School of Kinesiology, University of Michigan, Ann Arbor, MI

Abstract: Individuals with unilateral transfemoral amputation (TFA) are at increased fall risk compared to able-bodied individuals, largely due to the loss of somatosensory feedback. Direct nerve stimulation can elicit phantom foot sensations and improve walking confidence. Sensations may also be evoked through electrodes implanted into reinnervated muscle. Regenerative Peripheral Nerve Interfaces (RPNIs) are biological constructs formed by wrapping muscle grafts around residual nerves. Electrical stimulation of RPNIs in the upper arm elicits sensation in the phantom hand, but no studies have explored lower-limb RPNIs. In this first in-human trial, we explore sciatic nerve RPNIs to determine the location and quality of elicited sensations in the foot and distal leg. A 55-year-old man had five RPNIs created on his sciatic nerve and 8 intramuscular electrodes (Synapse Biomedical) implanted into each RPNI, two residual muscles and a ground in subcutaneous fat under IDE (G230230) and IRB (HUM00235849). Four months post RPNI implantation, the participant's sensory perception threshold for each RPNI was identified by stimulating the electrode in bipolar configuration with a square waveform at 20 Hz, 100 μs pulse width, 11 μs interphase interval using a Digitimer-DS7a (Cephalon). An adaptive staircase method was used to modulate the amplitude in steps of 0.20 mA, 0.10 mA and 0.05 mA. The amplitude was increased if the participant expressed that he did not feel sensation and decreased if sensation was reported. Thresholds were calculated as the average of the 4 reversals at the 0.10 mA step. The participant then indicated the area of sensation on a 3D model of the leg and the quality of the sensation using a psychometric questionnaire. The average perception threshold across RPNIs was 6.15 ± 1.55 mA. At the threshold, stimulation of the RPNIs elicited sensation in distinct locations of the participant's phantom foot and calf. Specifically, stimulation of RPNIs 1-5 elicited sensations on (1) the dorsomedial surface of the foot and big toe, (2) the plantar surface of the big toe, (3) the dorsal surface of the fifth toe, (4) the heel and posterior/lateral aspect of the calf and (5) the central and dorsal surface just above the fourth toe. These regions match the expected innervation of the distal sciatic nerve branches, and all sensations were described as "almost natural", "not painful", most like "vibration", and occurring "just under the skin." This exploratory trial demonstrated that stimulation of sciatic nerve RPNIs elicits sensory feedback in individuals with TFA and can be utilized to explore how phantom foot somatosensory sensation impacts gait and balance.

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Late-Breaking Poster

LBP077: E.02. Somatosensation – Touch

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Program #/Poster #: LBP077.03/LBP035

Topic: E.02. Somatosensation – Touch

Support: ONR N00014-23-1-2842
NSF GRFP Grant No. 1937968

Title: Differential predictability and consistency of perceptual threshold and dynamic range in afferent transcutaneous electrical nerve stimulation

Authors: *R. S. JAKES, L. MCGANN, D. J. TYLER;
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Abstract: Transcutaneous electrical nerve stimulation can provide critical somatosensory feedback, but variability in afferent activation across participants and time remains poorly characterized. Generalizable neural haptic interfaces require understanding how anatomical and day-to-day effects shape perceptual thresholds and dynamic range. We examined inter- and intra-participant variation in threshold charge (Q_{min}) and maximum comfortable charge (Q_{max}) across digits and sessions using a wearable neural interface. Fourteen able-bodied participants (7 male) were fit with adjustable dry electrode rings on the thumb, index, middle, and pinky fingers, positioned over the medial digital nerve to maximally evoke distal phalanx sensation. Q_{min} and Q_{max} were measured in all participants; eleven repeated the protocol in a second session to assess within-participant consistency. Linear mixed-effects models tested effects of sex, finger, ring size, mediolateral electrode placement, and pre-session confidence on charge. Nonparametric tests compared across digits and sessions. Q_{min} was the most predictable from the measured physical factors, with finger identity ($p < 0.001$) and mediolateral electrode position ($p = 0.009$) significantly contributing to the model. Fixed effects accounted for 41% of model variance; adding participant ID as a random effect increased explained variance by 9%. Q_{max}, by contrast, was far more individual-specific, with participant ID increasing explained variance by 43% and female participants exhibiting a 53% wider dynamic range despite nearly identical median Q_{min} values. Surprisingly, neither ring size nor pre-session confidence were measurably predictive of Q_{min} or Q_{max} in this exploratory study, despite their respective anatomical and psychological effects. Intra-participant, both Q_{min} and Q_{max} shifted markedly between sessions ($p < 0.001$; mean 27%), with variable directionality and without consistent co-variation. Still, Q_{max} was more consistent within an individual than across the population ($p < 0.001$), whereas variability in Q_{min} within a participant was comparable to that observed across all participants. Overall, predictable population-level physical factors systematically influenced perceptual thresholds, while maximum comfortable activation is highly individual but not necessarily reflective of pre-calibration expectations. Further, there was significant test-retest variability in charge required for afferent activation. These findings suggest that maximizing usable dynamic range may

depend more on understanding how users define Q_{max} in the absence of pain or muscle contraction.

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Late-Breaking Poster

LBP077: E.02. Somatosensation – Touch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP077.04/LBP036

Topic: E.02. Somatosensation – Touch

Title: Three-dimensional reconstruction of the spinal cord superficial dorsal horn

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Abstract: The spinal cord integrates inputs from a range of dorsal root ganglia (DRG) sensory neuron types that differentially encode innocuous and noxious tactile, thermal, and chemical stimuli. How the spinal dorsal horn receives and integrates DRG sensory neuron signals for output to the brain remains a majorunanswered question. To investigate the organizational logic of this early somatosensory processing region, we generated a large-scale (1500 × 500 × 190 μm) electron microscopy (EM) connectome of the superficial (lamina I-III) lumbar spinal dorsal horn. We used genetic labeling of eight sensory neuronsubtypes—three low-threshold mechanoreceptors (LTMRs), two polymodal high-threshold mechanoreceptors (HTMRs), two peptidergic nociceptors, and a cold thermoreceptor—to visualize these neurons under EM. Using contrastive learning, we developed a machine learning model toautomatically classify the eight subtypes, enabling discovery of subtype-specific synaptic connectivity patterns. Our analysis revealed structured, segregated excitatory pathways within the superficial dorsal horn. Peptidergic nociceptors and cold thermoreceptors formed synapses onto putative $Tacr1^+$ lamina I projection neurons, suggesting monosynaptic transmission routes for noxious tactile and thermal anterior lateral tract (ALT) pathways. In contrast, LTMR and polymodal HTMR signals appear to be mainly processed via multi-layered feedforward circuits that converge onto putative $Gpr83^+$ ALTprojection neurons, suggesting integrative processing of innocuous touch signals. Interestingly, local inhibitory circuits displayed modular and homotypic inhibition motifs. Subsets of inhibitory interneurons both received input from and formed synapses onto the same sensory neuron subtype via axo-axonic synapses that mediate presynaptic inhibition. These inhibitory interneurons also formed axo-dendritic synapses onto excitatory interneurons that shared the same sensory input. These findings reveal a highly modular network architecture in the superficial dorsal horn, with direct monosynaptic pathways for rapid nociceptive

transmission and layered polysynaptic pathways for integrated tactile signal transmission to the brain via distinct ALT pathways

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Late-Breaking Poster

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Topic: E.02. Somatosensation – Touch

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Sheng Foundation

Title: Coordinate transformation in the brainstem trigeminal nucleus

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Abstract: Accurate goal-directed movements require information about effector position and ongoing motion to be integrated into sensory feedback. Here, with high-speed videography, we examined three-dimensional tongue kinematics as mice re-aimed their licks by reacting to subtle tactile events on the left, center or right surface of the tongue. Because a tactile event on the left side of the tongue can specify a centered spout on right licks, or a left spout on straight licks, task performance requires a coordinate transformation from a tongue- to head-based reference frame. In past work, we showed that superior colliculus (SC) neurons encode tactile events in tongue, head, and mixed reference frames, suggesting that the SC implements a coordinate transformation necessary for touch-based re-aiming. Yet another possibility is that the SC inherits these representations from lower levels of the sensory hierarchy. To test this idea, we recorded neurons in the brainstem spinal trigeminal nucleus (SpV), the first relay center for tongue tactile inputs into the brain with projections going to SC. As expected, SpV neurons represented tactile events at low latencies (<10 ms) in a tongue based reference frame, with a strong bias in activation from ipsilateral contacts. Yet surprisingly, SpV neurons could also represent tactile signals in mixed and head-centric frames at similarly low latencies. This suggests that precise tongue position at a moment of spout contact is already incorporated into tactile feedback signals at the lowest possible level of the central sensory hierarchy. Notably, SpV signals additionally represented diverse aspects of task structure, including go cue responses, memory of spout position, and detailed lick cycle information. Our findings show that task-related information, including that necessary for a tongue-to-head based coordinate transformation, is already present at the lowest level of the central sensory hierarchy.

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Topic: E.02. Somatosensation – Touch

Support: Edwin H. Richard and Elisabeth Richard von Matsch Distinguished Professorship in Neurological Diseases (to E.S.-A.)

Title: From Hands to Feet: Experience-Driven Plasticity in Secondary Somatosensory Cortex in People Born without Hands

Authors: *Z. DENG[1], F. A. MARTINEZ-ADDIEGO[1,2], Y. LIU[3,1], E. STRIEM-AMIT[1]; [1]Georgetown University, Washington, DC; [2]School of Psychology, Georgia Institute of Technology, Atlanta, GA; [3]Institute of Neuroscience, Institute of Neuroscience, CAS, Shanghai, China

Abstract: Previous studies have shown that congenital handlessness can alter body part representation in the primary somatosensory cortex (SI). In individuals with upper-limb dysplasia (IDs; people born without hands), adjacent body parts predominantly take over the deprived hand territory. However, how congenital hand loss and compensatory experiences reshape secondary somatosensory cortex (SII) organization in humans remains unclear. Here, we used task-based and resting-state functional magnetic resonance imaging (fMRI) to investigate how compensatory foot use changes body representation in SII in IDs. Interestingly, IDs showed foot selectivity in the left SII hand area, defined in typically developed individuals (TDs). Furthermore, foot activity in the same left SII hand area in IDs was significantly higher than in TDs during a separate action execution experiment. However, there was no significant difference between foot activity in IDs and hand activity in TDs. Notably, this reorganization in the left SII hand area cannot simply be explained by the intrinsic organization in TDs, as the same area does not show foot preference even when selectivity was computed among non-hand body parts. Instead, this reflects a functional reorganization dependent on IDs' personal sensorimotor experience. Resting-state functional connectivity results showed that congenital handlessness also alters the functional connectivity between the higher-order somatosensory and primary motor cortex. Our findings suggest that the secondary somatosensory cortex exhibits experience-dependent plasticity, extending beyond the reorganization possible in SI. Together, it reveals a hierarchical principle of cortical plasticity, where reorganization in the primary somatosensory cortex is constrained by somatotopic principles while higher-order somatosensory cortex may reflect functionally-driven or experience-dependent plasticity.

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Stratton VA Medical Center

Title: Data-Driven Subgrouping in Stroke Based on Multidimensional Clinical Motor Assessments

Authors: *D. GUPTA[1,2], L. GARCIA[3], C. JOHNSON[4], R. D. ROJAS[3], V. CHAN[5], D. J. REINKENSMEYER[6], A. J. FARRENS[7];
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Abstract: Objective: Clinical motor assessments (CMA), designed to quantify motor impairments, use tasks that inherently rely on somatosensory feedback. Somatosensory deficits significantly influence movement performance and recovery, are heterogenous, and only partially compensated for by vision. As a result, CMA scores reflect a combination of sensory and motor impairments that are challenging to dissociate and track independently. There is a need for assessment frameworks that disentangle sensory and motor deficits, to better personalize rehabilitation strategies and interpret functional gains in both domains.
Methods: A cohort of 46 individuals with stroke (18-85 yrs, 13f/33m), participated with informed consent (UC Irvine IRB #476) in a CMA battery as part of a clinical trial on robotic finger training (NCT04818073). We applied a nonlinear dimensionality reduction technique -t-distributed Stochastic Neighbor Embedding (tSNE)- to jointly analyze participants performance across baseline CMA scores, which was highly variable, to determine whether a multidimensional representation could reveal distinct subgroups of participants. We used robotic and EEG assessments of proprioception and finger strength to determine if identified subgroups had different patterns of motor and sensory impairments.
Results: The t-SNE embedding revealed three distinct clusters (moderate embedding consistency, Adjusted Rand Index: 0.6 ± 0.2, 190 pairwise t-SNE reruns). Clusters corresponded to a continuum of poor, moderate, and good performance levels (clusters 1, 2, and 3, respectively) when aligned with pairwise CMA scores. Clusters showed significant differences in

finger proprioception ability (Kruskal-Wallis Test, H(2)= 6.62, p= 0.036), finger strength (H(2)= 17.40, p= 0.0002), and a neural marker of attention and proprioceptive processing -contingent negative variation (CNV)) elicited during proprioceptive testing (H(2)= 7.11, p= 0.029). Cluster 1 had low proprioception, finger strength, and CNV; cluster 2 had higher proprioception (p= 0.04) and CNV (p= 0.024) compared to cluster 1; cluster 3 had the highest finger strength (p= 0.0001). We are analyzing whether these clusters explain differences in response to robotic finger training.
Conclusion: This multidimensional approach provides a framework for disentangling sensory and motor contributions to functional outcomes, highlighting obscured sources of variability when relying on clinical motor scores alone. By identifying subgroup characteristics, such analyses may enable more precise evaluation of intervention effects and guide the personalization of rehabilitation strategies.

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Late-Breaking Poster

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Topic: E.02. Somatosensation – Touch

Support: NIH Grant R01 NS134834

Title: Functional transposition of referred phantom hand sensations through cortical sensory remapping

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Abstract: Restoring sensory feedback remains a major challenge for achieving intuitive control of prosthetic limbs. Regenerative peripheral nerve interfaces (RPNIs), small muscle grafts implanted around residual peripheral nerves, provide a biological interface that supports bidirectional control: in addition to amplifying motor signals, they can evoke somatosensory sensations when electrically stimulated. For upper limb prostheses, sensations at the fingertips are functionally most relevant for manual dexterity. For referred sensations that occur in more proximal and therefore less functional sites, we developed a protocol to move them towards sites with greater functional utility based on cortical remapping. In an individual with a right transradial amputation, we assessed the effectiveness of this protocol by targeting two out of

three RPNIs to move from their initial locations at the base of the thumb and little finger to the distal fingertips respectively, while the third RPNI served as an internal control. In biweekly sessions, the targeted RPNIs are stimulated to evoke referred sensations, with visual feedback guiding their perceived location. By shifting this location upward each session, sensations are gradually remapped toward the fingertips over the course of the protocol. Our preliminary findings indicated that referred sensations became more variable in size and location during the early stages of the remapping. Comparison of the perceived sensations before and after each remapping session also revealed a significant increase in both the stimulation perception threshold ($p = 0.0017$), the minimum current required to elicit a sensation, and the area of the perceived sensation ($p = 0.0413$). The increased perception threshold may reflect sensory habituation resulting from repeated stimulation during the remapping session. The concurrent increase in size of the sensation area is most likely related, as higher stimulation amplitudes are associated with larger referred sensation areas (Pearson's $r = 0.53$, $p = 0.017$). Although no directional shifts toward the fingertips have yet been observed, the increased variability in the perceived location could be an indication of enhanced cortical plasticity in related brain regions. These results provide early evidence that the sensory remapping protocol may induce reorganization in the sensory cortex. Continued adherence to the protocol may eventually result in a persistent transposition of the perceived sensations in the phantom limb. This approach could restore sensory feedback in functionally relevant sites and ultimately enable more natural and intuitive control of prosthetic limbs.

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Late-Breaking Poster

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Topic: E.02. Somatosensation – Touch

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Stratton VA Medical Center
NIH/NIBIB P41-EB018783 (Wolpaw)

Title: Eliciting single trial median nerve somatosensory evoked potentials for non-invasive brain computer interfaces

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Abstract: Objective: Recording robust somatosensory evoked potentials (SEPs) from median nerve stimulation at the single-trial level is challenging with noninvasive electroencephalography (EEG) because of the low signal-to-noise ratio (SNR). This limits their utility for real-time neurorehabilitation. In this study, we present and evaluate methodological optimizations designed to elicit SEPs with higher SNR, for real time measurement, with lesser reliance on post-processing.
Methods: In twelve healthy participants, we assessed SEPs at three pulse widths (0.1, 0.5, 1msec) using low-frequency stimulation (0.5 Hz $\pm$ 10%). The stimulation intensity was guided by sensory nerve action potentials (SNAPs) and compound muscle action potentials (CMAPs), measured at an innervated nerve and muscle. All data was collected with informed consent (IRB #1726675 and #1584762). The Evoked Potential Operant Conditioning System platform was used to monitor SNAP and CMAP in real time. We used a 19-channel dry active headset (DSI-24, BCI2000 software, 300Hz) for EEG, bipolar electrodes (AMT-8, 3200 Hz) for SNAP and CMAP, and a constant current electrical stimulator (DS8R) for median nerve stimulation. EEG was pre-processed with temporal and spatial filtering with minimal post-processing.
Results: SEP P50 and N70 were reliably elicited in healthy participants across all tested pulse widths with minimal discomfort. N70 amplitude increased significantly with pulse width (χ^2= 17.64, p= 0.0001, w= 0.80), while P50 amplitude remained unchanged. SNR also showed a significant pulse width-dependent increase (χ^2= 7.82, p= 0.02, w= 0.35) with improvements of 40% and 52% at 0.5 and 1 msec, respectively. N70 single-trial separability significantly improved at 1 msec pulse width (AUC of 0.83, χ^2= 8.17, p= 0.017, w= 0.34).
Significance: Robust median nerve stimulation based SEPs can be measured at single trials with methodological optimizations such as a longer pulse width, low frequency, a consistent afferent excitation via the SNAP and CMAP responses, and a robust EEG acquisition system. This setup can be useful for real time feedback-based applications for rehabilitation.

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Late-Breaking Poster

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Title: The ultrastructural synaptic underpinning of rapid thalamocortical activation of layer 4 inhibitory interneurons

Authors: *A. AGMON[1], G. MIRZAEE[1], Y. ZAMAN[1], R. MESTEMACHER-MCCLANAHAN[1], M. ROSENSTEEL[1], N. EGAWA[2], T. ETO[2], T. MIYAZAKI[2], F. S. BORGES[3,4], S. DURA-BERNAL[4], Y. KUBOTA[2];
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Abstract: Thalamocortical axons relay sensory information to cortical layer 4. Optogenetic activation of thalamocortical axons ex-vivo, or punctate stimulation of peripheral receptors in-vivo, elicit in layer 4 brief, ultrafast (400 Hz) local field potential oscillations called ripplets. We previously showed that ripplets are triggered by direct thalamocortical activation of layer 4 excitatory, regular-spiking (RS) neurons and fast-spiking (FS) inhibitory interneurons, followed by rhythmic reciprocal synaptic exchange between FS and RS cells. FS interneurons fire nearly 1 ms earlier than RS cells on each ripplet cycle including the first; the basis for this rapid activation of FS cells is not fully understood. To address this question we acquired a volumetric electron-microscopic image dataset from layer 4 of barrel cortex of an adult female mouse in which thalamocortical axons expressed tdTomato. Using correlated light-electron microscopy we identified thalamocortical axons and reconstructed them in 3D, together with postsynaptic aspiny (presumed FS) interneurons. Thalamocortical axons retained their myelin sheath as they entered layer 4, losing this sheath only as they approached their targets. In nearly every case, the unmyelinated axonal segment made its first synaptic contact on a basket cell soma or proximal dendrite, at a short distance (5-30 μm) from the myelinated parent branch and at an equally short distance from the postsynaptic basket cell body. A single axon often made multiple adjacent contacts on the same basket cell dendrite. In contrast, thalamocortical synapses on spines of (presumed) excitatory neurons were made at a wide range of distances, considerably further from the presynaptic myelinated branch and from the postsynaptic cell body. Computational modeling indicated that the combined effect of a short spike propagation path along the unmyelinated presynaptic axon and of minimal electrotonic delay along the postsynaptic dendrite could account for the rapid activation of FS cells observed experimentally. Multi-compartment network simulations of thalamocortical axons and postsynaptic RS and FS cells were able to reproduce 400 Hz oscillations, provided that thalamocortical inputs on basket cells were made on or very close to their cell bodies, as observed experimentally. We conclude that thalamocortical axons do not make synapses at random, but seek out and synapse first on basket cell somata and proximal dendrites. This spatial configuration results in rapid activation of FS interneurons, in turn generating an early disynaptic IPSP in excitatory cells, thus enforcing their synchronous firing during ripplet oscillations.

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Late-Breaking Poster

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Title: Impact of peripheral somatosensory neuron dysfunction on the development and function of brain circuits for social behavior

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Abstract: Sensory disruptions, including atypical responses to touch, are highly prevalent in autistic individuals. Notably, touch hypersensitivity correlates with greater severity of core autism spectrum disorder (ASD) symptoms, including altered social behaviors. Although tactile over-reactivity is a common symptom among autistic individuals, the neurobiological mechanisms linking disrupted somatosensory processing to social behavior deficits in autism remain poorly understood. Our prior work has shown that several mouse models for ASD exhibit touch over-reactivity that is driven by abnormal function of peripheral somatosensory neurons innervating the skin. We demonstrated that peripheral somatosensory neuron dysfunction during development leads to disruptions in primary somatosensory cortex (S1) function as well as social impairments in adult mice. In the present study, we employed conditional mouse genetics, anatomical tracing, in vivo electrophysiology, in vivo calcium imaging, and behavioral approaches to investigate the mechanisms through which aberrant sensory inputs lead to social behavior alterations in mouse models for ASD. We find that peripheral somatosensory neuron dysfunction, due to *Shank3* mutations, leads to altered S1 connectivity with other brain regions that encode touch and socially relevant stimuli. Disruptions to how light-touch information is encoded in these regions downstream of S1 ultimately caused reduced physical social interactions in *Shank3* mutant mice. Together, our findings reveal a peripheral sensory neuron to brain circuit pathway that drives physical social interactions and demonstrate how disruptions to this pathway contribute to social behavior deficits in ASD models.

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Late-Breaking Poster

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Topic: E.02. Somatosensation – Touch

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Title: High gamma and beta electrocorticography activity represents perceived vibrationintensity in human somatosensory cortex

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Abstract: Tactile sensation provided through haptic feedback is known to improve functions and user performance. Brain-computer interface (BCI) offers to measure cortical activity associated with tactile feedback in real time, particularly high-gamma (HG) signals recorded from electrocorticography (ECoG) have been reported to vary with vibrotactile frequency and to differ across different touch events and beta signals have been reported to be modulated by vibration amplitude. In this study, we investigate HG and beta activity in the somatosensory cortex to determine whether it reflects touch perception itself or only represents the haptic stimulation input. To understand how neural physiological responses reflect perceived intensity of a touch event, three amplitude levels of fingertip vibrations were randomly delivered to an individual with implanted ECoG arrays over speech and upper extremity sensorimotor representations and measured the reported levels of perceived intensity for varying vibration amplitudes. HG and beta spectral powers were used to identify the mapping of the hand and determine neural responses corresponded to the vibration stimulus. Localized HG activity in the right cortex was identified using high amplitude vibration. HG activity was modulated by both the amplitude of haptic vibration at the fingertips and the perceived intensity. Regression analysis revealed a stronger association between HG activity and perceived intensity than with vibration amplitude. Desynchronized beta oscillations were also observed during the late stimulation phase, approximately 250 milliseconds after event onset. These findings suggested that HG activity better reflects perceived intensity than vibration amplitude. Neural activity, particularly HG and

beta activity, could provide insights on the perceived quality of haptic sensations. This study demonstrated the feasibility of using neural activity to identify perceived haptic intensity. Cortical responses to vibration at each fingertip revealed the localization of the unique neural response to the tactile stimulus. HG spectral activity reflected both the vibration amplitude and perceived haptic intensity at different spectral power levels following the degree of vibration amplitude as well as perceived intensity. Beta spectral activity was associated with the vibrotactile haptic stimulus.

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Late-Breaking Poster

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Title: Calcium dynamics of S1HL neurons encode hindlimb traction forces

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Abstract: Weight-bearing is a fundamental constraint on sensorimotor control, yet how the hind-limb primary somatosensory cortex (S1HL) encodes gradient load remains unclear. **(1) Model.** We established a head-fixed, treadmill-compatible mouse paradigm that applies parametric traction via shin-mounted micro-weights (0-35% body mass) to the hind limbs, allowing stable locomotion and stationary stances while precisely manipulating axial load. **(2) CaMKII$^+$ dynamics under different shin weights.** Using two-photon calcium imaging of layer 4/5 CaMKII$^+$ neurons in S1HL during quiet stance and belt locomotion, we quantified event rates, $\Delta F/F$ amplitude, and pairwise correlations across weights. Load increases neuronal firing events and amplitude with state-dependent kinetics. **(3) Distinct firing characteristics across loading states.** Hidden-Markov model (HMM) and generalized linear model (GLM) revealed separable ensembles tuned to *unloaded*, *moderate*, and *high* load, with load-selective cells showing increased reliability and reduced shared variability, indicating sharpened population codes under higher traction. **(4) Receptive-field organization for weight tasks.** Functional mapping

uncovered heterogeneous load-receptive fields: some subsets preferred ipsilateral shin loading, others contralateral or bilateral loading; these fields are partially overlapping, suggesting a proprioceptive basis for load representation in S1HL. Together, these results demonstrate that S1HL is a load-sensitive brain region whose $CaMKII^{+}$ dynamics flexibly reconfigure with hind-limb weight, offering a cortical substrate for adaptive gait and posture under changing biomechanical demands.

Disclosures: B. Li: None. **N. Liu:** None. **F. Yang:** None.

Late-Breaking Poster

LBP077: E.02. Somatosensation – Touch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP077.14/LBP046

Topic: E.02. Somatosensation – Touch

Support: NIDCR Grant R01DE027236
NIA Grant R01AG069227

Title: Cortical encoding of lingual contacts in feeding

Authors: *D. TANG[1], F. I. ARCE-MCSHANE[2,3];
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Abstract: Precise tongue movements during feeding rely on somatosensory feedback from the oral cavity. Neural processing of these sensory signals is crucial for regulation of tongue movements for each phase of food manipulation, chewing, and swallowing. However, the frequent self-touches between the tongue and upper oral structures during feeding phases have not yet been described due to the challenge of tracking tongue movements inside the mouth. We hypothesize that sensory information about contacts between the tongue and surrounding oral structures, such as the palate and the teeth, is critical for tongue control and thus robustly encoded in the orofacial sensorimotor cortex. We used bilateral video radiography and implanted markers on the lingual mucosa to track 3D tongue movements and identify lingual contacts while rhesus macaques (n=3) engaged in natural feeding. Simultaneously, we recorded neuronal activity using chronically-implanted microelectrode arrays in four cortical regions: rostral primary motor cortex (M1), caudal M1, Area 3a/3b, and Area 1/2. The tongue moved predominantly from posterior to anterior on the upper oral structures during all phases of feeding, and anterior to posterior strokes increased during food manipulation prior to chewing. The tongue exhibited phase-specific stroke patterns across all animals, including increased contralateral contact during sided chewing. Significant decreases in both the frequency and duration of tongue strokes (Wilcoxon rank sum test, $p< 0.05$) were observed after a series of nerve blocks eliminated tactile feedback from the oral cavity, but the changes in stroke pattern were subject-dependent. All neurons in areas 3a/3b of somatosensory cortex (S1, n=21) exhibited

depressive activity during contact compared to no contact, and a subportion (n=6) showed selectivity towards the angle of the stroke. Finally, we trained a K-Nearest Neighbor (KNN) classifier to predict states of lingual contact from neural data with the hypothesis that lingual contact states are represented by similar patterns of neural activity. Accuracy of classifying lingual contacts was above chance levels in each cortical region both naturally and under nerve block conditions for the most commonly occurring contact states. Classification accuracy based on spiking activity of M1 neurons always outperformed classification using S1 neurons. These results suggest that feeding phase-specific tongue strokes against the upper oral structures rely on tactile feedback, and that the orofacial sensorimotor cortex represents lingual contacts at both individual neuron and population levels.

Disclosures: D. Tang: None. **F.I. Arce-McShane:** None.

Late-Breaking Poster

LBP077: E.02. Somatosensation – Touch

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP077.15/LBP047

Topic: E.02. Somatosensation – Touch

Support: NIH R01 NS-116277
Simons Collaboration on the Global Brain

Title: Natural scene statistics in touch

Authors: N. TUMMALA[1], A. L. FAIRHALL[2], ***M. J. HARTMANN**[3];
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Abstract: Sensory systems have evolved to exploit the statistical structure of their inputs. While analyses of natural scene statistics in vision and audition have advanced our understanding of neural coding and perception, the statistical structure of tactile stimuli remains comparatively unexplored. Here, we characterize the "tactile prior," i.e., the statistical structure of surfaces in the environment independent of how they are sampled by an organism. We then examine how they are encoded by two distinct tactile systems, the rodent vibrissal (whisker) system and the human hand. To estimate the tactile prior, we analyzed a large dataset of natural and human-made object meshes sampled at sub-millimeter resolution (Zweifel et al., bioRxiv, 2022). For each mesh, we computed surface curvature across multiple spatial scales. Curvature is an intrinsic, pose-invariant geometric descriptor that has been linked to receptive field organization in the somatosensory cortex (Zweifel et al., bioRxiv, 2022). Our analyses reveal that the curvature statistics of natural objects share key features with those reported for visual and auditory scenes, including heavy-tailed distributions, long-range correlations, and spatial scale invariance. In contrast, human-made objects exhibit markedly different statistics, with more

pronounced features at distinct spatial scales and reduced scale invariance. These findings suggest that although touch uniquely requires direct physical contact with the environment, it may share computational principles that shape neural coding across sensory modalities and organisms. We are now using mechanical and neural simulation tools to examine how different tactile systems might exploit the tactile prior. In the rodent vibrissal system, we are using WHISKiT (Zweifel et al., PNAS, 2021) to simulate the mechanical signals delivered to mechanoreceptors at the base of the vibrissae during whisker-object interactions. In the human hand, we are using Touchsim (Saal et al., PNAS, 2017) to simulate the spiking responses of cutaneous mechanoreceptors during skin-object interactions. Our poster will present related results. Overall, our methods and findings establish a statistical foundation for diverse lines of inquiry in sensory neuroscience, haptics, and robotics. These include generating testable predictions about neural and perceptual mechanisms, improving tactile rendering methods, and developing control strategies and perceptual algorithms for artificial touch. We thank Dr. Nadina O. Zweifel for providing the object dataset, Olivia Y. Lee for collecting additional object scans, and Megan E. Black for running WHISKiT simulations.

Disclosures: N. Tummala: None. **A.L. Fairhall:** None. **M.J. Hartmann:** None.

Late-Breaking Poster

LBP077: E.02. Somatosensation – Touch

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Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP077.16/LBP048

Topic: E.02. Somatosensation – Touch

Support: JST CREST JPMJCR21P5 to TH

Title: Neural correlates of texture-related sensations induced by novel haptic technology in the somatosensory cortex

Authors: *H. TOGO[1], K. YAMAGUCHI[1], D. ZYMELKA[2], T. TAKESHITA[2], Y. TAKEI[2], H. YAMAMOTO[3], T. NAKAMURA[1], K. YOSHINAGA[1], T. HANAKAWA[1];
[1]Kyoto University Graduate School of Medicine, Sakyo-ku, Kyoto, Japan; [2]National Institute of Advanced Industrial Science and Technology, Tsukuba, Ibaraki, Japan; [3]Kyoto University Graduate School of Human and Environmental Studies, Sakyo-ku, Kyoto, Japan

Abstract: Objects with different textures can produce a variety of "the sense of touch," which is expressed in Japanese onomatopoeia as, for example, *mowa-mowa* (fluffy) or *gasa-gasa* (rough). However, little is known about how the brain processes texture information, inducing vivid and conscious tactile experiences. This is partly because haptic technology has been unavailable to produce a variety of tactile experiences in an experimental setting. The present study aimed to develop haptic technology that produces rich tactile experiences through an ultra-thin piezoelectric actuator, called a Haptics Film (HF). We used functional MRI at 7T to identify the neural correlates of tactile experiences produced by HF. Participants were asked to rate their

tactile sensations with a set of onomatopoeias using a 7-point scale during the application of HF stimuli with different combinations of acceleration factor and frequency (20-45 Hz). Principal component analysis and *k*-means clustering classified the ratings into three categories: "rough/*gasa-gasa*", "fluffy/*mowa-mowa*", and "vibratory/*pulu-pulu*". Through HF, high frequency-high acceleration stimulation produced the "rough/*gasa-gasa*"-type tactile perception, and low frequency-low acceleration stimulation did the "fluffy/*mowa-mowa*"-type tactile perception. To investigate neural correlates of these tactile experiences, four representative HF stimuli (duration = 5 s) defined by two acceleration levels and two peak frequencies (20 and 45 Hz) were presented in a 7-Tesla MRI system. Task-related fMRI was acquired while participants reported whether sensations were perceived as "rough/*gasa-gasa*" or "fluffy/*mowa-mowa*". The analyses of task-related brain responses revealed the involvement of bilateral postcentral sulci during "fluffy/*mowa-mowa*" experiences compared to "rough/*gasa-gasa*" experiences. The activity in the postcentral sulci also showed significant interactions between the acceleration and frequency factors. Multi-voxel pattern analysis (MVPA) demonstrated that neural activity patterns within bilateral postcentral sulci enabled reliable two-class classification of "rough/*gasa-gasa*" versus "fluffy/*mowa-mowa*" sensations with accuracy exceeding 60%. These findings suggested that the combination of acceleration and frequency of vibrotactile stimulation influences tactile perception, and that bilateral postcentral sulci play a crucial role in distinguishing different texture-related sensations.

Disclosures: H. Togo: None. **K. Yamaguchi:** None. **D. Zymelka:** None. **T. Takeshita:** None. **Y. Takei:** None. **H. Yamamoto:** None. **T. Nakamura:** None. **K. Yoshinaga:** None. **T. Hanakawa:** None.

Late-Breaking Poster

LBP078: E.03. The Chemical Senses

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP078.01/LBP049

Topic: E.03. The Chemical Senses

Support: Department of Defense CDMRP
University of Auckland Doctoral Scholarship

Title: Molecular and cellular characterization of the Parkinson's disease olfactory bulb

Authors: *A. GARTON, K. LEHNERT, M. A. CURTIS, J. C. JACOBSEN;
University of Auckland, Auckland, New Zealand

Abstract: Parkinson's disease (PD) is a multifactorial neurodegenerative disease that manifests clinically at least six years after initial pathological changes. The molecular mechanisms that lead to neurodegeneration in PD remain poorly understood, and no disease modifying-treatments currently exist. This highlights the importance of investigating early PD, as 50-80% of dopaminergic neurons in the substantia nigra have already been lost at the time of diagnosis. The

olfactory bulb (OFB) is among the first regions to exhibit PD pathology, and up to 95% of PD patients have olfactory dysfunction which precedes motor symptoms by 4-10 years. However, the molecular and cellular organization of the human OFB remains largely uncharacterized, limiting insights into these early pathogenic events in PD. Characterization of the human OFB would provide a foundation for identifying early disease biomarkers and therapeutic targets in PD. Thus, the aim of this project was to characterize the cellular and spatial organization of the human OFB using single-nuclei RNA-sequencing (snRNA-seq) and spatial transcriptomics, and to provide first insights into early molecular PD pathology in this system. snRNA-seq of postmortem human OFB tissue from three controls and one PD case revealed 21 transcriptionally distinct cell populations including 12 neuronal and 9 non-neuronal populations. Spatial transcriptomics performed on four sections (two from a PD case and two from a control case) enabled gene expression to be mapped across five histologically defined layers. This provided insight into the laminar organisation of major cell types in the OFB. Novel lamina-specific markers *ENC1* and *NEUROD2* were localized to the anterior olfactory nucleus, and *MEIS2* and *PCP4L1* to the granule cell layer. Using this integrated approach, four granule cell subtypes were resolved, including a previously unclassified *CALB2-/FOXP2-* subtype. Two distinct glutamatergic neuronal populations localized to different OFB lamina. Importantly, a novel population of GABAergic neurons were enriched in the PD case, highly expressed *SNCA*, and localized to the granule cell layer, suggesting a potential role in early PD-related pathology. Together, this provides the first multi-dimensional insight into the cellular and spatial dimensions of the human OFB, offers new insights into early lamina-specific changes in the PD OFB, and lays the groundwork for investigating early disease processes in PD.

Disclosures: A. Garton: None. **K. Lehnert:** None. **M.A. Curtis:** None. **J.C. Jacobsen:** None.

Late-Breaking Poster

LBP078: E.03. The Chemical Senses

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP078.02/LBP050

Topic: E.03. The Chemical Senses

Support: NIH Grant DC101532

Title: Evidence that interglomerular inhibition generates non-monotonic concentration-response relationships in mitral/tufted glomeruli in the mouse olfactory bulb

Authors: L. LEONG[1], D. WHARTON[2], N. SUBRAMANIAN[3], B. KARAMCHED[2], R. BERTRAM[4], ***D. A. STORACE**[1];
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Abstract: The role of intra- and interglomerular networks in the olfactory bulb (OB) in transforming olfactory receptor neuron (ORN) input across concentration changes remains poorly understood. We addressed this question by implementing a mathematical model of the OB input-output transformation in which the output of each glomerulus is a function of its ORN input, local and lateral inhibition. The model produced outputs with concentration-response relationships that depended on the input ORN Hill coefficient and half-activation value. Some glomeruli responded with monotonic increases or decreases, while others responded with non-monotonic decreases then increases or increased then decreased. The model yielded several novel predictions that challenged recent findings in the field, including the existence of an abundance of non-monotonic responses and that inhibition across the interglomerular network should increase with excitation. We tested these predictions using single and dual-color *in vivo* 2-photon Ca^{2+} imaging from ORN and MTC glomeruli in awake mice. MTC glomeruli responded to odors with monotonic and non-monotonic concentration-response relationships in an odor-specific manner. Notably the mean excitation and suppression across the glomerular population were significantly correlated with one another and half of the MTC glomeruli exhibited some degree of non-monotonicity. The magnitude of non-monotonicity in MTC glomeruli was significantly correlated with the affinity of its ORN input and decreasing MTC glomeruli were innervated by low affinity or non-responsive ORN input. The results support a model in which rising levels of local and lateral inhibition will generate heterogeneous concentration-response relationships, which we propose will facilitate odor discrimination.

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Late-Breaking Poster

LBP078: E.03. The Chemical Senses

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Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP078.03/LBP051

Topic: E.03. The Chemical Senses

Support: IBS-R001-D1

Title: Distributed neural dynamics underlying sensory-to-motor transformation during olfactory decision making

Authors: *J. DO, D. LEE;
Center for Cognition and Sociality, Institute for Basic Science, Daejeon, Korea, Republic of

Abstract: Perceptual decision-making requires the transformation of sensory inputs into motor outputs through intermediate processes such as working memory and action planning. While higher-order areas are often emphasized in these processes, how these functions emerge across the brain during learning remains unclear. To address this, we combined acute and chronic Neuropixels recordings in mice performing an olfactory delayed match-to-sample task. In the

acute experiments, we recorded dozens of brain areas spanning the full olfactory decision-making pathway—from early sensory regions to hippocampal, frontal, and motor areas. Early sensory areas such as the anterior olfactory nucleus (AON) showed robust delay-period odor-selective activity and match/non-match category, dissociable from licking direction. In contrast, anterior-lateral motor cortex (ALM) encoded licking direction but not perceptual decision, while orbitofrontal (OFC) and prefrontal (PFC) cortices carried mixed decision and motor representations. To examine how these representations develop with learning, we performed chronic Neuropixels recordings in AON, OFC, and ALM, tracking the same neurons across weeks. Odor-selective delay activity in AON increased with learning, and categorical decision making signals became more prominent and stable. These learning-related changes were also observed in downstream areas, suggesting that task-relevant signals are increasingly transferred and utilized across regions. Together, our findings reveal a learning-dependent reorganization of decision-related neural activity across distributed brain regions, where early sensory areas not only maintain sensory information but also serve as critical hubs for initiating flexible, experience-driven sensorimotor transformations. This challenges classical hierarchical views and highlights the adaptive nature of brain-wide networks in linking sensation to action.

Disclosures: J. Do: None. **D. Lee:** None.

Late-Breaking Poster

LBP078: E.03. The Chemical Senses

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Topic: E.03. The Chemical Senses

Support: NIH Grant R01NS116584
Richard and Susan Smith Family Award for Excellence in Biomedical Research
Klingenstein-Simons Fellowship Award in Neuroscience
Innovative Research award from the Kavli Institute for Neuroscience at Yale University

Title: Differential inhibition drives heterogenous odor dynamics in the Drosophila expansion layer

Authors: *P. MISHRA[1], J. M. JEANNE[2];
[1]Yale University, New Haven, CT; [2]Department of Neuroscience, Yale University, New Haven, CT

Abstract: Behavioral choices in animals emerge from sophisticated computational motifs operating across multiple neural scales. The compression-expansion circuit represents a conserved architecture shared across brain regions and species. Given that the sensory landscape carries rich spatiotemporal information, how do these circuits sharing common motifs fulfill contrasting functional demands? We propose that differential feedback inhibition within the

expansion layer creates a repertoire of functional motifs, facilitating heterogeneous dynamical responses in the *temporal* domain. The *Drosophila* olfactory circuit provides a platform to mechanistically dissect various intrinsic circuit components in the mushroom body (MB) - the expansion layer -towards the emergence of such dynamical odor processing. To examine the population response of Kenyon cells (KCs; the intrinsic neurons of the MB), we employed both voltage and calcium imaging from four KC-subtypes. We designed the stimuli to capture different aspects of odor information - valence and temporal patterns, and build an exhaustive cell-specific response landscape for different odor parameters. We found α'β' neurons to exhibit faster adaptation kinetics than αβ-core neurons, where KCs response amplitudes to stimulus ON-OFF phase correlates with odor valence. Interestingly, specific KC-types showed greater heterogeneity in response dynamics, expanding encoding capacity in a cell-specific manner. We reasoned that the stereotyped odor information arriving from the compression layer, or the random sampling of these inputs by KCs would be insufficient to elicit such heterogeneity in *temporal* odor response dynamics. Therefore, we examined the role of local circuit inhibition by APL, an interneuron in MB. We bath applied GABAAR- and GABABR- specific blockers independently and in combination, at different concentration ratios.Strikingly, the blockade of inhibition suppressed adaptation and enhanced temporal summation of responses to high-frequency odor stimulus in αβ-core KCs,with comparatively smaller impact on α'β' KCs. This differentially tunedinhibition was dependent on odor identity and arose from distinct engagement of the different inhibitory receptors, especially GABABR - type. Our results provide strong evidence that the differential dynamics of inhibition (dependent on odor identity, cell-type, and receptor activation profiles) contribute to heterogeneities in dynamics of odor responses in the expansion layer. Thus,deferentially tuned inhibition could serve as a flexible computational node inmultimodal brain regions, optimizing *temporal* encoding space.

Disclosures: P. Mishra: None. **J.M. Jeanne:** None.

Late-Breaking Poster

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Program #/Poster #: LBP078.05/LBP053

Topic: E.03. The Chemical Senses

Support: JSPS KAKENHI JP23K27473
AMED-PRIME JP23gm6510022

Title: Periglomerular cell odor represetation plasticity in the odor discrimination task

Authors: *A. IDE[1], Y. SUZUKI[1,2], M. SAKAMOTO[1,2], I. IMAYOSHI[1,2];
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Abstract: The olfactory system mediates various odor-driven behavioral responses, including associative learning between odor cues and rewards. As the first processing center, the olfactory bulb is critical for odor detection, discrimination, and valuation. Periglomerular cells (PG) in the olfactory bulb are GABAergic interneurons that receive inputs from olfactory sensory neurons and provide strong inhibition onto principal neurons (mitral and tufted cells, M/T cells) within the glomeruli. Previous studies have suggested that PG cells contribute to sharpening M/T cell responses by extending their dendrites and inhibiting neighboring cells. However, how dynamic changes in PG cell activity at the single-cell level and population levels contribute to different types of olfactory-associative learning remains unclear. Here, we performed chronic *in vivo* two-photon calcium imaging to monitor the PG cell activity under two conditions: passive odor exposure and a go/no-go odor discrimination task. Passive odor exposure involved repeated presentation of the odor pair without behavioral demands. In the discrimination task, the odors were assigned as Go and No-Go cues linked to reward and punishment, with mice trained to lick in Go trials and to withhold licking in No-Go trials. Passive exposure led to a gradual decrease in the amplitude of odor responses as well as in the number of odor-responsive PG cells, yet responses to Go and No-Go odors remained distinguishable. In contrast, during the go/no-go odor discrimination task, the odor-responsive cell populations were largely maintained across days, but as learning progressed, more cells became responsive and their activity patterns for Go and No-Go odors grew increasingly distinct. Additionally, PG cell activity increased in Go trials, whereas it decreased in No-Go trials. Our findings demonstrate that PG cells undergo learning-dependent plasticity, strengthening responses to reward-predicting odors and sharpening the contrast between Go and No-Go representations.

Disclosures: A. Ide: None. **Y. Suzuki:** None. **M. Sakamoto:** None. **I. Imayoshi:** None.

Late-Breaking Poster

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Location: SDCC Hall B

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Program #/Poster #: LBP078.06/LBP054

Topic: E.03. The Chemical Senses

Title: Metal Organic Framework (MOF) Modification of Carbon Fiber Microelectrodes for Enhanced Sensitivity in Neurochemical Detection

Authors: *T. ALSHAMMARI[1], A. G. ZESTOS[2];
[1]The American University, The Catholic University, University of Hafr Al Batin, Arlington, VA; [2]Chemistry, American University, Washington, DC

Abstract: Metal–Organic Framework (MOF) Modification of Carbon Fiber Microelectrodes forEnhanced Sensitivity in Neurochemical DetectionAbstract: Dopamine is an important neurotransmitter that is used to regulate reward, learning,cognition, and helps our understanding of several disorders such as Parkinson's Diseaseand addiction. It is frequently measured with fast-scan cyclic voltammetry (FSCV), whichis an advanced electrochemical

method extensively employed for the real-time detectionof neurotransmitters. Carbon fiber microelectrodes (CFMEs) are coupled with FSCV dueto their high biocompatibility, spatiotemporal resolution, capability to target specific brainsubregions, and they do not elicit a significant immune response, while producing minimaltissue damage upon chronic implantation *in vivo*. FSCV utilizes fast voltage scanning atCFMEs to detect sub-second fluctuations in dopamine concentrations in the brain, basedon the shape and position of cyclic voltammograms (CVs), which provide a chemicalfingerprint for neurochemical detection. However, the sensitivity of CFMEs with FSCV fordopamine detection is limited and cannot measure basal levels of neurotransmitters butcan be enhanced through metal organic framework (MOF) modification.This study examines the modification of carbon fiber microelectrodes with iron-basedMOF (MIL- 88B(Fe) to enhance dopamine detection through debye-debye interactions,intermolecular charge transfer, and enhanced electrode surface roughness. Our resultsindicate that MIL-88B(Fe) MOF-modified electrodes exhibit a significant increase inoxidative current compared to bare, unmodified CFMEs and show enhanced sensitivityfor neurotransmitter detection, especially at low dopamine concentrations approximately300 nm. The modified electrodes exhibited high stability, keeping consistent responsesafter four hours of repeated dopamine injections and continuously applying the triangledopamine waveform. Moreover, scan rate experiments confirmed the adsorption-controlled mechanism, showing a linear response between dopamine concentration andpeak oxidative current ($R^2 = 0.983$) within the physiologically relevant range (10 nM to1μM). Furthermore, we successfully co-detected and identified dopamine in complexsolutions including hydrogen peroxide (H2O2) and tyrosine. The findings indicate that MIL-88B(Fe) modified-CFMEs provide efficient sensors for precise and enhancedneurochemical detection using FSCV. Future work will provide enhanced measurements*ex vivo* or *in vivo* for proof of principle measurements.

Disclosures: T. Alshammari: None. **A.G. Zestos:** None.

Late-Breaking Poster

LBP078: E.03. The Chemical Senses

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP078.07/LBP055

Topic: E.03. The Chemical Senses

Title: Local field potentials in the olfactory bulb of wild-type mice and a mouse model of autism

Authors: *E. HAILE[1], Z. A. FYKE[2], J. D. ZAK[3];
[1]University of Illinois at Chicago, Chicago, IL; [2]Cell Biology & Anatomy, University of Illinois at Chicago, Chicago, IL; [3]Biological Sciences, University of Illinois Chicago, Chicago, IL

Abstract: Local field potentials in the olfactory bulb of wild-type mice and a mouse model of autism Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized in part by heightened sensory sensitivity, which shapes how individuals interact with their environment. The olfactory system plays a key role in detecting, interpreting, and distinguishing

volatile sensory cues. Although recent work has shown that olfactory processing is altered in ASD, the neural mechanisms underlying these changes remain poorly understood. In this study, we investigated olfactory bulb network activity in wild-type mice and a mouse model of autism(*Fmr1*-KO) using extracellular local field potential recordings during patterned olfactory nerve stimulation that mimicked respiration. We then measured group differences in odor perception using innate behavioral assays. We first examined beta and gamma oscillatory bands of local field potentials in brain slices of wild-type and *Fmr1*-KO mice, which reflect interactions between the olfactory bulb and cortex (beta) and between mitral and granule cells with in the bulb(gamma). Oscillatory power was significantly reduced in both bands in *Fmr1*-KO mice compared with wild-type controls (beta band power :granule cell layer, 59.01± 17.64% reduction in *Fmr1*-KO, $P = 0.0012$; mitral cell layer, 65.00± 18.77% reduction, $P = 0.0100$; gamma band power: granule cell layer, 53.01± 17.65% reduction, $P = 0.0048$; mitral cell layer, 57.60±18.02% reduction, $P = 0.0028$). The attenuation of oscillatory power was consistently observed across a range of olfactory nerve stimulation intensities (100µA - 500µA). These findings indicate a disruption of olfactory network synchrony in *Fmr1*-KO mice, which may underlie altered sensory processing. To further investigate how these network disruptions may affect olfactory perception, we devised a behavioral assay that measured perceptual thresholds and odorant avoidance in wild-type and *Fmr1*-KO mice to four odorants across a range of concentrations. Odorant sensitivity was reduced in *Fmr1*-KO mice as aversive behaviors developed at higher odorant concentrations compared to wild-type controls. These perceptual changes in *Fmr1*-KO mice may result from a disruption of olfactory network synchrony observed in brain slices. Future work will examine how disruptions in network oscillatory power in the mitral and granule cell layers affect information propagation and processing in the piriform cortex, a hub for odor recognition and learning.

Disclosures: E. Haile: None. **Z.A. Fyke:** None. **J.D. Zak:** None.

Late-Breaking Poster

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Program #/Poster #: LBP078.08/LBP056

Topic: E.03. The Chemical Senses

Support: DC007703

Title: A novel approach to investigating anticipatory cortical responses to taste associated cues

Authors: *E. BARASH[1], D. B. KATZ[2];
[1]Psychology and Biology, Brandeis University, Waltham, MA; [2]Dept Psychology, Brandeis University, Waltham, MA

Abstract: Survival is inextricably tied to consumption decisions; ingestion of toxic foods cause illness/death, while nutrient-rich foods promote health. Thus, it is paramount to understand how

food cues (e.g., the color of a fruit) guide approach-avoidance decisions regarding potentially nourishing (or sickening) foods. While cue-driven-association research is common, it is still unclear whether cue-associations evoke sensory codes. To bridge this gap, we created a novel experimental framework aimed at training cue-food reward associations in an electrophysiology-friendly manner that enables us to separate the effects of a reward's valence from its identity. We designed a paradigm featuring cue-trigger/retrieval-reward sequencing, pairing visual-auditory cues with unique chemosensory taste concentrations — palatable sucrose and sodium chloride, and aversive sodium chloride. Across several sessions, rats come to subtly adapt their approach or avoidance to cues based on reward palatability. As satiation increased during sessions, individual preferences emerged even among the palatable options, leading to stratification in total consumption by the session's end. Preliminary electrophysiological data from gustatory cortical (GC) neurons reveal, prior to taste delivery, clear responses that predict GC responses to the tastes themselves, but in reverse—strong taste responses predicted by weak cue responses, and vice-versa. Integration of behavioral and electrophysiological data allows us to investigate how the neural encoding of "anticipatory responses" in GC correlates with true taste responses in terms of identity and palatability.

Disclosures: E. Barash: None. **D.B. Katz:** None.

Late-Breaking Poster

LBP079: E.04. Interoception

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Topic: E.04. Interoception

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Title: Feeling the pressure: aging-related bladder sensory decline and its rescue by dietary fatty acids

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MARTINEZ[1,7], J. K. ASMUSSEN[5], K. P. K. STIETZ[11], C. M. VEZINA[11], V. VASQUEZ[6], A. BEYDER[3,4], K. L. MARSHALL[1,7,12];
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Abstract: The nervous system integrates chemical and mechanical cues to sustain vital physiological functions. PIEZO ion channels are specialized mechanosensors that transduce stimuli applied to the cell membrane, such as stretch and indentation, into biological signals. These channels are critical for processes including touch sensation, proprioception, blood pressure regulation, and urinary function—many of which decline with aging. Lower urinary tract symptoms are highly prevalent and often impactful, affecting approximately 70% of individuals over 40. Given the central role of PIEZO channels in urinary physiology and their potential contribution to aging-related dysfunction, the discovery of novel, non-invasive tools to manipulate their activity is essential. The biomechanical properties of cell membranes, such as stiffness and fluidity, are largely determined by the fatty acid (FA) composition of their phospholipid bilayers. Altering membrane FA composition via *in vitro* supplementation was shown to differentially modulate PIEZO activity. We hypothesized that dietary supplementation with FAs that increase membrane stiffness could reduce PIEZO activity *in vivo* and mitigate aging-related bladder dysfunction. Using liquid chromatography-mass spectrometry (LC-MS), we found that long-term dietary supplementation (4-8 weeks) with a membrane-stiffening FA enriched both dorsal root ganglia (DRG) and bladder tissues in mice. Electrophysiology assays on DRG sensory neurons from these mice revealed reduced rapidly-inactivating and intermediately-inactivating mechanocurrent densities as well as increased displacement threshold required to elicit mechanically gated currents, indicating PIEZO channels inhibition. Like humans, aged mice exhibit bladder dysfunction, characterized by increased urinary frequency and urgency. Remarkably, urinary behavior assays in aged mice showed reduced voiding frequency and improved continence after a 4-week FA-enriched diet compared to baseline (chow diet). We also found that smooth muscle-specific deletion of *Piezo1* recapitulated the phenotypic rescue effect of PIEZO-inhibitory FA diet in aged mice. Furthermore, analysis of human genotype-phenotype associations revealed that ultra-rare *PIEZO1* variants may be an underlying risk factor for early-onset neuromuscular bladder dysfunction. Together, these findings identify PIEZO channels as key mediators of aging-related urinary dysfunction and demonstrate that dietary modulation of membrane properties is a powerful approach to probe mechanosensation and a potential therapeutic strategy for bladder and other mechanosensory disorders.

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Late-Breaking Poster

LBP079: E.04. Interoception

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP079.02/LBP058

Topic: E.04. Interoception

Title: Altered cortical sensory processing during passive joint loading in females with increased ACL injury risks: ERP N1 Evidence

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Abstract: BACKGROUND: Females are 2-4x more likely to sustain anterior cruciate ligament (ACL) injuries, with greater anterior knee laxity (AKL) being a strong, independent risk factor. Although the ACL transmits afferent signals during joint loading, resultant cortical sensorimotor integration during loading remains underexplored in injury prevention research. The event-related potential (ERP) N1 component reflects rapid cortical processing of sensory input and may reveal neural adaptations associated with altered sensory information in the lax knee. This study examined N1 amplitude during passive knee joint loading in females with high vs. low knee laxity. METHODS: Forty-four physically active females (ages 18-30; mean = 21.6 ± 3.4) were evenly stratified into low (≤5mm; mean = 4.1 ± 0.8) and high (≥7mm; mean = 8.3 ± 1.4) laxity groups. AKL was measured using a KT2000 arthrometer. Anterior tibial translation (ATT) was measured while a 130N anteriorly directed force was applied to the posterior tibia using a novel knee arthrometer (patent No. 12,285,273; 4 blocks x 6 trials). Electroencephalography (EEG) was recorded from 32 channels (10-20 system) with event markers occurring at ATT onset. ERP epochs were extracted from -200 to 1000 ms, baseline corrected, bandpass filtered, and averaged across C3, Cz, and C4 electrodes. N1 component amplitude was measured between 50-200ms and compared between groups using independent t-tests. RESULTS: High laxity females exhibited significantly larger N1 amplitudes during passive joint loading compared to those with lower AKL (high AKL: -4.09 μV ± 1.4; low AKL: -3.25 μV ± 1.3; $p = 0.02$, $d = 0.614$). CONCLUSIONS: High-laxity females demonstrated greater sensorimotor cortical responses to passive joint loading, indicating sensorimotor integration patterns. It is unknown at this time how such patterns may be associated with injury mechanisms. ERP N1 amplitude has potential to serve as a neural biomarker of elevated injury risk, offering a novel addition to current screening approaches. Future work incorporating neurophysiological assessments

alongside biomechanical measures is needed to enhance early detection of at-risk athletes and inform more targeted, neuro-responsive injury prevention strategies.

Disclosures: B. Bacon: None. **T. Haynes:** None. **E. Delgado guzman:** None. **T. Blackburn:** None. **D. Monroe:** None. **E. Drollette:** None. **S. Shultz:** None. **R. schmitz:** None.

Late-Breaking Poster

LBP079: E.04. Interoception

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP079.03/LBP059

Topic: E.04. Interoception

Support: NIH R01-DK135696

Title: TRPV1 and TRPM8 channels are involved in mouse urinary bladder micturition

Authors: *M. MASINO[1], N. R. TYKOCKI[2];
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Abstract: Transient receptor potential ion channels such as melastatin type 8 (TRPM8) and vanilloid type 1 (TRPV1) are temperature and chemical sensors involved in nociception. TRPM8 is sensitive to cool temperatures (8°-28°C) and chemically induced by menthol/mint. TRPV1 is sensitive to high temperatures (>42°C) and is also activated capsaicin. They are distributed throughout the urinary bladder in afferent nerves and smooth muscle cells; however, their exact role in micturition remains unknown. Sensitized TRPV1 channels increase afferent nerve signaling and impact bladder sensation, but it is unclear if TRPM8 and TRPV1 channels interact. We hypothesize TRPV1 and TRPM8 channel activation increases mechanical compliance in the urinary bladder. Bladders from male C57Bl/6 mice (ages 10-14 weeks) were cannulated on the Pentaplanar Reflected Image Macroscopy (PRIM) System to simultaneously record intravesical pressure, geometry, and infused volume during ex vivo bladder filling. From these recordings, mechanical compliance is calculated as the Cauchy stress and stretch. To determine the implications of activating one or both channels on bladder compliance, experiments were performed in the presence of the TRPV1 agonist capsaicin (200 nM), the TRPM8 agonist menthol (600 μM), or menthol and capsaicin together. Capsaicin alone had no effect on bladder pressure, volume, or biomechanics. After menthol exposure, a larger volume was required to reach the same pressure. These bladders also stretched more for the same stress, indicating increased compliance. Surprisingly, the increase in compliance caused by menthol was reversed when capsaicin was added after menthol. These findings suggest that TRPV1 and TRPM8 function in opposition to one another in terms of regulating bladder compliance during filling. Additional studies will determine the location of TRPV1 and TRPM8 in the bladder wall and possible mechanisms by which these channels can reversibly alter bladder compliance. Funded by NIH R01-DK135696.

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Late-Breaking Poster

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Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

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Topic: E.04. Interoception

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New York Stem Cell Foundation, Robertson Neuroscience Investigator Award
McKnight Foundation Scholar Award
Klingenstein-Simons Award in Neuroscience
Searle Scholars Award
Simons Foundation Autism Research Initiative
Pew Biomedical Scholars Award

Title: Dorsal root ganglion neuron dysfunction contributes to autism-related gastrointestinal deficits in mice

Authors: *Y.-C. HSIEH[1], Y.-W. NOH[2], K. CLAUSING[3], L. L. OREFICE[2];
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Abstract: Chronic gastrointestinal (GI) problems, including GI pain, are highly prevalent in autism spectrum disorder (ASD). Although GI dysfunction is a significant issue for autistic individuals that also correlates with exacerbated social difficulties and anxiety, the etiology of GI abnormalities in ASD is unknown. In this study, we used conditional mouse genetics, histology, imaging, in vitro and in vivo electrophysiology, as well as behavioral methods to identify whether GI dysfunction is prevalent in mouse models for ASD and the mechanisms through which ASD-associated gene mutations may cause GI problems in mice. We found that disparate mouse models for ASD exhibit increased GI pain behaviors. Further analyses revealed alterations in the neural pathways that convey sensory information from the gut to the central nervous system (CNS). These disruptions were associated with abnormal processing of visceral sensory signals in the CNS and heightened behavioral responses to GI stimulation. Finally, selective manipulations of specific gut-innervating neurons were sufficient to impact GI pain-related behaviors as well as other ASD-relevant phenotypes in adult mice. Together, these findings identify a novel GI tract to CNS pathway that contributes to GI problems and related behavioral issues in ASD.

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Late-Breaking Poster

LBP079: E.04. Interoception

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP079.05/LBP061

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH NICHD HD092941-01

Title: The effect of vagus nerve stimulation on microglial expression in the nucleus tractus solitarii of the brainstem of rat pups with necrotizing enterocolitis (NEC)

Authors: M. CHANG[1], N. IWAKOSHI[2], M. BAKER[3], G. MLADENOV[4], A. RADULESCU[4], ***C. G. WILSON**[5];
[1]Pomona College, Claremont, CA; [2]Loma Linda University, Loma Linda, CA; [3]Department of Pediatrics, Division of Neonatology,, Intermountain Healthcare, Billings, MT; [4]Surgery, Loma Linda University, Loma Linda, CA; [5]Pediatrics & Basic Sciences, Loma Linda University, Loma Linda, CA

Abstract: Necrotizing enterocolitis (NEC), characterized by necrosis of the intestinal lining, is a severe gastrointestinal disease that primarily affects premature and low birth weight infants, and can lead to systemic inflammation. While treatments for NEC exist, due to its complex etiology and association with prematurity, NEC remains one of the leading causes of morbidity and mortality in the neonatal intensive care unit. Survivors often face long-term consequences, including neurodevelopmental disorders and digestive system sequelae. The vagus nerve carries afferent signals from the gut to the nucleus tractus solitarius (NTS) in the brainstem, the first-order target of visceral afferents in the brain. Previous work from our group has shown that inflammation in the viscera can initiate production of neuroinflammatory markers within the NTS. Vagus nerve stimulation (VNS) has been used for decades to treat patients with conditions such as epilepsy, depression, and rheumatoid arthritis by activating a cholinergic anti-inflammatory reflex pathway. Our lab has shown that both electrical VNS and tactile stimulation of the ear (sham VNS) reduced the incidence, severity, and mortality of Sprague-Dawley rat pups in an NEC model. Rat pups were divided into six groups: NEC induction (no VNS; n=15), NEC with sham VNS (n=21), NEC with actual VNS (n=20), control (no NEC, no VNS; n=19), control with sham VNS (n=18), and control with actual VNS (n=19). We hypothesize that VNS attenuates the expression of inflammatory markers in the brainstem of rat pups with NEC. We tested this hypothesis using immunohistochemistry and unbiased stereology to quantify microglia stained for Iba1. From our study, we have put together a preliminary dataset with: NEC-no VNS (3), NEC-sham VNS (3), NEC-VNS (3), control-no VNS (3), control-sham VNS (2), control-VNS (6). Our preliminary data shows that NEC pups have significantly higher numbers of microglia in the NTS than control pups without VNS ($p=0.0051$) and control pups with VNS ($p=0.017$). Furthermore, sham VNS significantly reduced microglia in pups with NEC compared to NEC pups ($p=0.0018$), in contrast to VNS-treated pups ($p=0.086$). These

preliminary findings support a link between gut and neuroinflammation in neonates and the use of VNS to reduce inflammation in patients suffering from NEC.

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Late-Breaking Poster

LBP079: E.04. Interoception

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP079.06/LBP062

Topic: D.01. Neurotoxicity, Inflammation, and Neuroprotection

Support: NIH Grant DK141106
NIH Grant AR070116
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Title: Regulation of body inflammatory responses by peripheral sensory systems

Authors: *X. MENG[1,2,3], Z. WANG[1,2,3], A. IIJIMA[1,2,3], B. KIM[1,2,3];
[1]Icahn School of Medicine at Mount Sinai, New York, NY; [2]Friedman Brain Institute, New York, NY; [3]Allen Discovery Center for Neuroimmune Interactions, New York, NY

Abstract: In addition to their well-established role in sensing internal cues, the vagal sensory neurons (VSNs) are increasingly implicated in immunomodulation via initiating multiple brain-body axes. VSNs fine tune immune responses partly through their abilities to directly sense cytokines such as interleukin-1β and interleukin-10, yet it remains unclear if other signals sensed by VSNs like nutrients and metabolism could also be capable of regulating immune functions. We hypothesize that metabolism-sensing vagal afferents enhance anti-inflammatory responses via a brain-body axis in disease. Here, we demonstrate that selective silencing of the GLP-1 receptor (GLP1R) in nociceptive sensory neurons exacerbates skin inflammation in a murine model of psoriasis, marked by increased epidermal thickness and elevated Psoriasis Area and Severity Index (PASI) scores, without affecting body weight or systemic inflammation. To delineate this potential brain-skin circuit, we will utilize anatomical tracing, in vivo imaging of the nodose ganglion, and whole-brain c-Fos mapping, alongside optogenetic manipulations. Importantly, given the established safety of GLP1R agonists in humans, this work could reveal a previously unrecognized neuroimmune pathway with therapeutic potential across inflammatory and autoimmune diseases.

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Late-Breaking Poster

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Program #/Poster #: LBP079.07/LBP063

Topic: E.04. Interoception

Support: NIH Grant R01MH135267

Title: Manipulation of interoceptive signals alters task-related and spontaneous behaviors in an approach-avoidance conflict task

Authors: *A. PAL[1], M. CARDENAS[1], K. M. GOTHARD[2];
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Abstract: Interoceptive signals are thought to guide deliberate decision-making and shape spontaneous actions. To test the contribution of interoception to measurable behaviors in an approach-avoidance task, we altered the physiological state of the body, and thereby the interoceptive afferents. Two rhesus monkeys received injections of glycopyrrolate, a parasympathetic blocker that does not cross the blood-brain barrier. The monkeys chose to either receive juice in return for tolerating a non-painful heat stimulus or press a switch to stop heat and forgo the juice. They completed 30 high-heat trials (46-48 °C) and 30 low-heat trials (42 °C) before and after subcutaneously receiving glycopyrrolate or saline control. After glycopyrrolate injection the monkeys' heart rate (HR) was 15% higher than control (*t*-test, $p<0.0001$). As previously reported (Cardenas et al., 2025), glycopyrrolate reduced heat tolerance: monkeys stopped high-heat trials earlier (Kolmogorov-Smirnov test, $p=0.005$). They also stopped more low-heat trials after glycopyrrolate compared to saline injections (Chi-squared test, $p<0.001$). An increase in HR preceded heat termination: HR rose during the 6 seconds before the monkey pressed the switch, continued rising for 4 s after the press, then returned to baseline. While this HR pattern predicted whether monkeys pressed the switch, the precise timing of the press relative to the onset of the heat stimulus was not predicted by HR. Monkeys responded to the heat stimuli not only by switching it off but also by engaging in spontaneous behaviors, such as "tapping" (contact with the switch without pressing), "lifting" (raising the hand without touch), and "readjustment" (shaking, kicking, restless feet). These behaviors were amplified by glycopyrrolate but not saline (Mann-Whitney U test, $p=0.005$). Taken together, the behavioral and autonomic changes show that manipulating interoceptive afferents triggers spontaneous, potentially compensatory behaviors that contribute to the task-related tolerance of aversive stimuli.

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Late-Breaking Poster

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Program #/Poster #: LBP079.08/LBP064

Topic: E.04. Interoception

Support: NIH-HL173002
NSF 2334697

Title: Distinct peripheral innervation patterns of two subsets of jugular sensory neurons

Authors: *Y. WANG[1], K. LAWSON[1], R. STEWART[1], Y. XING[1], Y. ZHU[2], W. HANCOCK[1], L. HAN[1];
[1]Georgia Institute of Technology, Atlanta, GA; [2]The Hong Kong Polytechnic University, Hong Kong, Hong Kong

Abstract: Vagal sensory neurons (VSNs) form a critical body-brain axis that monitors the physiological state of thoracic and abdominal organs. The vagal system is divided into nodose and jugular ganglia, which differ in molecular profiles and peripheral targets. Our previous studies have identified subsets of jugular sensory neurons that express Mas-related G protein-coupled receptors (Mrgprs). This receptor family is best known for its role in somatosensation and airway reflexes. Among these, MrgprC11 has been studied in the skin, where its activation evokes itch, and in the airway, where it mediates bronchoconstriction. However, the broader distribution and functional significance of Mrgprs$^+$ jugular neurons in the internal organs remains unclear. Here, we mapped MrgprC11$^+$ and MrgprD$^+$ jugular afferents across organ systems and demonstrated distinct peripheral innervation patterns for these two subsets. MrgprC11$^+$ fibers, in addition to the dense innervation in the airway we previously reported, provide extensive innervation to the gastrointestinal (GI) tract, with the highest density in the esophagus and colon. MrgprC11$^+$ axons were found to be localized to the muscularis externa, forming intraganglionic laminar endings (IGLEs) that were closely associated with the myenteric ganglia. This suggests that MrgprC11$^+$ afferents primarily contribute to motility-related reflexes rather than to sensing luminal nutrients, as no fibers projected into the mucosal villi. In contrast, MrgprD$^+$ fibers were restricted to the pharynx and absent from all the thoracic and abdominal organs we examined, suggesting a unique role of MrgprD$^+$ vagal afferents in airway defense response. Our results define molecularly distinct vagal sensory pathways and demonstrate that MrgprC11$^+$ and MrgprD$^+$ jugular neurons make specialized contributions to visceral and airway reflexes.

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Late-Breaking Poster

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Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

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Topic: E.04. Interoception

Support: Singapore National Research Fellowship (NRFF13-2021-0087)
A*STAR Career Development Fund (C233312017)
National Medical Research Council, under its Young Individual Research Grant (OFYIRG23jul-0065)

Title: A vagal liver-brain circuit for inflammation sensing and response

Authors: *N. ZHANG, S. LUO;
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Abstract: As a gateway between the gastrointestinal tract and the internal circulation, the mammalian liver is uniquely positioned to sense and mount both behavioural and immune responses to incoming immune challenges that enter the liver via the gut. This requires functional coordination of the nervous and immune systems. Although the existence of vagal sensory neurons innervating the liver portal vein is known, their sensory function and molecular characterization is relatively unexplored. Using CUBIC tissue-clearing technique, we identified $Phox2b^{+}$ vagal nerves predominantly innervate the hepatic portal vein. Through projection-based single-cell transcriptomics, we further revealed that these vagal sensory neurons express receptors for key immune mediators released by liver macrophages during inflammation or injury. Moreover, an inflammatory challenge administered directly to the liver via a portal vein catheter strongly activated this liver-brain vagal circuit. This activation led to marked modulation of sickness behaviours, including reduced food intake, decreased locomotor activity, and lowered energy expenditure, partially mediated by downstream brain regions such as the nucleus of the solitary tract (NTS), paraventricular nucleus (PVN), and parabrachial nucleus (PBN). Additionally, chemogenetic activation of this circuit increased Kupffer cell accumulation around the portal region, indicating its role in regulating peripheral immune responses. In summary, our findings define a molecularly and anatomically distinct neuroimmune feedback circuit by which peripheral immune signals from the liver are conveyed to the brain to regulate feeding behaviour and local immune responses.

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Late-Breaking Poster

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Topic: E.04. Interoception

Support: Startup funds from the University of Florida (Z.Y.)
National Institutes of Health (NIH) grant R01DK139131 (Z.Y.)

Title: Connectomic mapping of pharyngeal and gut sensory circuits in adult Drosophila

Authors: *D. S. GIAKOUMAS[1,2], Z. YAO[2];
[1]University of Iowa Neuroscience Graduate Program, Iowa City, IA; [2]Biology, University of Florida, Gainesville, FL

Abstract: Connectomic mapping of pharyngeal and gut sensory circuits in adult *Drosophila*
Dimitrios S. Giakoumas[1,†] , Zepeng Yao[1]
[1] Department of Biology, University of Florida, Gainesville, FL 32611[†] Interdisciplinary Graduate Program in Neuroscience, University of Iowa, Iowa City, IA, 52242
† = current affiliation
Feeding is regulated by both external sensory signals, such as taste, and internal sensory signals originating from the pharynx and gut. The recent completion of the Full Adult Fly Brain (FAFB) connectome presents an exciting opportunity to map these sensory inputs and their downstream circuits. While the external gustatory receptor neurons (GRNs) have been relatively well characterized, the internal pharyngeal and gut sensory neurons remain less understood. Here, we systemically identify their axonal projections in the FAFB connectome and examine their downstream circuits. We find that the stomodeal nerve, which carries afferent signals from the gastrointestinal tract to the brain, contains multiple types of sensory axons with distinct morphology and downstream connectivity. In addition, we identify sensory axons derived from different pharyngeal sense organs and speculate that chemosensory and mechanosensory neurons project to distinct regions of the subesophageal zone. Characterization of the second- and third-order neurons reveals the brain regions that receive inputs from pharyngeal and gut sensory neurons. Key differences between these internal sensory neurons and the external GRNs will also be discussed. Together, this study provides a foundation for further analysis of feeding-related internal sensory circuits and may offer insights into how external and internal sensory signals are integrated to regulate feeding behavior.

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Late-Breaking Poster

LBP079: E.04. Interoception

Location: SDCC Hall B

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Program #/Poster #: LBP079.11/LBP067

Topic: E.04. Interoception

Support: NIH Grant 1R01AT011676
NIH Grant 1R01HL169853-01

Title: Lung-innervating Vip+ vagal neurons control allergen-induced responses

Authors: *Z. ZHU[1], Y. SU[2], X. SUN[3];
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Abstract: Vagal sensory neurons innervating the lung control respiratory physiology and immunity, yet the subtypes mediating responses to specific inputs, i.e. allergen remain undefined. Here, we identify Vip^+ and $Tac1^+$ neurons as two vagal subsets with non-overlapping expression and divergent innervation profiles. Selective ablation of Vip^+, but not $Tac1^+$, neurons led to reduced airway hyperreactivity and type 2 cytokine expression, whereas chemogenetic activation of Vip^+ neurons led to elevated responses. Bulk RNA sequencing of vagal ganglia following allergen challenges revealed upregulation of *Ngfr*. *Ngfr* is enriched in Vip^+ neurons, and NGFR signaling is required for Vip^+-mediated airway hyperreactivity. Furthermore, Vip^+ neurons project to the nucleus of the solitary tract (nTS) in the brainstem, and unilateral genetic ablation reduced Fos^+ activation in the ipsilateral nTS. These findings specify a vagal population that bridges peripheral allergen sensing and central output, revealing a neuroimmune mechanism along the body-brain axis that contributes to asthma.

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Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.01/LBP068

Topic: E.05. Auditory and Vestibular Systems

Support: Korea Health Industry Development Institute (KHIDI)
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National Research Foundation of Korea RS-2024-00509145
Samsung Science & Technology Foundation SSTF-BA2101-11

Title: TMEM145 is an essential component of the stereociliary link structures in outer hair cells

Authors: *J. ROH;
Yonsei University College of Medicine, Seoul, Korea, Republic of

Abstract: Outer hair cells (OHCs) in the cochlea possess specialized stereociliary link structures that are indispensable for auditory function. These include horizontal top connectors (HTCs), which interconnect adjacent stereocilia, and tectorial membrane (TM)-attachment crowns (ACs), which anchor the tallest stereocilia to the TM. The previously identified molecular components of these structures, stereocilin, otogelin, otogelin-like, and tubby, lack transmembrane domains, implying the requirement for anchoring proteins. In this study, we identify TMEM145, a transmembrane protein containing a Golgi dynamics domain, as a critical component of OHC stereocilia. TMEM145 was expressed in both OHCs and spiral ganglion neurons, with specific localization to TM-ACs and HTCs in OHCs. *Tmem145* knockout (KO) mice exhibited profound hearing loss by three weeks of age, accompanied by a complete absence of distortion product otoacoustic emissions, indicative of OHC dysfunction. Immunostaining and scanning electron microscopy revealed that TM-ACs and HTCs were absent in *Tmem145* KO mice. In heterologous expression systems, TMEM145 interacted with stereocilin and tubby, promoting their extracellular secretion. Furthermore, TMEM145 expression was undetectable in S*tereocilin* KO and tubby mutant mice, suggesting interdependence among these proteins. Collectively, these findings establish TMEM145 as an essential membrane protein required for the structural integrity of OHC stereocilia and provide new insights into the molecular architecture of cochlear hair cells and their role in auditory function.

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Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.02/LBP069

Topic: E.05. Auditory and Vestibular Systems

Title: Prospective short-term observation for spontaneous recovery of sudden sensorineural hearing loss

Authors: *S.-J. OH;
Pusan National University, Busan, Korea, Republic of

Abstract: Importance A short-term (1-week) observation period may help identify patients with SSNHL who recover spontaneously without delaying treatment, thereby reducing unnecessary corticosteroid use and clarifying their therapeutic benefit in those without early improvement. Objective To determine the rate of spontaneous recovery within 1 week of onset and to evaluate the effect of corticosteroid treatment in patients without early recovery. Design, Setting, and Participants A prospective observational study conducted at a single tertiary referral center. Forty-four patients with SSNHL who presented within 3 days of onset were enrolled between September 2023 and December 2024. Exposure One-week observation from onset, followed by corticosteroid therapy only in patients with insufficient early recovery(No/slight improvement). Main Outcomes and Measures Pure-tone average (PTA), word recognition score (WRS) and hearing gain at 3 months. Logistic regression was used to identify predictors of spontaneous recovery. Results Among 41 patients who completed the 3-month follow-up, 13 (31.7%) showed complete or partial recovery after 1 week and were classified into the observation group. The remaining 28 patients (68.3%) received corticosteroid therapy. At the end of the observation period, the observation group showed significantly better PTA, WRS, and hearing gain than the treatment group (all $p < 0.001$). Initial PTA was the only significant predictor of spontaneous recovery, with a cutoff value of 71 dB. In the treatment group, PTA improved significantly from the end of observation to 3 months (mean change: 33.8 ± 23.9 dB, $p < 0.001$), and WRS improved by 63.9 ± 31.8%. Conclusions and Relevance Approximately one-third of patients with SSNHL recovered spontaneously within 1 week. Initial PTA was the strongest predictor of spontaneous recovery, with a threshold of 71 dB. Short-term observation without immediate corticosteroid treatment may be considered in patients with initial PTA better than 71 dB, provided that early improvement is observed. For patients with limited early recovery, corticosteroid therapy resulted in meaningful hearing improvement, comparable to outcomes reported in previous studies of immediate steroid treatment. This suggests that a 1-week observation period does not compromise the therapeutic efficacy of steroids.

Disclosures: S. Oh: None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.03/LBP070

Topic: E.05. Auditory and Vestibular Systems

Title: Analysis of auditory hair cell and gene expression changes induced by accumulation of nanoplastic particles in zebrafish models

Authors: *I. LEE;
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Abstract: Objectives: The aim of our study was to analyze the phenotypic changes in auditory hair cells and the alterations of gene expression levels by nano-plastic accumulation in zebrafish.**Methods**: (1) Zebrafish maintenance: Wild-type zebrafish adults and Brn3c: mGFP transgenic zebrafish were raised and maintained automatic circulation aquarium system following guide for the care and use of laboratory animals. Zebrafish embryos were collected from spawning adult zebrafish after 0.5hpf and cultured using E3-MB solution in incubators at 28±1°C. At 72hpf, the embryos were exposed to 0.1, 1, 10 μm non-functionalized polystyrene microbeads, which were in the form of aqueous suspensions in distilled water at a concentration of 2.5mg/mL.(2) Single cell RNA sequencing: We performed that zebrafish embryos treated with nanoplastic particles on day 5 were analyzed by single cell RNA sequencing. Based on this analysis, the clustered cell proportion was counted after clustering. In addition, representative genes of each clustered cell type were analyzed. (3) Differentially expressed genes (DEGs) analyzing: After conducting quality control on single-cell RNA sequencing data, cluster annotations were assigned based on known marker genes obtained from the public database ZFIN. Differential gene expression analysis was performed to identify genes with significant expression differences.**Results**: The survival rate of zebrafish exposed to 0.1, 1, and 10 μg/mL of polystyrene (PS) showed no significant differences. To investigate morphological changes during development, confocal imaging of hair cells was conducted, but no meaningful phenotypic alterations were observed in the nanoplastic-exposed group. Nevertheless, analysis of Differentially Expressed Genes (DEGs) revealed expression changes in genes related to hair cells. Genes such as *col1a1a, krt5* and *fgfbp2b* exhibited a significant increase in expression compared to the control group, while genes *rpl38* showed a significant decrease.**Conclusions**: Nanoplastic particle exposure caused changing genetic expression of hair cell in zebrafish at developmental stages. Further study is needed to investigate mechanism of hair cell damage. Further study is needed to gain a more comprehensive understanding of how each gene contributes to the onset of diseases through the accumulation of nanoplastics.

Disclosures: I. Lee: None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.04/LBP071

Topic: E.05. Auditory and Vestibular Systems

Support: NIA/NIDCD R01AG073157
VA RRDT IK2RX003271
VA RRDT I01RX005007

Title: Long-term effects of cumulative noise exposure in the vestibular periphery

Authors: M. ANDERSON[1], D. BAUER[1], S. POWERS[2], R. A. ALTSCHULER[3], *C. E. STEWART[4];

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Abstract: It has been established that noise exposure dose-dependently damages the inner ear and has the potential to cause hearing and vestibular loss as well as impaired mobility. We have previously demonstrated transient effects of a single 6-hour 110dB SPL noise exposure on hearing and vestibular function, assessed with auditory brainstem response (ABR) and vestibular short-latency evoked potential (VsEP). More recently, 3-hour broadband 110dB SPL noise exposures have been repeated every 2-weeks over an 8-week period (4 exposures total). Exposure to this paradigm caused increased balance beam crossing time that recovered within weeks after the final noise exposure. However, when visual information was not available, rats that appeared to recover from repeated noise exposure under normal vision conditions still crossed the balance beam more slowly. This suggests that when the vestibular periphery is damaged, sensory reweighting towards increased dependence on vision may occur. In the current study, we ask how this repeated noise exposure paradigm impacts the vestibular periphery of young adult rats (7-9 months of age), 1-month and 1-year after completion of the noise exposure series. VsEP was assessed in noise-exposed and age-matched control rats 1-month or 1-year after the final noise exposure, at 10 or 21-months of age, respectively. Ears were collected and immunostained for quantitative assessment of hair cells, calyceal terminals, and synaptic ribbons. Whole-mounted vestibular sensory epithelia were imaged using a Leica Stellaris 5 confocal microscope and quantified in Imaris 10.2. Repeated noise exposure reduced VsEP responses 1-month and 1-year after the final noise exposure and caused progressive vestibular damage. This suggests that short-term noise-induced damage persists and may worsen into middle and late-adulthood. The presence of these deficits, even 1-year after exposure to repeated noise, suggest that relatively small amounts of noise exposure, when repeated, persistently damage the vestibular periphery. These results highlight the importance of limiting noise exposures, even before measurable hearing or vestibular loss occurs.

Disclosures: M. Anderson: None. **D. Bauer:** None. **S. Powers:** None. **R.A. Altschuler:** None. **C.E. Stewart:** None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.05/LBP072

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01

Title: Enhancing EEG Signals in Chinchillas Through Data-Driven Artifact Removal

Authors: *A. MUKESH[1], M. PATRA[2], M. G. HEINZ[3];
[1]Purdue University, West Lafayette, IN; [2]Biomedical Engineering, Purdue University, West Lafayette, IN; [3]Speech, Language, Hearing Sciences and Biomedical Engineering, Perdue University, West Lafayette, IN

Abstract: Chinchillas are widely regarded as a valuable animal model for auditory neuroscience, owing to their broad hearing range, cochlear structure, and temporal processing capabilities that closely resemble those of humans. They offer critical insights into the neural basis of hearing loss and auditory scene analysis. However, most existing electrophysiological approaches in chinchillas rely on invasive techniques such as implanted electrodes or chronic craniotomies, which restrict repeatability, reduce animal welfare, and limit the feasibility of long-term studies. To address these limitations, our lab is developing a non-invasive scalp EEG platform for chinchillas using a custom-designed, reusable cap that enables high-quality recordings from awake animals. This system allows us to monitor auditory neural responses across multiple sessions with minimal disruption to natural behavior. However, performing non-invasive EEG in small animals introduces substantial preprocessing challenges, including high muscle noise, motion artifacts, and variable signal quality. To overcome these limitations, we are developing data-driven artifact identification techniques, drawing inspiration from established human EEG preprocessing workflows. In particular, we adapt techniques such as Independent Component Analysis (ICA) and extend them with information-theoretic scoring metrics, including mutual information, inter-trial consistency, and kurtosis, to better identify and suppress non-neural components. Importantly, we exploit the structure of our experiment by presenting the same auditory stimuli at different SNRs and across multiple repeats, which allows us to use the consistency of neural responses across conditions to help guide artifact removal in a stimulus-aware but unsupervised manner. Preliminary result shows that this approach progressively reduces noise and artifacts, particularly in low-SNR conditions where conventional methods often fail. By employing unsupervised methods to identify and remove the inconsistent components across multiple stimuli repeats and SNR, we observed that evoked responses such as event-related potentials become more consistently observable across trials. Our work demonstrates the feasibility of combining non-invasive EEG in animal models with data-driven artifact suppression methods adapted from human pipelines, contributing toward a scalable and ethically viable platform for auditory neuroscience.

Disclosures: A. Mukesh: None. **M. Patra:** None. **M.G. Heinz:** None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.06/LBP073

Topic: E.05. Auditory and Vestibular Systems

Title: An updated model of the functional organization of primate auditory areas on the STG

Authors: *X. SONG;
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Abstract: The classic model of the primate auditory cortex (Hackett & Kaas 2000, Kaas, 2011) proposed a three-tier functional hierarchy along the medial-lateral (or dorsal-ventral) axis, consisting of the core, belt, and parabelt areas, with tonotopic gradients only observed in a few subregions such as A1, R, RT, AL, and ML. Using our recently developed through-skull imaging technique, we performed functional mapping across the entire superior temporal gyrus (STG) in awake marmosets, including the classic auditory cortex and its adjacent regions extending rostrally to the temporal pole. The results reveal that: (1) Besides the major tonotopic gradient in A1 that spanning from the very low to the very high frequency ends of the hearing range of the species, there are another two gradients that also represent the entire frequency range, one locates from RT (low) to RPB (high), the other locates rostrally beyond the classical auditory cortex and near the temporal polar area. (2) Comparative responses across these three gradients resemble the medial-to-lateral three-tier functional hierarchy, supporting a progressive functional hierarchy from caudal to rostral regions; (3) Measurements of pitch-sensitive areas also support a hierarchical structure composed of at least two discrete functional modules along the caudal-to-rostral direction; (4) Measurements of conspecific vocalization-sensitive areas similarly support a vocal processing system consisting of at least three discrete functional modules from caudal to rostral; (5) Additional tests using natural sounds show that areas closer to the temporal pole tend to extract higher-order auditory information. Together, these findings support an updated model of the functional organization of the primate auditory areas along the STG, incorporating a progressive functional hierarchy with at least three levels along the caudal-to-rostral axis.

Disclosures: X. Song: None.

Late-Breaking Poster

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Topic: E.05. Auditory and Vestibular Systems

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MCIN/AEI PREP2023-148541OB
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JCYL SA218P23

Title: Cortical prediction errors signal the difference between internal predictions and unexpected input

Authors: *A. HOCKLEY[1,2,3,4,5], L. H. BOHÓRQUEZ[4,3,5], C. GALLIMORE[1,2], J. P. HAMM[1,2], M. S. MALMIERCA[4,3,5];

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Abstract: Neural processing of sensory stimuli is modulated by context. Predicted stimuli in regular patterns are modelled internally, suppressing responses. Responses to unexpected stimuli are increased in the form of prediction errors, which enhance the salience of, and guide attention toward, unpredictable stimuli. Predictive neural mechanisms and the informational content of prediction errors remain unclear, but hierarchically organized predictive circuits, both within cortical layers and between brain regions appear key. Theoretical models often frame prediction errors as a difference signal between prediction and input, but recent animal data show prediction errors in visual cortex instead as enhanced sensory responses. Here we study the information content and hierarchy of prediction errors by recording single neurons in the anesthetized rat and decoding between responses to different auditory oddball stimuli, with a focus on the inferior colliculus, primary auditory cortex (A1) and medial prefrontal cortex (n's = 186, 637 & 175, respectively). We show that neurons encode frequency and context hierarchically, with lower sensory processing regions encoding frequency and higher-order areas encoding context. A1 neurons weakly encoded frequency but strongly encode predictability context as prediction errors. A cascade paradigm revealed that A1 neurons encode the direction of frequency change. Most strikingly, when presenting a fixed deviant and variable standard paradigm we found greater prediction errors when there was a larger difference between the regular stimuli and unexpected stimulus, both for ascending (+1 vs +0.5 oct; 30.1% larger) and descending (-1 vs -0.5 oct; 16.4% larger) stimuli, a result replicated in visual cortex. These data reveal that cortical neurons compute prediction errors as a difference signal between prediction and sensory input and provide neurophysiological evidence for predictive coding theories.

Disclosures: A. Hockley: None. **L.H. Bohórquez:** None. **C. Gallimore:** None. **J.P. Hamm:** None. **M.S. Malmierca:** None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

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Program #/Poster #: LBP080.08/LBP075

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01 MH131684

Title: Characterizing and mitigating auditory confounds in transcranial ultrasound stimulation

Authors: *N.-F. CHEN[1], J. R. BROWN[1], M. MOHAMMADJAVADI[1], B. KOP[1], R. T. ASH[2], G. POPELKA[1,3], K. BUTTS PAULY[1];
[1]Department of Radiology, Stanford University, Stanford, CA; [2]Department of Psychiatry and

Behavioral Sciences, University of California San Francisco, San Francissco, CA; [3]Department of Otolaryngology, Stanford University, Stanford, CA

Abstract: Transcranial ultrasound stimulation (TUS) is an emerging technique for non-invasive neuromodulation, but its interpretation is often confounded by unintended auditory perception that can obscure experimental outcomes and limit reproducibility. To address this challenge, we systematically measured airborne and TUS-induced auditory thresholds, identified the principal conduction pathway, and validated a practical mitigation strategy. We enrolled 23 healthy participants (mean age: 25.73 ± 1.11 years; 12 females) with normal hearing (airborne thresholds ≤25 dB HL, 0.5-16 kHz). Both airborne and TUS auditory thresholds were determined using a two-alternative forced-choice adaptive staircase, with the median of three runs defining the final threshold for each pulse repetition frequency (PRF). A 500 kHz TUS transducer (40 mm focal depth) positioned at FCz delivered 200 ms amplitude-modulated pulse trains (0.125-16 kHz PRF) while participants were fitted with calibrated circumaural earphones to attenuate airborne sound from the TUS transducer. Results revealed U-shaped audiograms for both airborne thresholds (maximal sensitivity at 2 kHz, 9.45 ± 0.96 dB SPL) and TUS thresholds (maximal sensitivity at 2 kHz, -5.72 ± 2.30 dB re 1mW/cm^2) with elevated thresholds for lower and higher frequencies. To investigate the TUS conduction pathway, an acoustic absorbing pad was placed between the TUS transducer and the scalp to attenuate bone conduction transmission in a subset of 19 participants. This resulted in elevated TUS auditory thresholds across all PRFs (all *p*s < 0.05), with an average elevation of approximately 10 dB, indicating bone conduction transmission as the primary audio pathway for TUS. Further, applying Tukey ramps to the sonication pulses significantly reduced audibility at PRFs below 0.5 kHz compared to unramped sonications. In the ramping experiment, peak intensities were maintained at constant levels (maximum I_{sppa} = 67.32 W/cm^2) while duty cycles of unramped pulses were reduced to equalize total integrated energy between ramped and unramped conditions, suggesting that pulse envelope ramping effectively reduces audibility. These findings quantify TUS-induced auditory percepts, identify that TUS reaches the auditory system primarily by bone conduction, and validate signal ramping as an effective mitigation strategy for auditory confounds. This work establishes a framework for designing and interpreting TUS experiments, underscoring that controlling auditory co-stimulation is critical for rigorous application of TUS in both research and therapeutic contexts.

Disclosures: N. Chen: None. **J.R. Brown:** None. **M. Mohammadjavadi:** None. **B. Kop:** None. **R.T. Ash:** None. **G. Popelka:** None. **K. Butts Pauly:** None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.09/LBP076

Topic: E.05. Auditory and Vestibular Systems

Support: NSF grant 2219521

Title: Neural correlates of statistically-driven auditory selective attention

Authors: *A. R. NIDIFFER, E. C. LALOR;
University of Rochester, Rochester, NY

Abstract: Selectively listening to acoustic signals is crucial in acoustically complex environments. Traditionally, attention is understood as an interplay between goal-directed top-down modulation and bottom-up stimulus salience. However, attention can also be guided by the observer's prior expectations. A potentially important driver of such expectations is the presence of statistical regularities in the acoustic environment. Temporal statistical regularities encountered as syllabic transitional probabilities have long been shown to affect perception and learning. Notably, acoustic regularities can affect performance and learning even if they occur along a dimension that is irrelevant for the task at hand. The venerable 'probe signal' psychoacoustic paradigm has shown that listeners asked to detect pure tones in noise will show markedly different perceptual thresholds for tone frequencies whose probability of occurrence differs - even though tone frequency is task-irrelevant. The listener's expectation - based on the global probability of each tone frequency - can dramatically affect low-level perception. While this may suggest an exaggerated response to the expected signal, error-based accounts predict the opposite pattern: enhancement of unexpected, rarely occurring stimuli. Here, we present preliminary data from a human EEG experiment that asks how cortical electrical responses are modulated when tone-in-noise detection is changed by learning about the probability structure of a task-irrelevant auditory dimension. We use a simple go/no-go task, in which listeners are asked to detect a single tone in noise, presented at their detection threshold. These tones are presented at two different but neighboring frequencies, one highly probable and the other rarely occurring. Simultaneously, we acquire behavioral data from a large number of subjects in an online experiment to ensure that the effects of stimulus statistics on perception are robust. Importantly, our task is one that can be performed without overt verbal instruction, such that non-human animals can learn it. This allows us to investigate the question of statistically-driven selective attention across multiple levels of neural and behavioral explanation.

Disclosures: A.R. Nidiffer: None. **E.C. Lalor:** None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.10/LBP077

Topic: E.05. Auditory and Vestibular Systems

Support: MVLS/EPSRC Studentship

Title: A resting-state fMRI analysis into the neural correlates of cybersickness.

Authors: *N. SNEDDON[1], Y. HUANG[1], G. LI[2], S. BREWSTER[1], F. E. POLLICK[1];
[1]University of Glasgow, Glasgow, United Kingdom; [2]University of Bath, Bath, United Kingdom

Abstract: Cybersickness, a prominent barrier to virtual reality use (VR), is often thought to arise due to impaired sensory inhibition during visuo-vestibular conflicts. The insula - critical for interoception, affect-regulation, and multisensory integration - has been consistently implicated in motion-related sickness onset and severity. Behavioural factors including interoceptive awareness and anxiety also influence susceptibility to cybersickness. Despite this, the neural and behavioural factors underlying cybersickness susceptibility remain understudied. We conducted a resting-state functional magnetic resonance imaging (fMRI) study measuring posterior and anterior insula connectivity patterns before and after cybersickness induction with a VR tunnel-travel task. Participants completed two resting-state fMRI scans (each lasting 12 minutes): one before and one after induction. The sample included motion sickness-susceptible participants (*N = 16; 9 female*) and motion sickness-resistant participants (*N = 8; 4 female*), with gender counterbalanced across groups. Current anxiety scores were measured before and after cybersickness induction and trait interoceptive awareness was measured at the end of the study. Group-level analyses revealed significant differences in posterior insula connectivity patterns between resistant and susceptible participants ($p < .001$ *uncorrected;* $q < .05$, *FDR corrected*). Pre-cybersickness induction, resistant participants showed increased connectivity with the bilateral cerebellum. Following cybersickness induction, susceptible participants showed increased connectivity with the frontal gyrus, whereas resistant participants showed increased connectivity with the temporal pole and parahippocampal gyrus. Within-group contrasts (Pre>Post) indicated that susceptible participants displayed decreased anterior insula connectivity with the supramarginal gyrus and lateral occipital cortex. Analysis of the behavioural data using an aligned rank transformation (ART) ANOVA on anxiety scores showed significant main effects of Time ($F(1,22) = 14.46$, $p < .001$) and Group ($F(1,22) = 11.12$, $p = .003$). A linear model further revealed group differences in interoceptive self-regulation ($p = .009$) and trusting ($p = .007$). Data collection is ongoing but preliminary analyses suggest that cybersickness susceptibility involves heightened anxiety and altered interoceptive processing, underpinned by distinct insular functional connectivity patterns. This study supports the insula's central role in cybersickness and provides a potential neural target for future interventions.

Disclosures: N. Sneddon: None. **Y. Huang:** None. **G. Li:** None. **S. Brewster:** None. **F.E. Pollick:** None.

Late-Breaking Poster

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Program #/Poster #: LBP080.11/LBP078

Topic: E.05. Auditory and Vestibular Systems

Support: JST CREST JPMJCR22P5

Title: Humans overestimate downward pitch angles: asymmetry in subjective pitch angle estimation

Authors: *T. HIRATA[1], N. KAWAI[1,2];
[1]Nagoya University, Nagoya, Japan; [2]Academy of Emerging Sciences, Chubu University, Kasugai, Japan

Abstract: Vestibular cues provide information about three-dimensional head angular velocity from the semicircular canals and translational acceleration from the otolith organs. This information is crucial for estimating self-motion, and the perception of self-motion appears consistent during forward and backward tilts and accelerations. However, we found that people overestimate the subjective tilt angle during downward pitch compared to upward pitch. In the experiment, nine participants wore a head-mounted display while seated in a chair that tilted 15° upward and downward and experienced five different frequencies (0.09, 0.11, 0.15, 0.23, and 0.42 Hz) of sinusoidal pitch rotation. At each frequency, the chair tilted to a maximum of 15° upward or downward. Each pitch condition was presented in three cycles, repeated four times in random order. Thus, participants experienced a total of 20 pitch trials. After each pitch rotation, participants used a controller to report their subjective maximum upward or downward pitch angle. The results showed that subjective pitch angle estimation was unaffected by pitch rotation frequency. However, downward pitch angles were overestimated more than upward pitch angles, whereas upward pitch angles showed relatively minor errors. This fact suggests that additional information processing may occur, such as frequent experience with backward sway (e.g., when sitting down or lying on a bed), or in accordance with somatosensory information. We also recorded eye movements during pitch rotation to evaluate vestibulo-ocular reflex (VOR). The VOR gain, defined as the ratio of eye to head angular velocity, is known to reflect head rotation estimated from vestibular cues (Merfeld et al., 1999). Thus, if the VOR gain shows asymmetry in upward and downward pitch, the cause of the overestimated pitch angle might be due to properties of the vestibular system. We found that the VOR gain did not differ significantly between upward and downward pitch. On the other hand, subjective pitch estimation errors increased as a function of the VOR gain, irrespective of direction, indicating that the VOR gain reflects the uncertainty of head rotation estimates derived from vestibular cues rather than experience-based bias. Our findings clarify that self-pitch perception is not solely determined by vestibular cues, but is also influenced by prior experience and/or somatosensory information.

Disclosures: T. Hirata: None. **N. Kawai:** None.

Late-Breaking Poster

LBP080: E.05. Auditory and Vestibular Systems

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP080.12/LBP079

Topic: E.05. Auditory and Vestibular Systems

Support: MURI N00014-20-1-2163

Title: Mild Hypoxia Significantly Worsens Vestibular Performance.

Authors: *K. KAINEC[1,2], J. G. OAS[3], K. PETTIJOHN[4], C. COX[5], M. TEAFORD[6], D. M. MERFELD[7];
[1]Otolaryngology, The Ohio State University, Beavercreek, OH; [2]Acceleration and Sensory Sciences, The Naval Medical Research Unit - Dayton, Dayton, OH; [3]Oak Ridge Institute for Science and Education, Oak Ridge, TN; [4]Acceleration and Sensory Sciences, The Naval Medical Research Unit - Dayton, Beavercreek, OH; [5]Acceleration and Sensory Sciences, The Naval Medical Research Unit - Dayton, Springfield, OH; [6]Department of Psychology, University of Tennessee at Chattanooga, Chattanooga, TN; [7]Otolaryngology - Head & Neck, The Ohio State University, Columbus, OH

Abstract: Hypoxia from breathing air at altitudes greater than 10,000ft has been reliably demonstrated to diminish sensory, muscular, and cognitive function. Several lines of evidence—including early symptoms of hypoxia, and high metabolic demands of the vestibular system—suggest that behaviors mediated by vestibular function, like balance and the perception of self-motion, are more susceptible to hypoxia-related detriments than those of other sensory systems. However, there is a critical lack of studies examining vestibular performance at altitudes lower than 10,000ft. Here, vestibular performance was examined in 23 healthy participants and 5 participants with unilateral hypofunction at 0ft and again across 7 normobaric altitudes ranging from 4000-17500ft. To quantify vestibular function, the smallest magnitude of motions that patients could reliably sense was tested using established methods for quantifying vestibular perceptual thresholds for earth-vertical (upward/downward) translations using 1Hz single cycles of sinusoidal acceleration. To simulate effects of hypoxic exposure, participants breathed air with the partial pressure of oxygen reduced to levels that simulated 0-17500ft altitudes at normobaric pressure. To quantify hypoxia-related physiological changes, SpO_2 and pulse rate were recorded using fingertip pulse oximetry. Lastly, linear mixed-effect models were used to examine the effects of test, condition, and whether decreases in SpO_2 could predict worsened Z-translation thresholds. As intended, SpO_2 decreased by about 1.5% at 4000ft ($p = .07$), and decreased significantly more as altitude increased, reaching a 21% decrease at 17500ft ($p < .01$). Concurrently, pulse rate increased by 3.5 bpm at 4000ft ($p= .04$) reaching a 15-bpm increase at 17500ft ($p < .01$). In healthy participants, perceptual thresholds for up and down motions did not significantly worsen at 4000ft ($\beta = .03$cm/s, $p = .94$) nor 6000ft ($\beta = .22$cm/s, $p = .66$), but there was marginal evidence detriments started at 8000ft ($\beta = .42$cm/s, $p = .09$) and got worse as altitude increased to 17500ft ($\beta = 1$cm/s, $p < .01$). Further, reductions in SpO_2 significantly predicted worsened thresholds ($\beta = .04$cm/s, $t(21.77) = -2.26$, $p = .03$). In participants with unilateral hypofunction, thresholds significantly worsened by 2.3cm/s at 4000ft ($p<.01$), 1.4cm/s at 6000ft ($p = .03$), and 3.0cm/s at 8000ft ($p < .01$). Reductions in SpO_2 again predicted large threshold detriments ($\beta = -.66$cm/s, $t(73.36) = -2.83$, $p < .01$). These results suggest that caution may be warranted when breathing air with reduced oxygen while performing behaviors that require accurate spatial orientation.

Disclosures: K. Kainec: None. **J.G. Oas:** None. **K. Pettijohn:** None. **C. Cox:** None. **M. Teaford:** None. **D.M. Merfeld:** None.

Late-Breaking Poster

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Program #/Poster #: LBP080.13/LBP080

Topic: E.05. Auditory and Vestibular Systems

Support: JST CREST / JPMJCR22P5

Title: Vestibular sensory information alters perception of the horizon: Reclining postures bring the horizon closer to the observer.

Authors: *T. KAYUKAWA[1], N. KAWAI[1,2];
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Abstract: Even when lying down to watch television, the screen does not appear tilted. Visual perception typically dominates other sensory experiences, with only a few documented instances where other senses, such as auditory or tactile, influence visual perception. In this study, we demonstrated that vestibular sensory information alters the perception of a horizontal bar. Participants utilized a head-mounted display (VIVE Pro Eye, HTC VIVE) while seated on a motion platform (Yaw3, Yaw, VR) capable of tilting 15° forward and 45° backward, controlled by a computer. The chair then oscillated slowly and stopped at one of the following angles from vertical: 0° (vertical), 5°, 15°, 30°, and 45°. Thirty participants were instructed to adjust a bar extending toward them in a gray virtual reality environment with reduced visual cues to appear horizontal relative to the floor. Participants completed 35 trials (five pitch angle conditions × seven initial rod angles: 0°, ±10°, ±20°, ±30°) in random order. Regardless of the initial rod angle, increased body reclination resulted in a greater deviation of their judgment of the bar's horizontal alignment from the true horizontal. A repeated-measures ANOVA (MATLAB R2024a) revealed significant main effects of body pitch angle [$F(1.24, 35.87) = 6.82$, $p = .009$, partial eta squared (ηp^2) = .191] and initial rod angle [$F(4.16, 120.73) = 11.74$, $p < .001$, partial eta squared (ηp^2) = .288], as well as a significant interaction [$F(8.64, 250.49) = 2.28$, $p = .020$, partial eta squared (ηp^2) = .073]. For the first time, we demonstrated that a rearward-leaning posture alters the perceived slope of the horizon. These results suggest that vestibular cues influence the perception of visual horizontality. The distortion of visual judgment by vestibular information may underlie spatial disorientation, a leading cause of aircraft accidents. This finding provides new insights into human spatial disorientation.

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Late-Breaking Poster

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Topic: E.06. Vision

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Title: Intrinsically photosensitive midget ganglion cells in primate retina

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Abstract: High acuity vision in primates is relayed to the brain by midget (MG) retinal ganglion cell (RGCs) axonal projections to the parvocellular region of the lateral geniculate nucleus (PMID: 3980768; 8254378; 7268423). In mice, a subtype of intrinsically photosensitive retinal ganglion cell (ipRGC), the M4 (ONs-α RGC), enhance image-forming vision due to the presence of melanopsin, which increases contrast sensitivity (PMID: 30017393). However, in primate, melanopsin has not been detected in MG RGCs—which account for over 80% of RGCs. We combined immunohistochemistry for RGC markers (RBPMS and melanopsin) with fluorescence in situ hybridization (FISH) in flat-mount retina to identify ipRGC types in non-human primate (NHP). We recorded from NHP RGCs using single-cell electrophysiology and high-density multielectrode arrays (HD-MEA) to characterize the functional properties of RGCs. After recording, the spatial locations of RGCs were mapped using FISH to pair MEA functional data with cell type identity. IpRGCs expressed high levels of *OPN4* mRNA and were sparsely distributed throughout the ganglion cell layer. Surprisingly, we find that *OPN4* mRNA is also expressed in high-density midget ganglion cells—confirmed by their co-expression of *TBR1* or *TPBG* mRNA. *OPN4* was not detected in putative parasol ganglion cells. Further, midget ganglion cells, but not parasol ganglion cells, express *EOMES* mRNA, a transcription factor which defines ipRGC identity. Cell-attached electrophysiology recordings were used to probe for MG intrinsic photosensitivity. Activation of putative melanopsin protein with blue light increased MG baseline spike rate at photopic light intensities, indicating that melanopsin can modulate image-forming vision at the level of the retina. Using MEA recordings, we identified groups of ipRGCs with differing sensitivity and response kinetics to blue light. RGCs responding to higher light intensity, with faster response kinetics, were present in higher density and many aligned with *TPBG*+ or *TBR1*+ MG RGCs. Our results: 1) support the presence of *OPN4* mRNA expression by MGs in single-cell RNA sequencing studies (PMID: 30712875), 2) provide additional evidence that MGs express transcription factors associated with ipRGC lineage

(PMID: 35191836), 3) demonstrate primate image forming vision is directly modulated by melanopsin phototransduction in the retina.

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Support: NSF CAREER 2047298
NIH F32 EY032776

Title: Local versus global rules of stimulus competition in the superior colliculus

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Abstract: Selective spatial attention is our ability to select the most important stimulus in space while ignoring distracting stimuli. Essential for this executive function are competitive interactions among the stimuli in the sensory field. Such interactions aid comparison of the salience of stimuli across spatial locations, identification of the most salient stimulus, and suppression of the representation of the 'other' less salient ones. The topographically organized intermediate and deep layers of the midbrain superior colliculus, SCid, are known to implement competitive interactions that are essential for selective spatial attention. Here, using the mouse SCid as the neural substrate, we investigated the largely unknown properties of these competitive interactions across space using extracellular electrophysiology. First, we characterized the spatial receptive fields (RFs) of SCid neurons, which consist of an excitatory center and a classical inhibitory surround that extends beyond the excitatory center, but which is spatially restricted with inhibition that decreases with distance from the RF center. We found that stimulus interactions between one visual stimulus centered in the RF (S1) and another located at an offset location also inside the RF (S2) follow a sub-additive rule. Second, and in contrast, when S2 was moved outside the RF, we found an extra-classical inhibitory surround that is global, extending far beyond the reaches of the classical surround. Specifically, we found that stimulus interactions with S1 centered in the RF and S2 located outside the RF follow a divisive rule. Strikingly, the suppression of S1's responses by S2 is constant in magnitude, independent of S2's location in space or its distance from the RF center. Preliminary modeling indicates that a single pool of inhibitory neurons cannot account for both the space-varying local (within RF) inhibition, and space-invariant global (outside RF) competitive inhibition, Together, these results predict the existence of two separate inhibitory circuits with distinct regimes of operation across the SCid

space map. Our findings offer insights into the mechanistic logic of stimulus interactions in SCid, which critically underlie spatial decision-making in mammals.

Disclosures: N.B. Kothari: None. **A. Banerjee:** None. **S.P. Mysore:** None.

Late-Breaking Poster

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Support: NSF CAREER 2047298
NIH R34NS111653

Title: Parvalbumin-positive inhibitory neurons in the intermediate layers of the mouse superior colliculus mediate divisive gain control

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Abstract: The intermediate and deep layers of the superior colliculus (SCid) are central to visually guided behaviors such as spatial attention, decision-making, perceptual categorization, multisensory integration, and orienting. Intrinsic GABAergic inhibition is known to play a key role in shaping these processes, yet the specific contributions of molecularly defined interneuron subtypes remain unknown, possibly due to the technical difficulty of measuring cell-type-specific responses in the SCid compared to the superficial layers. Here, we addressed this challenge by combining GRIN-lens-based endoscopic calcium imaging with optogenetics to record and manipulate defined neuronal populations in vivo. Using this approach, we demonstrated that parvalbumin-expressing (PV+) neurons in the intermediate SC inhibit visual responses of the local excitatory CaMKII+ neurons. Specifically, PV+ neurons control the response gain of the excitatory neurons with minimal effects on their selectivity to different stimulus properties. Moreover, PV+ neurons themselves exhibit sharp spatial tuning profiles and robust responses to a range of expansion speeds and motion directions of stimuli. Together, these findings report a methodological advance in the study of the intermediate/deep layers of the SC, identify PV+ interneurons as key modulators of visual processing in the intermediate SC, and reveal conserved strategies for inhibitory gain control across cortical and subcortical visual structures.

Disclosures: A. Banerjee: None. **S.P. Mysore:** None.

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Topic: E.06. Vision

Support: NS132288

Title: Neural activity differences in primary and secondary visual thalamus during visual perception and attention

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Abstract: Selective visual attention depends on multiple cortical and subcortical areas. Attentional modulation of visual neural activity has been thoroughly examined in higher order cortical areas of monkeys, but less so in higher order thalamic areas. Studies suggest that attention only weakly modulates responses in the lateral geniculate nucleus (LGN), while the higher-order pulvinar, which is more strongly interconnected with higher-order cortical areas, shows robust modulation during spatial attention. It is not known if these observations provide general organizing principles for neural activity in primary and higher order thalamus supporting perception and attention across mammals. Here, we performed Neuropixels recordings from the mouse dorsal LGN (dLGN) or the lateral posterior (LP) nucleus of the thalamus, the rodent analogue of the primate pulvinar, while they performed a psychometric visual attention task (Speed et al., 2020). Head-fixed water-restricted mice (N = 9) were trained to detect static gratings (20° wide) at one of two spatial locations. The gratings appear randomly in time, but in a single fixed location for a block of consecutive trials. Then, without warning, the grating appears in the other location for a block of consecutive trials. This spatial alternation elicits classic behavioral signatures of attention. At the same time, task-irrelevant bars (5% contrast) appeared randomly throughout the visual field, in order to map neural receptive field responses while attention is elicited at either spatial location. We found several differences in neural activity modulation in primary versus secondary visual thalamus. First, as expected, we found robust LGN spiking driven by the gratings, but responses were indistinguishable on successful versus failed detection trials (N = 7 mice, n = 14 days). In contrast, LP neurons showed greater responses on successful detection trials compared to failures (N = 6 mice, n = 17 days). Next, we examined how spatial attention modulates neural receptive field responses in LGN and LP. In LGN, attentional modulation of receptive field responses was minimal, whereas in LP receptive field responses were significantly more modulated, consistent with the greater modulation by trial outcome. Preliminary evidence also suggests that retinotopy plays a role in the degree of modulation by behavioral task variables. Taken together, our findings reveal that in mice performing a challenging psychometric spatial attention task, LP shows greater behavioral and

attentional modulation than LGN, highlighting distinct contributions of primary versus higher-order thalamic processing to visual behavior.

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Medical Faculty at the University of Bonn

Title: Terminal-specific corticothalamic feedback suppression in dLGN modulates V1 visual responses

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Abstract: Relay cells in the dorsolateral geniculate nucleus (dLGN) of the thalamus receive ~30% of their synaptic inputs from corticothalamic (CT) neurons in layer 6 (L6) of primary visual cortex (V1) (Sherman & Guillery, 2002). While effects of L6CT feedback on thalamic responses have been a topic of intense investigation, how CT feedback in turn shapes visual processing in V1 itself - the major target of dLGN relay cells - remains unknown. To assess the impact of CT feedback on V1 responses, we combined synaptic terminal-specific optogenetic suppression of L6CT axon terminals in thalamus with in vitro and in vivo electrophysiology. In Ntsr1-Cre mice, we expressed the GPCR-based inhibitory opsin eOPN3 (Mahn et al., 2021) selectively in L6CT neurons, enabling prolonged, light-triggered suppression of synaptic release at L6CT thalamic terminals without perturbing the direct influence of L6 neurons within cortex. We first used in vitro patch-clamp recordings to confirm the efficacy of terminal suppression. At baseline, electrical stimulation of L6CT axons evoked robust EPSCs in dLGN neurons. After photosuppression of L6CT terminals, we found that dLGN EPSC amplitudes were reduced and their coefficient of variation was increased, validating robust eOPN3-mediated inhibition. We next performed in vivo Neuropixels recordings V1 in head-fixed mice exposed to visual stimuli. We found that L6CT terminal suppression in thalamus (30 s light every 3 min) reduced stimulus-driven firing rates of V1 neurons during measurements of direction tuning, without affecting tuning width. Similarly, under L6CT terminal suppression, naturalistic movie presentations (5 s)

evoked weaker V1 responses. These effects indicate that V1, through CT feedback, contributes to its own gain of tuning and stimulus-driven excitability. We conclude that selective suppression of L6CT terminals in thalamus shapes V1 responses to both artificial and naturalistic visual stimuli, highlighting the critical role of CT feedback in shaping thalamocortical information flow.

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Title: Synchronous spiking in the corticothalamic circuit

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Abstract: Responses of neurons in sensory areas are variable. Understanding how this variability is correlated between neurons both within and across brain areas, and as a function of the relative tuning properties of these neurons, has vast implications for the study of sensory coding. We have previously shown that in primary visual cortex (V1), correlated activity at specific timescales across the neocortical population causes variable spiking responses in neurons within the neocortical circuit [1]. Here we ask whether the correlated activity, or synchrony, in the neocortex is inherited from thalamic inputs or emerges *de novo* in the neocortical circuit. We explore the physiological basis for cortical correlated activity by recording simultaneously from populations of neurons in the lateral geniculate nucleus (LGN) of the thalamus and its target, V1. To compare the synchrony in the LGN and V1, we recorded the spiking responses of tens of neurons simultaneously with neuropixels probes in the LGN of awake mice. We find synchrony is present in LGN, but is weaker than in V1. We separated LGN spikes fired in the burst versus tonic modes and found that spikes fired in the burst mode were more synchronous than tonic spikes. Synchronous spiking could exist independently for the LGN and V1, or be correlated across brain regions. From our simultaneous recordings we find that synchrony is shared between LGN and V1, and the strength of this synchrony depends on the receptive field similarity of neurons in each region. LGN and V1 are tightly coupled in a bidirectional circuit. Synchrony in V1 could be inherited from LGN projections. In addition, V1 may drive synchrony in LGN through corticothalamic projections. To determine whether

corticothalamic feedback contributes to LGN synchrony, we suppressed V1 excitatory activity by stimulating parvalbumin-positive interneurons optogenetically, and uncovered a profound reduction in the magnitude and timescale of LGN synchrony, and a suppression of LGN bursts. Our results indicate that corticothalamic drive critically sculpts LGN synchronous activity. By recording simultaneously from LGN and V1 populations, we have shown that synchronous spiking activity is shared across these regions, with strength depending on tuning similarity. Synchrony in the visual pathway does not emerge in an exclusively feedforward manner, as silencing corticothalamic projections reduces the strength of LGN synchrony. Our results inform an understanding of the physiological basis for variable neural responses by showing how synchronous activity is shared across visual areas in the awake mouse. References 1. Pattadkal et al., 2024, *bioRxiv*, 2024.10.15.618398.

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Support: NEI R01EY033950

Title: Top-down inputs show context-selective synchronization with V1 spiking following focal N-methyl-D-aspartate receptor blockade

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Abstract: Basic sensory processing deficits are a core feature of psychosis-related psychopathologies, such as schizophrenia. Among the most reliable is that of a pre-attentive, unconscious brain response termed the "mismatch negativity" (MMN) signal—an event-related potential that is enhanced when environmental regularities, such as a repeated sight or sound, are violated. MMN has been linked to impaired N-methyl-D-aspartate receptor (NMDAR) functioning in humans, as well as “analogous deviance detection” (DD) responses in rodents, and primates, implicating deficient excitatory neurotransmission as one major axis of dysfunction. Mice have provided a powerful model system to tease out the cell and circuit roles of NMDARs in predictive processing, with some studies showing increases in top-down suppressive axonal input to lower sensory areas, yet aspects of its influence during real-time sensory processing have remained unclear. Here, we sought to address this by measuring extracellular potentials (16-channel multielectrode probes) in the V1 and ACa of mice (n=10) during visual oddball sequences of full-field oriented square-wave grating stimuli (redundant, p=.9; deviant, p=.1) both

before and after V1 NMDAR block via local application of MK-801. We show that multiunit spiking activity (MUA) in infragranular layer 5 showed the greatest context-selective reductions during perception of both predictable and deviant stimuli. With respect to oddball versus control trials, the magnitude of MUA was significantly more modulated by the theta phase of frontal local field potentials from the anterior cingulate area (ACa; n=6). These data concord with past work demonstrating a suppressive input onto V1 from the ACa, potentially suggesting a bias of perceptual circuits towards internally-generated models when bottom-up signaling is disrupted.

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Title: Simultaneous functional and transcriptomic profiling of interneurons in mouse visual cortex

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Abstract: Understanding how transcriptomic cell identity relates to the functional response properties of interneurons in visual cortex will advance our knowledge of cortical circuit organization. Studies using Cre driver lines and GCaMP reporter lines to drive expression in interneuron subpopulations have revealed functional differences between subclasses. For instance, it has been observed that vasoactive intestinal peptide (VIP) and somatostatin (SST) expressing neurons show complementary contrast tuning, with VIP neurons responding preferentially to low- and SST neurons responding preferentially to high-contrast stimuli. These methods, however, cannot simultaneously measure transcriptomic and functional response properties across multiple cell types in individual animals. Because the internal and behavioral state of animals can influence the activity of these neurons, measuring their functional properties in different animals at different times is an unavoidable confound in current transgenic approaches. To address this, we developed a protocol that combines in vivo 2-photon calcium imaging with ex vivo spatial transcriptomics imaging in mouse primary visual cortex. During in vivo imaging, adult mice (n=6, 3 male/3 female, P147-P234) were presented with visual stimuli to measure tuning properties of inhibitory interneurons in V1. Spatial transcriptomics imaging was performed on 20 serial sections (20µm thick) of the same tissue via 10x Genomics Xenium

using a 299-gene panel targeting cell-type markers and GFP/Cre constructs. The spatial transcriptomics experiment outputs and the optical physiology image stacks were aligned in a common 3-D space, allowing for direct mapping of corresponding cells from one modality to the other (approximately 300 neurons analyzed per 2mm x 2mm x 20µm volume). We first recapitulated prior results, establishing a pattern of complementary tuning between VIP and SST neurons that is consistent with existing findings. Unlike previous studies, we were able to observe diverse tuning properties within parvalbumin (Pvalb) and lysosomal-associated membrane protein family member 5 (Lamp5) cell subclasses. Evidence suggests a correlation between supertypes and functional responses. All these cell types were identified and characterized within individual animals, overcoming a limitation of transgenic approaches that cannot simultaneously record from multiple cell types. This study provides an approach for relating transcriptomic identity with functional response properties across all interneuron subtypes in a single animal at once, enabling us to examine how these subpopulations interact.

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Title: Visual evoked neuronal entrainment to 3-6 Hz oscillations in the primary visual cortex may coordinate precise temporal sequences that encode stimulus information

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Abstract: Introduction: In mice, simple visual stimuli evoke 3-6 Hz traveling waves of neural activity that percolate across the cerebral cortex. After visual stimuli, some neurons become entrained to 3-6 Hz oscillations, particularly in the primary visual cortex (V1). Visual evoked traveling waves and neuronal entrainment are curtailed when mice are presented with visual stimuli while they are anesthetized by isoflurane. Theoretically, the coordination of neuronal firing by traveling waves could offer advantages for encoding stimuli during wakefulness. We sought to determine whether neuronal entrainment plays a role in organizing precise temporal sequences of neural activity that encode visual stimulus information. Methods: Neural activity

was recorded from the primary visual cortex (V1) and the posterior parietal area (PPA) while mice were shown static gratings of different orientations. Stimuli were presented when mice were awake and when they were anesthetized with isoflurane. To quantify differences in precise temporal sequences of activity, we computed dissimilarities between multi-neuronal firing patterns using Earth Movers Distance (the "SpikeShip" method, Sotomayor-Gómez et al (2023)). To evaluate neuronal entrainment, we calculated whether the probability of a neuron firing after the stimulus depended on the phase of the 3-6 Hz filtered current source density (CSD) at the channel closest to that neuron. Random shuffling of trials or Poisson neuron surrogates were used to generate null distributions for statistics. This project asks novel questions and applies new analysis methods to neural data previously described in Aggarwal et al (2022) and Aggarwal et al (2024).Results: In awake mice, temporal firing sequences evoked by static gratings discriminated between gratings of different orientations ($p<.01$). Discriminability was driven by neurons in V1, and discriminability was greater for entrained neurons than for unentrained neurons. Under isoflurane anesthesia, the discriminability of temporal sequences was disrupted. Conclusions: These results suggest that during wakefulness, neuronal entrainment to visual evoked oscillations may play a role in coordinating temporal sequences in V1 that encode stimulus information.

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Title: Coordination of visual and olfactory active sensing behaviors in freely moving mice

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Abstract: As animals explore the world around them, they use all of their senses to orient themselves, perform complex behaviors, and interact with their environment. The synchronization of sensory inputs across modalities, including olfaction and vision, is essential for executing such natural behaviors, yet little is known as to how this coordination occurs. Previous work has established that head and eye movements in the mouse are synchronized during free movement and facilitate visual processing. Additionally, synchronization of head movements to other active sensing behaviors like whisking and breathing have been demonstrated. Here, we aimed to understand if and how visual and olfactory active sampling

behaviors are synchronized in freely moving and behaving mice. To test this, wild-type C57BL mice were implanted with thermistors in the nasal cavity to measure respiration, and an eye camera, inertial measurement unit (IMU), and world camera were mounted to the head to record eye and head movements and view the mouse's visual field. Mice were placed in an open arena with small food rewards to encourage exploration. Throughout the recordings, both sniffing (inhalations above 4hz) and gaze shifting eye movements occurred in tandem when the animal was mobile, highlighting the active sensing components of these behaviors. Initial analysis indicates a coordinated pattern of gaze shifting eye movements and sniffing behaviors across a broad range of sniff frequencies, showing a coordination of gaze shifts with sniffing behaviors. This relationship weakens during periods of low frequency breathing, suggesting that there is a state-dependent alignment of gaze shifts and sniffing. Ongoing analysis will clarify whether the coordination shown between sniffing and gaze shifts is due to the direct synchronization of these two sensory inputs, or whether it is an indirect result of the head movements coupling to sniffing behaviors. A deeper understanding of the coordination of these two sensory modalities will allow for a better grasp of how the senses and other environmental cues are coordinated in order to inform natural behavior.

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Title: Neural representational geometry for observed actions reflects goals and sociality

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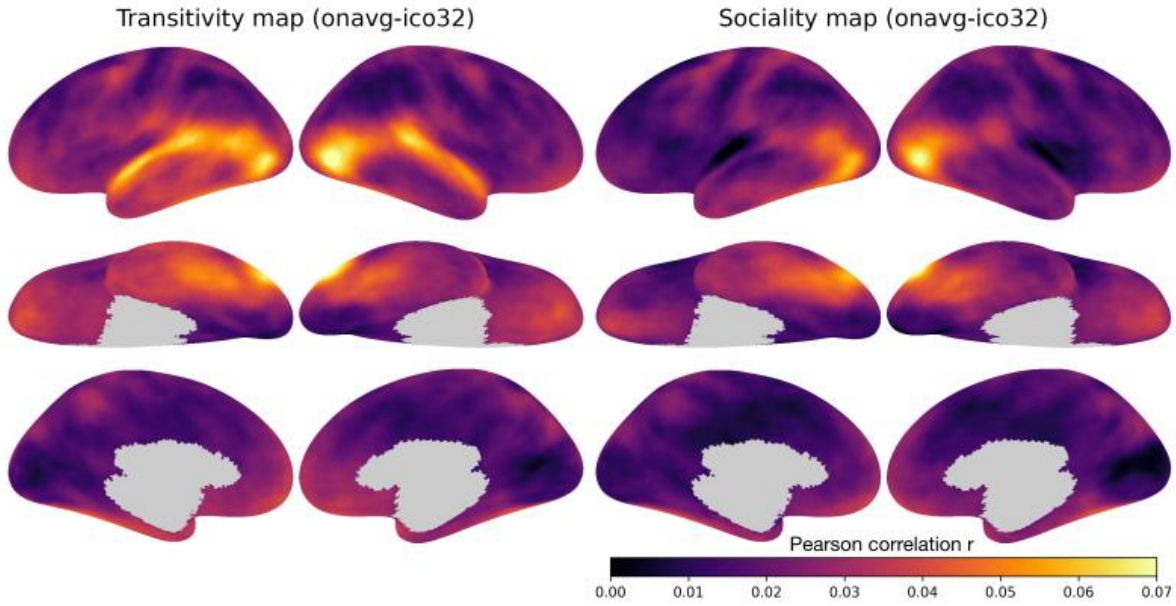
Abstract: Everyday actions occur within complex, rich, and dynamic contexts. However, most prior studies have examined actions in isolation, using controlled and decontextualized experimental stimuli. Such approaches limit our ability to assess the importance of context during naturalistic action perception. In this study, we measured brain activity with fMRI while participants (N = 24) viewed the documentary Monkey Kingdom that shows monkeys acting in their natural environment. We constructed representational dissimilarity matrices (RDMs) to capture two key dimensions of action: social interaction (sociality) and action goals (transitivity). These models were derived from behavioral arrangement tasks conducted online through Prolific with an independent sample of participants. Searchlight analysis revealed that both the transitivity and sociality models correlated with neural representational geometry in the lateral

occipitotemporal cortex, ventral temporal cortex, and premotor cortex—consistent with prior work using human action clips (Han et al., 2024 https://doi.org/10.1101/2024.11.26.624178). Notably, unlike earlier findings, we observed transitivity-related responses along the full length of the superior temporal cortex. These results suggest that the representational geometry of action goals may be more robustly expressed in naturalistic viewing, offering new insights into how the brain encodes actions in complex real-world contexts.



Disclosures: J. Han: None. **M. Feilong:** None. **J.V. Haxby:** None. **M. Gobbini:** None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.12/LBP092

Topic: E.06. Vision

Support: NIH R00MH116100
NIH U24NS113646
Vanderbilt Brain Institute Faculty Fellow Award (AMB)
Vanderbilt University Startup Funds (AMB)
International Human Frontier Science Program Organization [grant number: LT0001/2023-L] (JAW)
Dutch Research Council [grant number: VI.Veni.232.110] (JAW)

Title: Context-dependent deviance detection emerges in higher-order area neuronal spiking in mice and monkeys

Authors: *Y. S. XIONG[1], J. A. WESTERBERG[5], E. Z. SENNESH[2], H. NEJAT[3], D. RICCI[6], S. DURAND[7], B. HARDCASTLE[8], H. CABASCO[9], H. BELSKI[8], A. BAWANY[8], R. GILLIS[10], H. LOEFFLER[8], W. HAN[8], K. S. NGUYEN[8], V. HA[8], C. GRASSO[8], J. SWAPP[8], B. OUELLETTE[8], A. WILLIFORD[8], P. A. GROBLEWSKI[11], S. R. OLSEN[8], C. KISELYCZNYK[8], C. KOCH[11], J. LECOQ[9], A. V. MAIER[2], A. BASTOS[4];
[2]Dept. of Psychology, [3]Psychology, [4]Psychology and Vanderbilt Brain Inst., [1]Vanderbilt Univ., Nashville, TN; [5]Dept. of Vision and Cognition, NIN-KNAW, Amsterdam, Netherlands; [6]GSU, Atlanta, GA; [7]Neural Coding, [9]Mindscope, [10]Allen Inst. for Neural Dynamics, [8]Allen Inst., Seattle, WA; [11]Allen Inst. For Brain Sci., Seattle, WA

Abstract: Predictive coding is theorized to be a ubiquitous cortical process to explain sensory responses. It asserts that the brain continuously predicts sensory information and imposes those predictions on low-level sensory areas to shape perception and guide behavior. We tested predictive coding using a visual oddball task in mice and monkeys. By combining neurophysiology and optogenetics in multiple visual cortical areas, we refute predictive coding as a ubiquitous computation throughout neocortex. Highly predictable stimuli were never explained away, and highly unpredictable oddballs did not evoke omnipresent prediction errors. Visual sensory cortex robustly signaled highly predictable information and was dampened by repetition-based adaptation. Prediction-based modulations were restricted to higher-order cortex. Therefore, visual sensory processing is dominated by feedforward activation, with predictions modulating sensory responses, not defining them.

Disclosures: Y.S. Xiong: None. **J.A. Westerberg:** None. **E.Z. Sennesh:** None. **H. Nejat:** None. **D. Ricci:** None. **S. Durand:** None. **B. Hardcastle:** None. **H. Cabasco:** None. **H. Belski:** None. **A. Bawany:** None. **R. Gillis:** None. **H. Loeffler:** None. **W. Han:** None. **K.S. Nguyen:** None. **V. Ha:** None. **C. Grasso:** None. **J. Swapp:** None. **B. Ouellette:** None. **A. Williford:** None. **P.A. Groblewski:** None. **S.R. Olsen:** None. **C. Kiselycznyk:** None. **C. Koch:** None. **J. Lecoq:** None. **A.V. Maier:** None. **A. Bastos:** None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.13/LBP093

Topic: E.06. Vision

Support: NIH Grant EY034644

Title: Contextual influences on neural discriminability are non-uniform in primary visual cortex

Authors: M. BRODERICK[1], H. KOBAYASHI[1], ***S. J. KUHLMAN**[2,1];
[1]Physiology and Biophysics, University at Buffalo, Buffalo, NY; [2]State University of New York at Buffalo, Buffalo, NY

Abstract: Perception and sensory inference are profoundly shaped by the spatial arrangement of elements across the visual field. Contextual modulation of neural responses by surrounding stimuli is known to enhance perceptual performance in complex environments. Classic size-tuning studies indicate iso-oriented stimuli that extend into the receptive field surround predominantly drive suppression in primary visual cortex (V1). To determine if this property generalizes to stimuli that include surround elements that are non-continuous and spatially restricted, such as is found in complex natural images, we examined surround modulation in layer 2/3 V1 excitatory neurons in awake mice using two-photon calcium imaging. The stimulus set was derived from stimuli typically used to assess end- and side-stopping and consisted of 3 equally sized bars (2 x 15 degrees) in which one bar was centered in the neuron's classic receptive field and two flanking bars arranged in either a non-continuous collinear or lateral pattern, presented at 4 different orientations. In contrast to classic size-tuning stimuli, we found that collinear iso-oriented stimuli frequently evoked faciliatory responses and when considering all orientations, suppression was non-uniform. In total, 607 neurons were analyzed from 7 mice (neurons per animal: median, 86; range, 156-45). On average across animals, 47±6% of neurons exhibited asymmetric surround modulation. Strikingly, lateral flaking bars evoked significantly more suppression compared to collinear bars (modulation index collinear: -0.068±0.03, lateral: -0.140±0.03; p= 0.014, paired t-test, n=7 animals). To assess whether context asymmetrically influences neural discriminability at the population level, stimulus prediction accuracy was evaluated using k-NN classifiers. Prediction accuracy of stimulus orientation was significantly higher for collinear (0.73±0.04) compared to lateral flanking (0.57±0.04) stimuli (p= 0.008, paired t-test, n= 7 animals). These results establish that spatially restricted surround elements are capable of amplifying responses to receptive field-centered input in awake mice and provide a direct demonstration that collinear center-surround interactions improve neural discriminability. In summary, spatial integration across the receptive fields of individual neurons is essential for visually guided behavior, due to contributions to functions such as contour detection, depth perception, and motion disambiguation. Here we identified a previously unrecognized role for collinear center-surround interactions in the integration of local orientation information with global context.

Disclosures: M. Broderick: None. **H. Kobayashi:** None. **S.J. Kuhlman:** None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.14/LBP094

Topic: E.06. Vision

Support: Howard Hughes Medical Institute

Title: Distinct neural codes for identity in intact and Mooney faces in IT face patches

Authors: *S. AHN[1], Y. SHI[2], D. Y. TSAO[3];
[1]UC Berkeley, Berkeley, CA; [2]BBE, Caltech/UC Berkeley, Berkeley, CA; [3]UC Berkeley & HHMI, Berkeley, CA

Abstract: Perception of identity remains stable despite dynamic changes in appearance (e.g., motion, lighting, occlusion). How the brain achieves this stability is not well understood. We recorded from monkeys viewing continuous transition videos in which intact faces gradually morphed into Mooney faces—two-tone images that preserve coarse facial structure but remove many details of a natural face. Face identity was decodable in IT from both intact and Mooney faces, with lower accuracy for Mooney. Yet cross-condition generalization (from intact to Mooney or vice versa) fell to near chance, indicating that IT uses distinct codes for identity in each condition. Population analyses revealed distinct neuronal subgroups: ~25% responded selectively to Mooney faces, ramping with the emergence of Mooney structure, while others supported decoding only in intact conditions. These results suggest that seamless perception of identity may mask variable identity codes in IT, raising the question of how stability is achieved, possibly through interactions beyond IT.

Disclosures: S. Ahn: None. **Y. Shi:** None. **D.Y. Tsao:** None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.15/LBP095

Topic: E.06. Vision

Support: NIH Grant EY037193
Bernstein Foundation Grant

Title: Using 3D mesh-processing networks to understand IT coding of naturalistic images

Authors: *D. GAMBLE[1], C. E. CONNOR[2];
[1]Johns Hopkins University, Baltimore, MD; [2]Krieger Mind/Brain Inst, Johns Hopkins Univ, Baltimore, MD

Abstract: Studies of how neurons process natural images have been most fruitful at lower levels of visual processing, where 2D image statistics that neurons represent can be computed. At higher object-processing levels in inferotemporal cortex (IT), which represent the 3D reality underlying images, there have been longstanding gaps in identifying the information in a natural image that drives the responses of a given IT neuron. A major difficulty has been the lack of ground truth information about the real-world 3D shapes that IT represents. We addressed this gap by using: 1) photorealistic virtual reality (VR) to have 3D ground truth for naturalistic images, and 2) 3D mesh-processing neural networks trained to predict responses of individual IT neurons. We used linear probes to record neural responses in IT cortex of rhesus monkeys performing a fixation task. We built a genetic algorithm (GA) that evolved complex abstract 3D

objects presented in photorealistic VR scenes. The fitness criterion for the GA was neural spike rate, which drove stimulus sampling toward the high response region of the neuron. We also presented naturalistic objects (e.g. animals) based on commercial 3D models in photorealistic VR scenes. We built predictive models of individual IT neurons by training mesh NNs on hundreds of abstract 3D objects produced by the GA. Learned vertex weight patterns in these mesh NNs identify the unique 3D object surface information that drives responses across multiple GA stimuli. These mesh NNs identify the same surface information in naturalistic objects in high-response VR scenes (Fig. 1). This information can be quantified in terms of 3D object-relative position, 3D surface orientation, 3D surface curvatures, and curvature orientations. Thus, we are able to identify and quantify visual information that drives IT responses to natural scenes. This requires 3D ground truth for the naturalistic images, which is not currently computable from 2D photographic images.

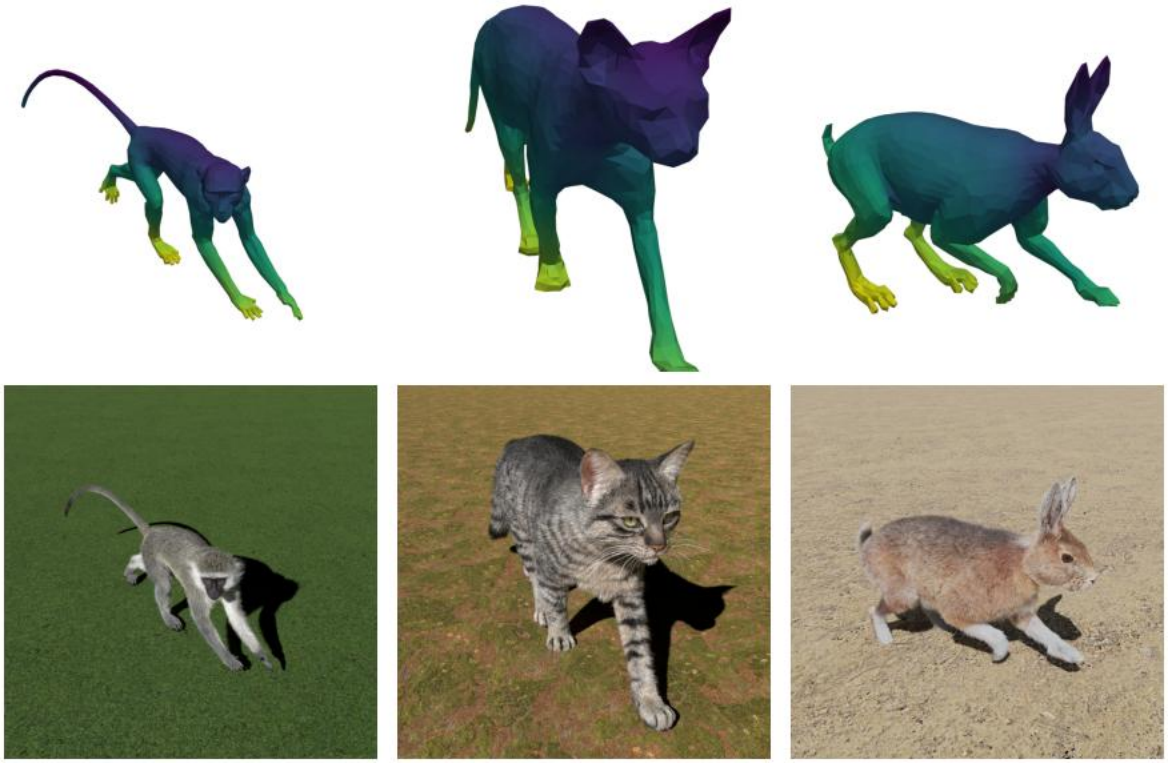


Fig. 1. For this IT neuron, the trained mesh NN identifies feet/paws planted on the ground as driving responses.

Disclosures: D. Gamble: None. **C.E. Connor:** None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.16/LBP096

Topic: E.06. Vision

Support: JSPS KAKENHI 25K14504

Title: Distribution of inhibitory neurons in the primary visual cortex of diacylglycerol lipase-α knockout mice

Authors: *K. KAMEYAMA[1], H. IMORI[1], M. AKIMOTO[1], K. SAKIMURA[2], M. KANO[3], Y. HATA[1];
[1]Faculty of Medicine, Tottori University, Yonago, Japan; [2]Brain Research Institute, Niigata University, Niigata, Japan; [3]Advanced Comprehensive Research Organization, Teikyo University, Tokyo, Japan

Abstract: Developmental plasticity is observed in the cerebral cortex during the early postnatal phase which is known as the critical period. In the visual system, monocular deprivation during the critical period causes a reduction of visual responses to the deprived eye in the primary visual cortex (V1). This ocular dominance plasticity (ODP) peaks at one month after birth in mice, and maturation of inhibitory neurons leads to the opening of the critical period of ODP. Endocannabinoids retrogradely modulate synaptic transmission. One of the major endocannabinoids in the brain, 2-arachidonoylglycerol (2-AG), is synthesized by diacylglycerol lipase-α (DGLα) in postsynaptic sites and binds to the cannabinoid receptor type 1 at presynaptic sites. Recently, we revealed that the timing of the critical period of ODP appeared precociously in DGLα knockout mice. While ODP was significantly suppressed especially in layers II/III and IV of DGLα knockout mice at the peak of the critical period, ODP was observed in these layers before the peak of the critical period. We also revealed that the frequency of miniature inhibitory postsynaptic currents was higher before the peak of the critical period in DGLα knockout mice than in wild-type mice. Thus, the precocious timing of ODP in DGLα knockout mice could be caused by the early maturation of inhibitory circuits. It was reported that parvalbumin-containing inhibitory (PV) neurons develop early in brain-derived neurotrophic factor overexpression mice and methyl-CpG-binding protein 2 null mice, both of which show the precocious timing of ODP compared with wild-type mice. Hence, PV neurons might mature early also in DGLα knockout mice. To examine this possibility, we compared the number of PV neurons between wild-type and DGLα knockout mice before the peak of the critical period. As a result, there was no difference between them in any cortical layers. Thus, the precocious timing of ODP observed in DGLα knockout mice may be caused by the enhancement of inhibitory synaptic transmission rather than the increase of PV neurons.

Disclosures: K. Kameyama: None. **H. Imori:** None. **M. Akimoto:** None. **K. Sakimura:** None. **M. Kano:** None. **Y. Hata:** None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.17/LBP097

Topic: E.06. Vision

Title: A meta-analysis of the La Hire-Purkinje phenomena of seeing one's own blind spots and a theoretical synthesis

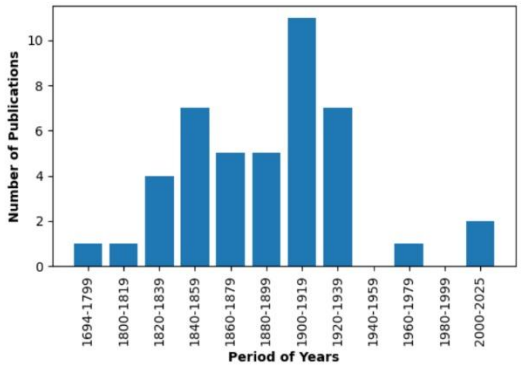
Authors: *C. WU[1,2];
[1]Perception and Cognition Research, Shanghai, China; [2]Perception and Cognition Research, Redmond, WA

Abstract: The blind spot (BS) in the human eye was discovered by Mariotte around 1668, but his demonstration of the BS is through the perceptual disappearance of an object falling into the BS. Presently, Mariotte's demonstration populates all the textbooks (in psychology, neuroscience, and ophthalmology) that touch upon the topic of BS; and this has led some researchers to claim that the other side about the BS phenomenology, namely to see one's own BS consciously, does not occur (e.g., Crick, 1994, p. 31, p. 54). Normally, one does not see their own BS; but under special conditions one can indeed see one or both of their eyes' BSes. A BS may manifest itself as a darker/lighter/colored spot on a lighter/darker/complementary background. This type of phenomena was first reported by La Hire in 1694, and subsequently rediscovered and extended by Purkinje and several others (hereafter, the La Hire-Purkinje phenomena or LPP). However, there has not been much active research on LPP after World War II (Figure 1). As pointed out by Brøns (1939, p. 114), LPP are of considerable theoretical interest. Also, during VSS (Vision Sciences Society) 2025, I demonstrated LPP to many vision researchers: Having gained their first-hand experience with LPP, many of them agree that LPP are worthy of further investigation. The current meta-analysis is based on the observations and experiments listed in Table 1. Phenomenologically, this analysis reveals that (1) the BS, the Purkinje Tree (the pattern of retinal blood vessels converging on the BS), and the Central Scotoma as seen by La Hire and Purkinje may show up independently; (2) each of these parts can exhibit itself as +/-AI (afterimage). Theoretically, correlating LPP with the neuroanatomical finding, by LeVay et al. (1985) in the macaque monkey's brain and by Adams et al. (2007) in the human brain, that the BS is represented in V1-L4, we can conclude that color sensation, as an essential component of visual consciousness, is generated and represented in V1-L4 (Figure 2); relating the +&-AI characteristics exhibited in LPP with prior studies on AI, we can claim that +&-AIs occur in V1-L4.

Table 1.
Investigators/authors and methods of entoptically seeing blind spots

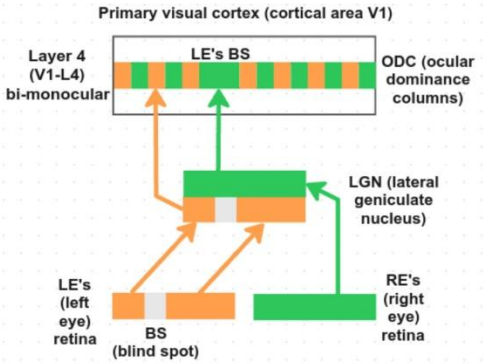
Investigator/author	Observational/experimental method				
	Change of adaptation	Eye movement	Eyeball pressing	Electrical stimulation	Magnetic stimulation
La Hire, P. de (1694)	✓				
Purkinje, P. (1819)	✓	✓	✓	✓	
Le Conte, J. L. (1881)		✓			
Brøns, J. (1939) Chapter IV. Review of prior studies	✓	✓	✓	✓	✓
Pearce, I. (1968)	✓				
Pau, H. (2000)	✓				
Wu, C. Q. (2011) Also, demo at VSS 2025 (Vision Science Society)	✓	✓			

Figure 1.
Numbers of publications about the La Hire-Purkinje phenomena during the years 1694–2025, distributed into periods of years according to density of publications



Note. The first period includes all the years between 1694–1799, the last includes all those after 2000, and all others are periods of every 20 years between 1800–1999.

Figure 2.
Blind spots are represented in V1-L4, a bi-monocular layer in that one eye's blind spot is represented by neurons in the other eye's ocular dominance columns



The first three stages in the human visual system: the retinae in the eyes, LGN in the thalamus, and V1

Disclosures: C. Wu: None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.18/LBP098

Topic: E.06. Vision

Support: DoD Grant TP220338

Title: A Novel Method to Assess the Optomotor Response in Animal Models of Traumatic Brain Injury

Authors: *S. FERGUSON;
Roskamp Institute, Sarasota, FL

Abstract: The optomotor assay is a useful method for assessing the functioning of the visual system in rodents. Within the current study, we have developed a novel neural network-based method for quantifying the optomotor response of mice in a blinded and unbiased fashion. The optomotor response is subtle and difficult to detect by conventional computer vision methods, but by leveraging advances in machine learning we have been able to achieve robust and accurate detection and quantification of the optomotor response. The ability to automatically quantify the optomotor response across cohorts of mice in a blinded and unbiased fashion using this model enables more consistent results.
Our group has previously found pathological and biochemical evidence of TBI-dependent damage to both the optic nerve and retina of mice after repetitive mild TBI. In the current study, the optomotor assay showed the expected curve of decreasing optomotor response duration and head movements with decreasing stripe thickness, illustrating the ability of our AI model to distinguish optomotor related head movements from random non-optomotor motion. We also detected highly significant impacts of repetitive mild TBI on the optomotor response. Both the total optomotor response duration and the frequency of optomotor positive head motions showed a significant TBI-dependent decrease. We also found a significant interactive effect of TBI with decreasing stripe thickness, due to the fact the TBI-dependent difference in the optomotor response is greatest at the lowest CPD with the thickest stripes, and the separation between TBI and sham is less pronounced with thinner stripes. This suggests that the TBI-dependent differences we observe are a real difference in the optomotor response detected by the AI, and not an aberration in how the AI perceives the TBI group due to overall changes in non-optomotor head movements of mice exposed to TBI.

Disclosures: S. Ferguson: A. Employment/Salary (full or part-time); Roskamp Institute, BioSRQ.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.19/LBP099

Topic: E.06. Vision

Support: BBSRC BB/Z517069/1
Wellcome Trust CC2108
Cancer Research UK CC2108
Medical Research Council CC2108

Title: Layer-specific representations of depth from motion parallax in the primary visual cortex

Authors: *C. A. CYPRANOWSKA, A. BLOT, P. ZNAMENSKIY;
The Francis Crick Institute, London, United Kingdom

Abstract: Navigating a dynamic three-dimensional world requires the ability to distinguish visual stimuli at different distances. To do this the visual system must infer the distance of visual cues based on information from two-dimensional retinal projections. We have recently shown that neurons in layer 2/3 of the mouse primary visual cortex (V1) have depth-selective responses arising from integration of visual motion and locomotion-related signals. However, it is unclear how depth-selective responses vary across the cortical laminae. To address this question, we recorded neuronal responses across cortical layers using two-photon calcium imaging in mice navigating a virtual reality environment where motion parallax was the only source of depth information. We found that although depth was encoded in the activity of neurons in V1 from layer 2 to layer 5, the properties of depth-selective neurons varied across cortical laminae. While layer 2/3 neurons almost exclusively responded by increasing their activity at their preferred depth, layer 5 neurons were often either excited or suppressed as a function of depth. Surprisingly, depth preferences varied across cortical depth within superficial layers, with an enrichment of far-tuned cells 100-200 μm below pia and of near-tuned cells 250-400 μm below pia. The biases in depth preferences between these laminae were driven by differences in preferred optic flow speeds. The enrichment of near and far preferring neurons in the superficial layers mirrors the laminar distribution of neurons projecting to higher visual areas AL and PM, respectively. These results suggest that different higher visual areas may preferentially receive signals encoding stimuli at different distances from the animal.

Disclosures: C.A. Cypranowska: None. **A. Blot:** None. **P. Znamenskiy:** None.

Late-Breaking Poster

LBP081: E.06. Vision

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP081.20/LBP100

Topic: E.06. Vision

Support: NIH/NEI R01EY031589

Title: Training to use peripheral vision after simulated central vision loss: behavioral outcomes

Authors: *E. CUTTS[1], M. MANIGLIA[2], P. DEMIRAYAK[3], M. RAGLAND[3], S. JAYAKUMAR[2], P. STEWART[4], J. MUNNEKE[5], A. SEITZ[6], N. B. TURK-BROWNE[7], K. M. VISSCHER[8];
[1]University of Alabama, Birmingham, Birmingham, AL; [2]University of California Riverside, Riverside, CA; [3]Neurobiology, University of Alabama at Birmingham, Birmingham, AL; [4]University of Alabama, Birmingham, Homewood, AL; [5]Northeastern University, Boston, MA; [6]Psychology, Art&Design, Communication and Speech Disorders, Northeastern University,

Boston, MA; [7]Psychology, Yale University, New Haven, CT; [8]Neurobiology, University of Alabama, Birmigham, Birmingham, AL

Abstract: Over 19 million Americans have macular degeneration, a disorder of the retina that, in its late stages, leads to central vision loss. Patients must adapt to this vision loss in order to do daily tasks involving vision. Many develop an area within the retina that avoids the blind spot, which they use preferentially for daily tasks, called the Preferred Retinal Locus (PRL). Learning to use this peripheral location involves perceptual learning. In an attempt to replicate this experience, we employed a simulated central scotoma in healthy, young, normally sighted adults using a gaze-contingent display. Each participant was assigned a "trained" retinal locus (TRL) in either the left or right peripheral visual field. Participants were assigned to a training paradigm which emphasized one of three domains of vision: low-level (visual sensitivity), mid-level (spatial integration), high-level (attention and eye movements), or a combination of the aforementioned domains. Participants underwent a battery of assessments that tested performance on these domains, as well as more ecological tasks including reading, both before and after training. This approach aims to better understand both the behavioral and neural effects of domain-specific visual training on visual performance in multiple domains of vision. We observed that improvements in performance on more low-level visual tasks correlated with improvements in performance on more ecological tasks. These results are consistent with the idea that training on low-level features in the artificial context of a training game may lead to improvements in real-world activities of daily living. This study moves the field toward a better understanding of what training paradigms will be most effective in response to central vision loss.

Disclosures: E. Cutts: None. **M. Maniglia:** None. **P. Demirayak:** None. **M. Ragland:** None. **S. Jayakumar:** None. **P. Stewart:** None. **J. Munneke:** None. **A. Seitz:** None. **N.B. Turk-Browne:** None. **K.M. Visscher:** None.

Late-Breaking Poster

LBP082: E.07. Visual Sensory-Motor Processing

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP082.01/LBP101

Topic: E.07. Visual Sensory-Motor Processing

Support: ANR-21-CE16-0037
Marie Skłodowska-Curie #860949

Title: Adaptive strategies in Danionella cerebrum navigation

Authors: *G. DEBREGEAS;
Laboratoire Jean Perrin, IBPS, Sorbonne Universite, CNRS, Paris, France

Abstract: The opto-motor response in zebrafish larvae has been extensively studied as a model of sensory integration and gain adaptation. However, the discrete, bout-like nature of zebrafish

navigation tends to obscure the sensorimotor computations at play in this process. To address this limitation, we turned to Danionella cerebrum, a miniature fish that exhibits continuous swimming at the larval stage. We used a virtual reality assay to investigate and model the behavioral and neural mechanisms that enables the animal to stablize its position using optic flow. Our data establishes that the adaptive response arises from logarithmic nonlinearities at the sensory (Weber-Fechner law) and motor (Henneman's size principle) ends, and does not require any predictive model as has been proposed for zebrafish. By 3 weeks of age, Danionella cerebrum transitions from continuous to burst-and-glide swimming. We propose that this developmental transition - which optimizes energetic efficiency - reflects a shift in the operating regime of the sensorimotor control system driven by an increase in the animal's swimming power.

Disclosures: G. Debregeas: None.

Late-Breaking Poster

LBP082: E.07. Visual Sensory-Motor Processing

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP082.02/LBP102

Topic: E.07. Visual Sensory-Motor Processing

Support: Chen BMI institute
Boswell foundation
R01NS123663

Title: Neural representation of hand and foot action in intraparietal cortex of non-human primate

Authors: *L. SHE[1], S. LEE[2], M. G. SHAPIRO[1], D. A. WAGENAAR[1], R. A. ANDERSEN[3]; [1]California Institute of Technology, Pasadena, CA; [2]Caltech, Pasadena, CA; [3]BBE, Calif Institute of Technology, Pasadena, CA

Abstract: The cortex within the intraparietal sulcus (IPS) in non-human primates (NHPs) is a brain region involved in planning eye movements and hand actions. Recent studies have shown that the homologue of anterior IPS in humans had broader roles, encoding the action of other body parts, observed actions and action verbs, and objects in allocentric coordinates. To understand the neural representation of IPS at both mesoscopic and single-neuron scale, we first performed functional ultrasound (fUS) imaging while the monkeys performed a visually guided action task. Comparing hand reach vs. grasp, we found that the parietal reach region (PRR) within the medial IPS showed distinct activity patterns during contralateral, but not ipsilateral hand. Specifically, PRR activity decreased more during preparation for contralateral hand reaches compared to grasps, while increasing more during the action phase of reaches. In contrast, the anterior intraparietal area (AIP), known to represent grasping, showed similar activation patterns for both hand reach and grasp actions, regardless of contralateral or ipsilateral hand. This suggests a more abstract representation of hand actions within AIP compared to the

PRR. Comparing hand vs. foot actions, the PRR showed increased activity during contralateral foot grasp compared to hand grasp, while AIP exhibited decreased activity. Electrophysiological recording of AIP using high density probes (Neuropixels) confirmed that hand or foot actions were decodable at the single neuron level and the hand action related variables (hand action type, and target locations) were represented as well. This study provides evidence of a broader role for both PRR and AIP and will help in developing less-invasive brain-machine interfaces using fUS imaging.

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Late-Breaking Poster

LBP082: E.07. Visual Sensory-Motor Processing

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP082.03/LBP103

Topic: E.07. Visual Sensory-Motor Processing

Support: Simons Foundation 542999
NIH 5F30EY035930-02

Title: The nature of visuomotor mismatch signals in mouse V1 and ACC/M2

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Abstract: A widespread hypothesis is that the brain builds internal models of the external world to contextualize sensory input. During visual processing, for example, changes in visual input resulting from self-motion must be distinguished from changes due to movement in the external world. It is presumed that internal models produce predictions of visual input given one's own movements. However, where or how these predictions are generated and how they are integrated with sensory signals is unclear. We recorded from the primary visual area (V1) and anterior cingulate cortex/secondary motor area (ACC/M2) in head-fixed mice. Mice traversed a virtual corridor with gratings along its walls, under a closed-loop condition in which the movement of the walls was tied to the mouse's running speed. During the corridor traversal, we included perturbations in which the wall ceased moving, which induced mismatches with the animal's presumed expectation of visual flow given its locomotion. In a subset of V1 and ACC/M2 units, these visuomotor mismatches evoked a significant increase (~10-15% of cases) in responsivity. Mismatch responses could emerge via a comparison of visual flow speeds with predicted flow given locomotion speed. Alternatively, these responses could arise from a neuronal preference for static visual stimuli. To assess neuronal selectivity for visual speed, as well as any relationship between sensitivity for visual and locomotion speed, we measured the slopes of visual speed and locomotion speed tuning curves, using passively viewed grating stimuli presented after closed-loop recordings. Mismatch responsive neurons in ACC/M2 and a subset of

those neurons in V1 had visual and locomotion speed tuning with opposite slopes. These neurons can be viewed as comparing visual and running speed, because they will have a locomotion speed invariant response when running is coupled with appropriate visual flow; a mismatch between locomotion speed and visual flow, on the other hand, will alter responsivity. However, another subpopulation of V1 mismatch-responsive units exhibited little to no sensitivity to locomotion speed. These mismatch responses could be explained by a simple preference for static stimuli. During closed-loop mismatch epochs, the neurons identified as 'comparators' exhibited locomotion-dependent mismatch responses, whereas neurons tuned solely to static stimuli exhibited locomotion-invariant mismatch responses. Our results suggest that some but not all visuomotor mismatch signals result from comparisons between visual and locomotion speed, and that these responses can be found in both frontal/motor and visual areas.

Disclosures: E. Kim: None. **A. Kohn:** None.

Late-Breaking Poster

LBP083: E.08. Multisensory Integration

Location: SDCC Hall B

Time: Tuesday, November 18, 2025, 1:00 PM - 5:00 PM

Program #/Poster #: LBP083.01/LBP104

Topic: E.08. Multisensory Integration

Title: Ground tilt representation in the cerebral coretex

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Abstract: Information about ground tilt at one's location is indispensable for integrating the body with its surrounding environment. However, how ground-tilt information, together with movement and posture information, is represented in the cerebral cortex remains unclear. To address this issue, we developed a new 6DOF platform that can rapidly and precisely impart ground motion to head-fixed mice. Using the Diesel2p large FOV two-photon mesoscope, we performed calcium imaging to simultaneously capture activity dynamics across broad cortical areas from the frontal to the parietal cortex while driving the platform through various motion patterns. We found a core area for the ground-tilt information at the parietal cortex, although tilt-direction neurons were found across the dorsal cortex. Neuronal populations preserved tilt-direction information within a common low-dimensional manifold across three distinct motion conditions, indicating a condition-invariant tilt code. Furthermore, to investigate shared dynamics across multiple cortical areas, we introduced broadcast-subspace analysis and revealed that tilt information occupied the second principal shared axis, following movement information. These results reveal the core cortical area for processing tilt information, its universal format, and its sharing across the dorsal cortex, thereby providing a framework for cortical information processing that integrates movement, posture, and environment.

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Late-Breaking Poster

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Program #/Poster #: LBP083.02/LBP105

Topic: E.08. Multisensory Integration

Support: DFG, SPP1665

Title: Functional state modulation of cortical stimulus representations revealed through state-aware decoding

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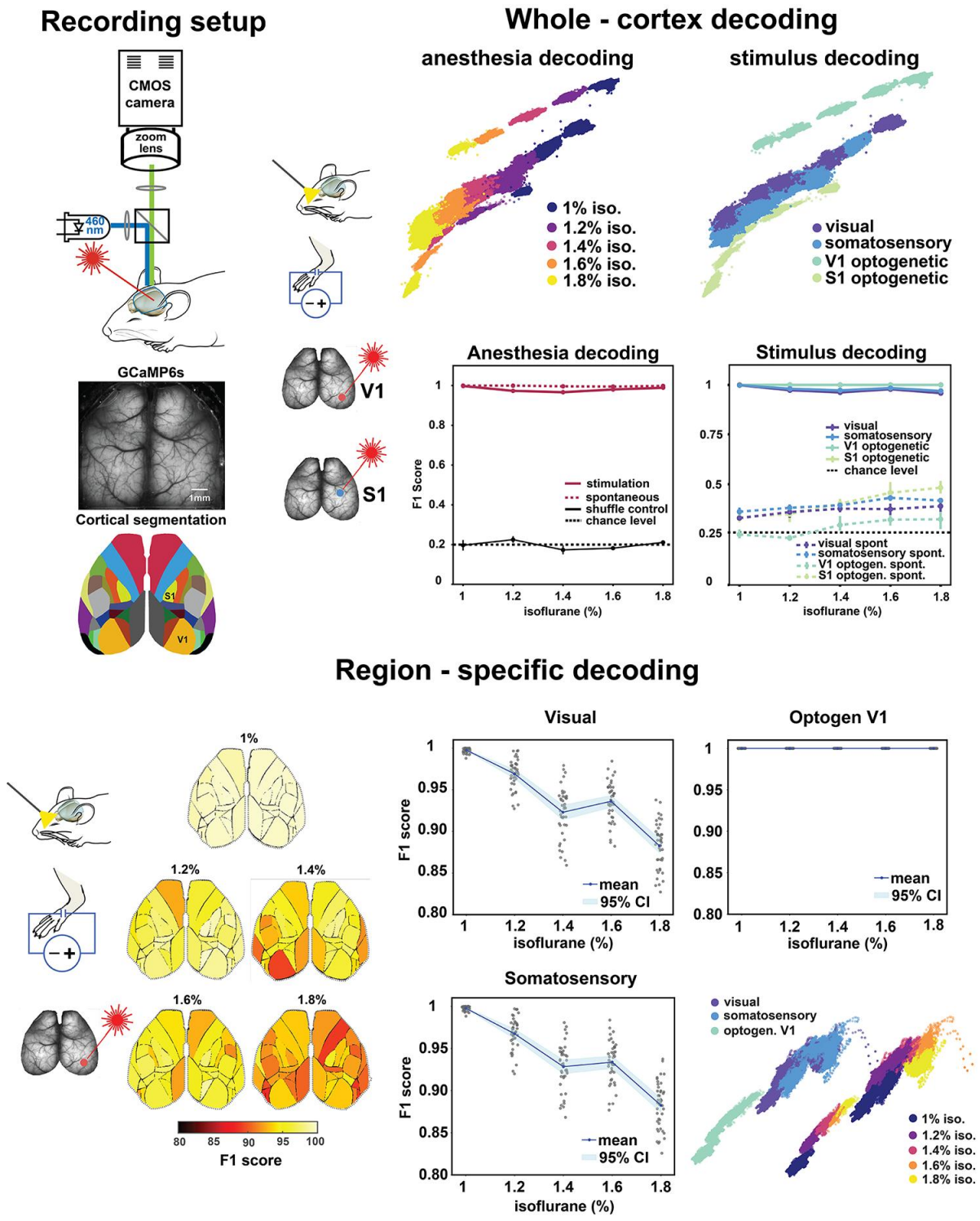
Abstract: Cortical representations of sensory stimuli vary with functional brain states, impeding network-level models of perception and the design of robust brain-machine interfaces. We developed a state-aware decoding framework that models functional states alongside stimulus-evoked cortical dynamics.Pan-cortical calcium imaging (GCaMP6s) was performed in transgenic mice (n=15) across graded isoflurane anesthesia (1.0-1.8%), capturing transitions from desynchronized to slow-wave activity with multisensory visual, somatosensory, or optogenetic (V1 or S1) stimulations. Consistent EmBeddings of high-dimensional Recordings using Auxiliary variables (CEBRA)[1] leveraged spatiotemporal features enabling joint decoding of stimulus type and anesthesia level.Classification accuracy exceeded 98% (F1 score) for both stimulus modality and anesthesia depth. Stimulus-specific spatiotemporal signatures persisted under surgical anesthesia despite dominant slow waves. Region-specific analysis revealed decodable information distributed across 40 cortical areas, extending beyond primary sensory zones. Sensory decoding declined from 99.4% to 88.7% between light and deep anesthesia ($p<0.0001$), indicating reduced cortical integration. In contrast, optogenetic stimulation maintained >99% accuracy across all levels, suggesting preserved intracortical processing independent of thalamocortical relay.These results challenge models attributing anesthesia-induced unconsciousness to blocked sensory input or impaired cortical representation. Instead, stimulus-specific information remains encoded within spatiotemporal dynamics, though with altered integration. Unlike sensory stimulations, optogenetic stimulation proved state-independent, supporting direct cortical stimulation approaches for probing consciousness. This study shows that cortical stimulus representations depend on functional states and introduces strategies to elucidate their interdependencies.[1]Nature 617 (7960): 360-68.



Disclosures: S. Bodea: None. **R. Gonzalez:** None. **S. Schneider:** None. **G.G. Westmeyer:** None.

Late-Breaking Poster

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Stratton VA Medical Center

Title: Electroencephalogram beta-frequency band is associated with proprioceptive processing and recalibration of passive finger movements

Authors: H. HAYES[1], M. TORRICELLA[2], D. J. REINKENSMEYER[3], D. GUPTA[4], ***A. J. FARRENS**[5];
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Abstract: Purpose: Proprioception, the sense of body movement, is impaired following many neurological conditions. While it is known to mediate rehabilitation and motor learning, proprioceptive processing and its plasticity are poorly understood. Here, we assess electroencephalography (EEG) during the proprioceptive "Crisscross" task in healthy adults to determine the neural representation of finger movement estimation and its recalibration with performance feedback. Specifically, we analyze beta suppression, known to be important in top-down control of sensory processing.**Method:** 24 healthy adults (18-34 y.o., 15 male), participated with consent. In Crisscross, the FINGER robot crossed the right index/middle fingers in symmetric, alternating flexion/extension trajectories (0-36 deg) at 3 random speeds (8,11,16 deg/s), ITI 2-3.5s for 120 trials (6 runs x 20 trials), with vision of the hand occluded. Crisscross was performed in two conditions. *Active:* participants pushed a button with their left hand at perceived finger crossing, and *Passive*: the experimenter pushed a button when they saw the fingers cross. One group received performance feedback (FB, n=12) after each button press. The other group (nFB) did not. Performance was quantified as absolute error magnitude. EEG data (19 chan, DSI-24, Wearable Sensing) was filtered (0.1- 30 Hz), denoised, baseline corrected (-0.2 to 0 s) and noisy epochs were removed (±100μV, <10% trials). Beta suppression (12-20Hz) was analyzed in epochs prior to finger crossing, when participants are evaluating their movement progression. We used a mixed model with fixed factors: task (active, passive), feedback (FB, nFB), crossing speed (slow, medium, fast), and their interaction.**Results:** In both tasks, significant beta suppression was observed over frontal (F3,Fz,F4) and sensorimotor electrodes of

the propriocepting hand (C3,P3,Cz), with greater desynchronization observed in the active task. The mixed model showed a significant interaction at P3 between tasks, feedback and speed ($p<0.039$). The FB group had significantly larger suppression in the active task for both the slow ($p<0.0.01$) and medium speed trials ($p<0.0001$), in which crisscross performance improved the most between groups (t-test, $p<0.01$). With feedback, the slow and medium speed trials had comparable desynchronization to the fast trials, known to attract greater attention. **Conclusion:** The increase in beta suppression at the contralateral sensory electrode during active task performance with feedback may reflect enhanced attention to proprioceptive processing and top-down sensory control, contributing to improved proprioceptive performance.

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Late-Breaking Poster

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Program #/Poster #: LBP083.04/LBP107

Topic: E.08. Multisensory Integration

Support: NIH NIDCD R01 DC020717

Title: Attention-dependent auditory responses in the human pulvinar

Authors: *T. ZHANG[1], E. CUNNINGHAM[2], W. C. STACEY[3], J. HITCHENS[1], C. KOHTZ[1], D. BRANG[4];
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Abstract: Sounds can modulate visual cortex activity, and attention plays an important role in audio-visual (AV) interactions. However, the mechanisms that enable sounds to affect visual processing, and the representational content of auditory responses in visual areas, remain poorly understood in humans. Recent research has highlighted the potential role of subcortical pathways, including the thalamus, in coordinating AV interactions. The pulvinar, the largest nucleus of the thalamus, supports attention and visual processes, but its role in AV interactions in humans has only been examined indirectly. While the pulvinar has traditionally been treated as unisensory structure, prior work in non-human primates demonstrates auditory responses when attention is allocated to auditory stimuli. The current study presents a multiple-case study examination of auditory and visual responses in the pulvinar and the anterior thalamic nucleus in humans using intracranial recordings (iEEG/sEEG) in patients with epilepsy. Specifically, we investigated whether and how the pulvinar responds to auditory, visual, and AV information in the presence and absence of attentional engagement. Using a custom-designed and 3D printed LED/speaker array, we presented high-density visual, auditory, and AV information spanning

~180º. Patients (n = 2) completed a central fixation task, detecting fixation color change in the center of the array (minimizing attention toward auditory and peripheral stimuli). To examine the presence of auditory responses in the thalamus when attention was expanded to include auditory stimuli, patients additionally completed one of two additional tasks: (1) the LED/speaker array was used with a AV attention task in which they detected a change in tone frequency *or* in LED segment color, or (2) speeded responses (left or right) to auditory, visual, or AV targets appearing to the left or right of fixation. This procedure enabled precise mapping for the spatial tuning of visual, auditory, and AV information in the thalamus under different levels of attention. Within the ventral anterior thalamic nucleus, we observed significant responses to both auditory and visual stimuli under both the visual and AV attention conditions. Conversely, the pulvinar only demonstrated significant responses to sounds during the AV attention condition. Our results provide direct evidence in humans that the pulvinar responds to auditory information selectively in multisensory contexts, potentially coordinating some previously observed multisensory effects, including direct interactions between auditory and visual cortex.

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Late-Breaking Poster

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Title: The Influence of Neural Haptics on Attention, Control, and Perception in Immersive Human-in-the-Loop Interactions

Authors: *L. MCGANN, R. S. JAKES, D. J. TYLER;
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Abstract: Evaluation of human-in-the-loop (HITL) systems such as prostheses often relies on performance metrics like time-to-completion (TTC) and accuracy. While valuable, these measures provide limited insight into user strategy—such as attention allocation and control—or into specific challenges posed by the system. Complementary measures, including gaze, which denotes attention, can capture these dynamics in real time and be used to study interface features such as haptic feedback. Haptics are widely assumed to aid function, but their contribution to performance or experience remains unclear. We used gaze, performance and subjective measures to study neural haptic stimulation during immersive body-motion control of a virtual robot arm. We hypothesized haptic feedback would improve performance, perception and attention freed from the controlled hand. Fifteen able-bodied human subjects completed system and task training, then a fragile object pick-and-place task in a 2×4 factorial design varying stimulation

(on/off) and task difficulty as modulated by object size relative to the placement target (small, medium, large, mixed), with nine trials per condition. Participants were randomized into a full counter-balanced Latin Square. Objective data from two participants was excluded due to a confounding change in the data collection protocol. In this pilot study, haptic stimulation reduced grasp force ($p < 0.001$) and improved confidence ($p = 0.021$) and ease of use ($p = 0.014$) but did not alter gaze metrics. In contrast, object size significantly influenced attention metrics: mean gaze-to-hand separation angle ($p < 0.001$), frequency of gaze revisits to the hand ($p = 0.013$), and timing of the first gaze shift away from the hand ($p = 0.003$). Size also affected grasp force ($p < 0.001$). Neither factor influenced TTC or trial result, though future work must examine the influence of learning plateaus. These results suggest that while neural haptics enhance grasp control, tactile feedback may contribute more to user perception without directly improving functional performance. Proprioception and task difficulty, however, may play a larger role in task execution as variations in required grasp aperture and placement precision drive shifts in attention. Altogether, this work emphasizes the need to supplement classic functional metrics with more sensitive and specific analysis tools—particularly gaze—to reveal subtle differences in attention, strategy and control that are otherwise overlooked. Such approaches can inform the design and evaluation of next-generation HITL systems, from advanced prostheses to rehabilitation interfaces, surgical robotics and more.

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