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Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.01/D1

Topic: A.03. Axon and Dendrite Development

Title: Role of Plexin-A3 in FGF signaling in Sox9-positive glial cells translocating to the indusium griseum during corpus callosum development: an immunohistochemcal evaluation

Authors: *K. YUKAWA[1], M. HOSSAIN[2], S. SASAKI[3], T. TSUZUKI[1], I. TAKAHASHI[1], T. KAWASAKI[4], T. NEGISHI[1];
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Abstract: The corpus callosum (CC) is the largest commissural axon tract connecting the two cerebral hemispheres. Plexin-A3 (PlxnA3) is a transmembrane receptor for semaphorins, a family of axon guidance molecules. *PlxnA3* is expressed in the cingulate cortex, from which callosal pioneer axons extend towards the midline during CC development. However, the role of PlxnA3 in this process remains unclear. Guidepost structures including the indusium griseum glia (IGG), midline zipper (MZ), and glial wedge (GW) facilitate the midline crossing of callosal axons through the action of axon guidance cues. During development, the somas of radial glial cells (RGCs) translocate from the GW in the ventricular zone to the indusium griseum (IG) at the pial surface, where they differentiate into mature astrocytes and form IGG. Our studies revealed that midline crossing of neuropilin1-positive pioneer axons at embryonic day 17.5 (E17.5) was significantly impaired in *PlxnA3* KO mice on a BALB/cA background compared with the wild type (WT) mice. Both GFAP-positive (GFAP+) cells and Sox9+ cells in the IG region were significantly reduced in *PlxnA3* KO brains. In WT mice, *Slit2* mRNA was expressed in GFAP+ cells in the IG and MZ, whereas in *PlxnA3* KO mice, *Slit2* mRNA was scarcely detected in the IG region at E17.5. These findings suggest that *PlxnA3* KO mice exhibit poorly formed IGG at E17.5, which may contribute to defective midline crossing of pioneer axons. The hypoplastic IGG may result from impaired somal translocation of RGCs in the absence of PlxnA3. Since FGF signaling is essential for RGC somal translocation, we examined the role of PlxnA3 in regulating Erk, a downstream effector of FGF signaling. Both the number of Sox9+ phospho-Erk (pErk)+ double positive cells and the percentage of pErk+ cells among Sox9+ cells were significantly reduced in the pathway from the GW to the IG in *PlxnA3* KO mice at E17.5, indicating decreased Erk signaling in the Sox9+ cells. To determine whether PlxnA3 affects activation of the FGF receptor (FGFR), we are currently quantifying the number of Sox9+ phospho-FGFR (pFGFR)+ double positive cells and the proportion of pFGFR+ cells among Sox9+ cells along the GW-IG pathway in both WT and *PlxnA3* KO mice. This presentation will discuss whether PlxnA3-mediated signal is integrated into FGF signaling at the level of FGFR activation.

Disclosures: K. Yukawa: None. **M. Hossain:** None. **S. Sasaki:** None. **T. Tsuzuki:** None. **I. Takahashi:** None. **T. Kawasaki:** None. **T. Negishi:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.02/D2

Topic: A.03. Axon and Dendrite Development

Support: NASA/INSGC
Valparaiso University

Title: Nell2 acts as an inhibitory axon guidance cue in the layer-specific retinotectal projection

Authors: C. NAKAMOTO, A. UNDERWOOD, J. KOLUNDZIJA, J. LUMAKOVSKA, *M. NAKAMOTO;
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Abstract: Layer-specific axon projection is a key feature of neural circuit architecture in both vertebrate and invertebrate nervous systems. However, the molecular mechanisms that establish layer-specific connectivity are not well understood. The chicken retinotectal projection serves as a useful model for studying this process. During development, retinal axons enter the tectum through the most superficial layer, *stratum opticum* (SO), and then leave the SO and arborize within specific retinorecipient laminae of the superficial *stratum griseum et fibrosum superficiale* (SGFS). Conventional retinal axons normally do not extend beyond the boundary separating the superficial retinorecipient and deeper non-retinorecipient laminae. Nell2 (also known as Nel) is a secreted glycoprotein predominantly expressed in the nervous system. We previously demonstrated that Nell2 acts as an essential inhibitory guidance cue in the establishment of eye-specific retinogeniculate projections in mice. In the present study, we investigated the role of Nell2 in the layer-specific retinotectal projection of the chicken visual system. We found that Nell2 is specifically expressed at the boundary between retinorecipient and non-retinorecipient tectal laminae (lamina g of the SGFS). *In vitro* axon outgrowth and growth cone collapse assays demonstrated that Nell2 exerts inhibitory effects on retinal axons. Furthermore, both gain- and loss-of-function manipulations of Nell2 expression in the developing tectum by *in ovo* electroporation disrupted the normal layer-specific pattern of retinotectal projection *in vivo*. These findings suggest that Nell2 acts as an essential inhibitory guidance cue that restricts retinal axons to retinorecipient laminae and contributes to the establishment of layer-specific retinotectal connectivity.

Disclosures: C. Nakamoto: None. **A. Underwood:** None. **J. Kolundzija:** None. **J. Lumakovska:** None. **M. Nakamoto:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.03/D3

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant 1R15NS101692-02A1
Skidmore College Faculty Student Summer Research Award

Title: Genetic regulation of neuromuscular development and connectivity modulated by DIP-α and Dpr10 in Drosophila melanogaster

Authors: *C. M. CHRISTIE[1], B. WU[3], R. A. CARRILLO[4], C. G. VECSEY[2];
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Abstract: Neuromuscular development in *Drosophila melanogaster* is highly stereotyped. However, failures still occur, and more research is needed to understand the molecular mechanisms underlying these failures. Synaptic specificity in larval motor neurons relies on interactions between the cell surface protein families Dpr and DIP. The heterophilic binding pair DIP-α and Dpr10 is required for proper innervation of muscle 4 (m4), and loss of either gene results in a failure to innervate. To identify additional interactors with the DIP-α and Dpr10 pathway, previous deficiency screens were conducted in female *dip-α/dpr10* mutants to identify regions that either up- or downregulate m4 innervation. Deficiency region DF7634 exhibited partial rescue of m4 innervation in *dip-α/dpr10* female mutants, ultimately suggesting additional modulatory factors within this region. In this study, we focus on the specific genes within this deficiency region that might be influencing DIP-α and Dpr10 binding and proper axonal target selection. Using targeted genetic crosses, larval dissections, immunostaining, and fluorescent microscopy, m4 innervation was quantified in third-instar larvae across multiple genotypes. Preliminary data indicate increased m4 connectivity in both male and female *dip-α* and *dip-α/dpr10* mutants when genes *mical*, *nerfin-2*, and *CG5359* within DF7634 are disrupted. These trends suggest that genetic factors within DF7634 may modulate synaptic targeting or stabilization at the neuromuscular junction. Understanding the specific roles of these genes will be essential for elucidating genetic interactions with the DIP-α and Dpr10 pathway.

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Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.04/D4

Topic: A.03. Axon and Dendrite Development

Support: NSF CRCNS award #2112862

Title: Serotonergic axons in the Pacific electric ray: Insights into stochastic self-organization in vertebrate brains

Authors: *D. ARROYO[1], S. JANUSONIS[2];
[1]Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA;
[2]Psychological and Brain Sci., Univ. of California Santa Barbara, Santa Barbara, CA

Abstract: All vertebrate brains contain dense meshworks of thin axons (fibers) that store and release serotonin. These serotonergic meshworks vary in density across brain regions and set a functional environment for all neural networks. Serotonergic signaling has been associated with many neural processes, including neuroplasticity. The self-organization of the serotonergic fibers remains an important problem. Some of the processes underlying this self-organization continue to operate after the initial development because serotonergic fibers can regenerate in adult mammalian brains, and fish brains grow in adulthood. We have recently shown that some key features of serotonergic meshworks can be captured with mathematical models based on spatial stochastic processes, with no guiding factors. Specifically, the trajectories of individual serotonergic fibers resemble anomalous (persistent) diffusion paths and can be modeled with fractional Brownian motion (FBM). We have demonstrated the potential of this approach in two phylogenetically distant species, the laboratory mouse and the Pacific angelshark. We investigated the brain of the Pacific electric ray (*Tetronarce californica*), with a focus on its serotonergic system. This species has several features important for comparative and computational neurosciences. First, its brainstem is dominated by the electric lobes, massive structures composed of giant neurons that send axons to the electric organs on each side of the head. The electric lobe presents a unique environment for serotonergic fibers in its sparse ("spongy") cellular structure and strong homogeneity, with no analogous structure in mammalian brains. Second, the telencephalon of the electric ray has an unusually simple geometry (it is oval-shaped in cross-section and has no ventricles), with no major physical "obstacles" (differentiated nuclei or axon tracts). It facilitates the verification of predictions generated by computer simulations of serotonergic fibers. An adult electric ray brain was fixed, embedded, and sectioned in serial sections. First, a section subset was imaged unstained to visualize major fiber tracts and then stained with thionine to reveal the basic cytoarchitecture of all brain divisions. Next, another subset of sections was used to visualize serotonergic fibers with immunohistochemistry. In addition, other cellular markers were investigated (e.g., Iba1/AIF-1). The results show that the distribution of serotonergic axons in the ray telencephalon is consistent with predictions of FBM-based models and point to an additional significance of the dorsal pallium in the buildup of the final fiber densities.

Disclosures: D. Arroyo: None. **S. Janusonis:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.05/D5

Topic: A.03. Axon and Dendrite Development

Support: NIH R21 NS141110
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Max and Anne Wien Professor of Life Sciences fund
NIH F31 NS127518
NSF-Simons Center for Mathematical and Statistical Analysis of Biology at Harvard #1764269
Harvard College Research Program
Harvard Program for Research in Science and Engineering

Title: Synthetic system for in vivo functional investigation of growth cone molecules with subcellular, stage, and subtype specificity

Authors: *J. KIM[1,2], D. E. TILLMAN[3,2], E. CHAI[2], J.-Y. KIM[2,3], J. D. MACKLIS[2];
[2]Dept of Stem Cell and Regenerative Biology, and Ctr. for Brain Sci., [3]Mol. & Cell. Biol., [1]Harvard Univ., Cambridge, MA

Abstract: Neurons employ distinct subcellular functions and underlying molecular machinery in soma, dendrite, and axon subcellular compartments. Long-range projection neurons (PNs), in particular, form specific circuits that support distinct nervous system functions. Precise assembly of these long-range connections depends on molecular programs regulated in subtype-, stage-, and subcellular-compartment-specific manners. During development, axons must elongate and navigate through complex environments under tightly regulated molecular control, ensuring that developing neurons connect with appropriate targets and establish functional circuitry. Growth cones (GCs) are specialized structures at the tips of extending axons that play central roles in axon elongation and guidance. Recent studies from our lab reveal striking molecular differences between distinct PN subtypes, and between their GCs and their parent somata, during circuit formation. However, the functions of these GC-localized molecules remain difficult to investigate *in vivo* with subtype, developmental stage, and subcellular specificity. To address this challenge, we developed a synthetic strategy for compartment-restricted molecular manipulation in developing cortical PNs. Using callosal projection neurons (CPN) as a model, we find that expression of fluorophores fused to an axonal targeting motif decreases protein expression in somata and enriches in GCs. We also performed subtype-specific subcellular sorting to confirm localization of targeted constructs in GCs, indicating that this approach enables GC-directed overexpression of protein *in vivo*. We further improved temporal control by restricting construct expression to specific developmental windows. We are advancing a complementary strategy for

GC-localized transcript knockdown using Cas13-based RNA-degrading effectors. We first tested whether the fusion of an axonal targeting motif hinders their RNA knockdown efficiency *in vitro*. We are validating this approach for subcellular-specific depletion of GC-enriched transcripts *in vivo*. We ultimately plan to use this approach to investigate subtype-, stage-, and subcellular-specific molecular mechanisms that govern circuit and synapse formation. Taken together, this work establishes a modular platform for investigating how GC-localized molecules regulate PN circuits with subtype-, stage-, and subcellular-resolution. This approach will enable mechanistic studies of circuit assembly with enhanced specificity and provide insight into how disrupted subcellular molecular regulation contributes to neurodevelopmental and neurodegenerative disorders.

Disclosures: J. Kim: None. **D.E. Tillman:** None. **E. Chai:** None. **J. Kim:** None. **J.D. Macklis:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.06/D6

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant R00GM132518

Title: The MOSMO/MEGF8/MGRN1 Complex Regulates EPHA4 Turnover to Control Axon Guidance

Authors: *L. GAO[1], P. PARASHARA[1], A. RIGLOS[2], G. SIAUW[1], S. ZHANG[3], D. LARTEY[1], J. KONG[1];
[1]Dept. of Biochem., [2]Dept. of Chem., [3]Dept. of Pharmacol., Univ. of Washington, Seattle, WA

Abstract: Axon guidance is crucial for forming organized neural networks during development and for axonal regeneration after neural injury. Although canonical axon guidance pathways have been identified, the mechanisms that regulate receptor abundance, localization, and signaling activity remain incompletely understood. Here, we investigate the regulation of Ephrin type-A receptor 4 (EPHA4), a key axon guidance receptor, by the MOSMO/MEGF8/MGRN1 (MMM) complex, a newly identified membrane-associated ubiquitination machinery previously implicated in G protein-coupled receptor regulation (Kong et al., 2021 & Parashara et al., 2025). A cell-surface proteomic screen identified EPHA4 as one of six receptors consistently elevated in MOSMO-, MEGF8-, and MGRN1-deficient cells, suggesting that EPHA4 is a substrate of the MMM complex. Biochemical analyses demonstrated that co-expression of MEGF8 and MGRN1 reduced EPHA4 protein abundance, while ubiquitination assays revealed enhanced EPHA4 ubiquitination in the presence of the complex. These findings indicate that the MMM complex promotes EPHA4 ubiquitination and turnover, thereby limiting its surface availability. To assess the functional significance of MMM-mediated EPHA4 regulation, we examined spinal motor

neurons differentiated from mouse embryonic stem cells. MGRN1-deficient neurons exhibited a 34.5% reduction in neurite length compared with wild-type controls ($p<0.0001$). Furthermore, axon guidance defects were observed in the developing limbs of *Mosmo*-, *Megf8*- (Engelhard et al., 2013), and *Mgrn1*-knockout mouse embryos, providing in vivo support for a functional link between MMM activity and EphA4 signaling. Together, these findings identify EPHA4 as a novel substrate of the MMM complex and suggest that ubiquitin-mediated control of EPHA4 turnover modulates neuronal responsiveness to guidance cues during neural circuit formation. This work provides new insight into the post-translational regulation of axon guidance signaling and may reveal therapeutic targets for disorders involving impaired axonal growth and connectivity.

Disclosures: L. Gao: None. **P. Parashara:** None. **A. Riglos:** None. **G. Siauw:** None. **S. Zhang:** None. **D. Lartey:** None. **J. Kong:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.07/D7

Topic: A.03. Axon and Dendrite Development

Support: NIH NIGMS Grant GM101701
Inoué Endowment Fund

Title: Imaging axon orientation across the rainbow: A retrospective investigation of Mitochondrial Rho GTPase-1's role in axon guidance

Authors: J. AFSAR-KESHMIRI[1], M. SHRIBAK[2], L. CONSTANTINE[1], O. THOMPSON[1], *A. K. MYERS[1];
[1]Hamilton Col., Clinton, NY; [2]Marine Biol. Lab., Woods Hole, MA

Abstract: During brain development, mitochondria must be transported to the axon growth cone and distributed along the axon. This process is mediated by a Mitochondrial Rho GTPase 1 (MIRO1), which complexes with the motor adaptor protein TRAK1 to facilitate interaction with kinesin and dynein motor proteins in a Ca^{2+}-dependent manner to allow fast transport of mitochondria along microtubules. In addition to mitochondrial transport, MIRO1 is involved in regulation of peroxisomal transport, mitophagy, and assembly of contact sites between the mitochondria and endoplasmic reticulum. Dysregulation of these essential processes have been implicated in both neurodevelopmental and neurodegenerative disease. While much of the current literature has focused on the consequences of *Miro1* deletion at the cellular level, we used a technique called Polychromatic Polarization Microscopy (PPM) to visualize how *Miro1* ablation may influence axon guidance retrospectively, by considering the orientation of axons, the size of axon tracts, and the morphology of gray matter regions where axons originate in the adult mouse brain. PPM takes advantage of the natural birefringence of axons conferred by their

myelin sheaths and filaments, to visualize axons in a label-free manner. Unlike other polarized light microscopy techniques, PPM reveals birefringent fibers in full-spectrum color in real time, as determined by the slow axis orientation of the fiber. The slow axis of myelin sheath is orthogonal to the longitudinal axis of the axon, and so the color can be used to ascertain the orientation of the axon across large histological sections. Using PPM, we have identified populations of cortical axons and large commissural axon tracts that may be diminished or misoriented in the adult mouse brain after conditional deletion of *Miro1* (*Miro1*^{CKO}) from excitatory neurons of the cerebral cortex . Future investigation of these traits at earlier stages of development are required to identify whether these changes arise during development, or if they are a result of neurodegeneration. Our results point to the potential underlying sources for the motor deficits and anxiety-like behavior observed in *Miro1*^{CKO} mice.

Disclosures: J. Afsar-Keshmiri: None. **M. Shribak:** None. **L. Constantine:** None. **O. Thompson:** None. **A.K. Myers:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.08/D8

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant R35NS122073
Adelson Medical Research Foundation, Grant No.04-7023433-##

Title: FARP1 Maintains Axon Initial Segment Architecture and Neuronal Excitability

Authors: *W. ZHANG[1], M. N. RASBAND[2];
[1]Neurosci., Baylor Col. of Med., Houston, TX; [2]Neurosci., Baylor Col. of Med. Dept. of Neurosci., Houston, TX

Abstract: The axon initial segment (AIS) is a specialized neuronal compartment that initiates action potentials and maintains neuronal polarity. These essential functions rely on a highly organized molecular architecture composed of densely packed macromolecular protein complexes. However, the composition and organization of these insoluble molecular assemblies is not fully known, hindering our understanding of AIS assembly and regulation. To address this challenge, we combined detergent extraction with AIS-targeted immunoproximity proteomics to systematically characterize the insoluble proteins of the AIS. Using this approach, we identified FARP1 as a previously unrecognized AIS-enriched insoluble protein. During early neuronal development, FARP1 transiently clusters in the submembrane region of the AIS. To determine its function, we employed CRISPR-mediated knockout, quantitative proteomics, and co-immunoprecipitation and we found that FARP1 associates with AnkyrinG (AnkG) and its interacting partners in a macromolecular complex. AnkG is required for the recruitment and maintenance of FARP1 at the AIS. Long-term loss of FARP1 in cultured neurons reduced AnkG

levels and several AnkG-dependent AIS proteins, leading to decreased neuronal excitability. In contrast, these changes were not observed in Farp1 conditional knockout mice. Together, our findings identify FARP1 as a previously unrecognized component of insoluble AIS protein complexes and reveal a role in maintaining AIS structure and neuronal excitability.

Disclosures: W. Zhang: None. **M.N. Rasband:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.09/D9

Topic: A.03. Axon and Dendrite Development

Support: Midwestern University Intramural Funding

Title: Induction of Neurite Outgrowth by Sesquiterpenes Ircinin-1, Palinurin, and Palinurinine A

Authors: *M. L. PIERCE[1], T. POYNTON[2], J. ABURAS[1], Z. CIESIELSKI[2], L. RODRIGUEZ[3], J. PARK[2], M. HAMANN[4], A. M. MAYER[5];
[1]Pharmacol., [2]Midwestern Univ., Downers Grove, IL; [3]Midwestern University, Chicago Col. of Osteo. Med., Downers Grove, IL; [4]Med. Univ. of South Carolina, Charleston, SC; [5]Pharmacol., Midwestern University, CCOM, Downers Grove, IL

Abstract: Introduction: The complexity of neurodegenerative and neuroinflammatory diseases, coupled with clinical and translational failures, have led many pharmaceutical companies to scale back investment in neuroscience drug development research. Marine natural products have demonstrated biological activity, including potent antimalarial, antimicrobial, and anti-neuroinflammatory activity. One class of marine natural products are sesquiterpenes, which have a 15-carbon skeleton built from three isoprene (5-carbon) units that are found in plants, fungi, and marine organisms where they are used for chemical signaling and microbial control. From an initial screening, ircinin-1, palinurin, and palinurinine A were further evaluated for dose-dependent effects on primary neuronal cultures.
Methods: To test neuritogenic effects, primary murine cortical cultures were fixed and stained with phalloidin and DAPI and imaged using Nikon Confocal Microscope. Total neurite outgrowth, number of processes, and number of branches were quantified using ImageJ with NeuronJ plug-in. For live-dead assays, cultures were stained with Fluorescein Diacetate (FDA) and Propidium Iodide (PI) and imaged using a Nikon Eclipse Ti2e inverted fluorescence microscope and processed using ImageJ. For further viability analysis, Cell Counting Kit-8 (CCK-8) was added to the cultures and absorbance was measured using the Agilent Biotek Synergy H1 plate reader. Concentrations ranging from 1nM-10μM were tested to assess dose-dependent effects of both compounds.
Results: In the dose-response assays, ircinin-1, palinurin, and palinurinine A significantly increased neurite length, number of processes and number of branches at various concentrations.

Assays for cell metabolism and cell death indicated minimal to no toxicity up to 10μM for both compounds at one and seven days in vitro (DIV).
Conclusion: The dose-response and live-dead assays show that ircinin-1, palinurin, and palinurinine A induce neurite outgrowth and complexity at multiple concentrations. These compounds showed minimal effects on cell viability and toxicity at DIV1 and DIV7. Further studies will be performed to assess the immunomodulatory potential of both compounds on both pro- and anti-inflammatory cytokines.

Disclosures: M.L. Pierce: None. **T. Poynton:** None. **J. Aburas:** None. **Z. Ciesielski:** None. **L. Rodriguez:** None. **J. Park:** None. **M. Hamann:** None. **A.M. Mayer:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR119.10/D10

Topic: A.03. Axon and Dendrite Development

Support: NIDCD DIR ZO1 DC000091-01

Title: Examining the Spatiotemporal Characteristics of GABA's Excitatory to Inhibitory Shift During Development of the Mouse Cochlea.

Authors: *H. J. BEAULAC, C. J. WEISZ;
NIDCD, NIH, Bethesda, MD

Abstract: Cochlear innervation by afferent and efferent pathways forms the canonical central-peripheral auditory circuitry. The spiral ganglion contains type I and type II afferent neurons (SGNs) within the cochlea while efferent medial olivocochlear (MOC) neurons of the central auditory system project directly to the cochlea. During auditory development, MOCs contact mechanosensory outer hair cells and form cholinergic synapses. MOCs additionally release GABA, activating presynaptic GABAB receptors and downregulating cholinergic activity. GABA release from MOCs also acts on GABAA receptors in type II SGNs. Intraneuronal chloride concentration is elevated in the neonatal brain due to the high expression and activity of chloride transporters generating chloride influx, causing GABA to depolarize the cell. This excitation via GABA receptors is implicated in synapse and neuronal development. As the brain matures, an upregulation of transporters that extrude chloride causes GABA receptor activation to hyperpolarize the cell, resulting in inhibition. During neonatal sensory development, does GABA produce a similar shift from excitatory to inhibitory activity in cochlear neurons in conjunction with changes in chloride transporter expression? We used calcium imaging as a proxy for cellular excitation to characterize the spatiotemporal changes in applied GABA-induced activity in the developing mouse cochlea. In parallel, we used immunohistochemistry to determine the chloride transporters that affect the change in polarity of GABA responses.
To examine calcium responses in SGNs following exogenous GABA application, we generated

Bhlhb5Cre; SalsaGCaMP6f mice, to express the GCaMP6f calcium indicator in SGNs. Using timelapse confocal microscopy, we imaged calcium activity in response to 30 sec of 1 mM GABA in ex vivo cochleae at P1-15. GABA-induced fluorescence increases, indicative of excitation, in type I and type II SGNs at P5-8, but not at P9+ (n=3-7).
To assess the distribution of chloride transporters, we used immunohistochemistry in C57 wildtype mouse cochleae (n=3-4, P1-15) to examine changes in expression. Cochleae were divided into apical, medial, and basal turns and labeled with antibodies including NKCC1. NKCC1 is present in SGNs at P1 and is expressed in supporting cells beyond P5. Additional labeling for KCC3, KCC4, and CCC9 is underway.
Preliminary results suggest that GABA excites SGNs early in development. A decline in excitation is observed <P9, suggesting that, like other neurons, chloride concentrations decline in SGNs during development. In the mature auditory system, the action of GABA on cochlear afferent neurons is likely inhibitory.

Disclosures: H.J. Beaulac: None. **C.J. Weisz:** None.

Poster

PSTR119: Dendrite and Axon Growth

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: A.03. Axon and Dendrite Development

Support: HRZZ IP-2024-05-4135
HRZZ DOK-NPOO-2023-10-7312

Title: Glycosylation signature of cortical development in human

Authors: *N. JOVANOV MILOSEVIC;
Croatian Inst. for Brain Research, Dept. of Biology, Sch. of Med. Univ. of Zagreb, Zagreb, Croatia

Abstract: The specific brain glycosylation of proteoglycans (PGs) and their spatial-temporal expression and reorganization during development were investigated at the protein and transcriptomic levels using immunohistochemical and RNA-seq analysis in 50 postmortem fetal and perinatal human brains. The results show that the PGs' glycosylation patterns are highly dynamic in humans between the mid-fetal period and the end of the first postnatal year. The chondroitin-sulfate proteoglycans, which are diffusely expressed in the intermediate zone, shift to the subplate zone and then to the cortical plate around 33 weeks of gestation, defining the sublamina of future cortical layers. The versican and keratan-sulfate expression specifies the limbic supra-callosal region and marginal zone at the mid-fetal period. They downregulate around 35 weeks of gestation, in concert with versican upregulation in certain neuronal populations, forming the earliest perineuronal nets. The glycosylation type of the PGs, as revealed by a set of different lectins (WFA, LEL, DSL, and WGA), shows region- and lamina-

specific expression patterns, confirming that this glycosylation contributes to future cerebral cortex region and circuit specification. A significant downregulation of all diffusely expressed PGs and their specific glycosylation pattern in the third trimester of the fetal period affects MRI signal intensity in the fetal and early postnatal brain, highlighting the importance of spatiotemporal PG developmental expression for diagnostic approaches and therapeutic strategies in perinatal medicine.

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Poster

PSTR119: Dendrite and Axon Growth

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Program #/Poster #: PSTR119.12/D12

Topic: A.03. Axon and Dendrite Development

Support: NIH Grant 1P20GM15670801

Title: Roles of Endocannabinoid Signaling in Auditory Nerve Development

Authors: *H. ALZOUGHOOL[1], S. GHOSH[2], B. WALTERS[3], P. THAPA[3];
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Abstract: The mammalian peripheral auditory system contains sensory hair cells (HCs), supporting cells (SCs) and spiral ganglion neurons (SGNs). Outer hair cells (OHCs) and inner hair cells (IHCs) are separated radially but ordered tonotopically. Type I SGNs form bouton synapses where multiple SGNs innervate each IHC. Type II SGNs innervate multiple OHCs by making 90^0 turns toward the higher frequency region from apex towards base. Type II SGNs provide nociceptive signals and influence efferent modulation, while type I SGNs carry the primary signals for auditory sensation. Cannabinoids, like THC, elicit psychoactive effects via interaction with endogenous cannabinoid receptors (e.g., CNR1). Endogenous cannabinoid signaling (ECS) including the receptors, biosynthesis enzymes, and ligands, regulates neurogenesis, axonal pathfinding, and synaptic transmission in the CNS. Recent RNAseq data suggests that ECS receptor *Cnr1* is copiously expressed in the developing SGNs. However, the effect of ECS in the development and function of the peripheral auditory system remains elusive. Here we sought to map the distribution of *Cnr1* and the biosynthetic enzyme *Dagla* in the otic vesicle during embryogenesis and postnatal maturation. In mice, SGN precursors delaminate from the otic vesicle at embryonic day (E)8.5, neurites extend towards the cochlear epithelium by E15.5. Synapses are formed by postnatal day 0 (P0) and pruned by P8-P10 before hearing onset. RNAScope *in-situ* hybridization in cochlear vibratome sections from CD-1 mice at E15.5, P0 and P8 revealed that *Cnr1* is already robustly expressed in the SGNs at E15.5 and persists throughout P0 and P8. *Dagla* expression was not readily detected at E15.5, though it was highly expressed in the SCs at P0 and P8. To examine the role of CNR1 signaling in the development of

SGNs, we collected P10 cochleae from *Cnr1*$^{-/-}$ mice and immunostained for NFH to label the neuronal projections and soma. Pre- and post- synaptic components of ribbon synapses were detected by immunolabelling for CTBP2 and GluR2 respectively. We observed that in *Cnr1*$^{-/-}$ mice, type II SGNs are disorganized, and some "misguided" type II fibers turn towards the apex instead of the base, suggesting perturbed axonal guidance. Furthermore, there were reduced numbers of post synaptic GluR2 puncta, suggesting decreased synapses in the apex of *Cnr1*$^{-/-}$ cochlea. Altogether, our preliminary data suggest important roles of CNR1 signaling in regulating innervation and synapse formation in the developing cochlea. We will further evaluate the effect of CNR1 loss on hearing by comparing auditory brainstem responses of the *Cnr1*$^{-/-}$ mice with their wildtype littermates.

Disclosures: H. Alzoughool: None. **S. Ghosh:** None. **B. Walters:** None. **P. Thapa:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.01/D13

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

Support: NIH Grant 5R01HD027056
NIH Grant T32GM149387

Title: The transcription factor Bar specifies molecular identity and axon guidance of motor neurons innervating transverse muscles in Drosophila motor neurons

Authors: *P. NEWSTEIN[1,2], E. BARTH[1,2], K. LEE[1,2], C. Q. DOE[1,2];
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Abstract: The processes that generate synaptic specificity are not well understood, despite their importance to human diseases. Emerging evidence suggests that homeodomain transcription factors (HDTFs) guide these processes. Given its advanced genetic toolkit and the fact that many of its neuron types and connectivity patterns have been defined, Drosophila melanogaster is a good model to study the generation of synaptic specificity. It is known that the HDTF Eve is responsible for specifying the identity of motor neurons that project out of the intersegmental nerve to innervate dorsal body wall muscles. Another HDTF, Nkx6, is responsible for specifying motor neurons that also exit through the intersegmental nerve, but instead innervate ventral body wall muscles. It is known that Eve and Nkx6 are mutually repressive. These data motivate a two-way model, where Eve activates dorsal fate and represses Nkx6, while Nkx6 activates ventral fate and represses Eve. However, it is currently unclear what genetic program is responsible for specifying MNs fated to innervate the transverse muscles through the segmental nerve, and how this program fits into the Eve-Nkx6 relationship. We confirmed that the HDTF Bar is expressed in the motor neurons targeting transverse muscles and not co-expressed with either Eve or Nkx6. We found that misexpression of the HDTF Bar is sufficient to inhibit the expression of both Eve

and Nkx6 in motor neurons. Furthermore, the transformed motor neurons misexpressing Bar expressed morphological features resembling the endogenous transverse-innervating motor neurons. For example, they exit the ventral nerve cord through the segmental nerve, not the intersegmental nerve. Additionally, these transformed neurons target the transverse muscles, not their normal dorsal or ventral muscles. Furthermore, we have observed defects in locomotor behavior in larvae where neurons with an endogenous dorsal-innervating fate were transformed into a transverse-innervating fate. Together, these results complicate the existing two-way model of Eve and Nkx6 mutual inhibition by including Bar as a third category that inhibits the other HDTFs and is responsible for generating motor neurons fated to exit the ventral nerve cord through the segmental nerve and innervate the transverse muscles. These findings contribute to the understanding of how multiple genetic programs downstream of HDTFs interact to establish precise neural connectivity.

Disclosures: P. Newstein: None. **E. Barth:** None. **K. Lee:** None. **C.Q. Doe:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.02/D14

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

Support: 5R01NS105783 (NIH)
Pharmacology Department (University of Nevada, Reno)

Title: PINK1 Regulation of CaMKII/IV Signaling in Synaptic Structure, BDNF Support, and Neuronal Activity

Authors: *R. K. DAGDA[1], M. WOODRUFF[2], S. SOMAN[2], M. BARANCHESHMEH[3], C. ARAM[4], M. KHODABANDEHLOO[5], S. MOHAMMADIAN[6], A. ALISHVANDI[7], R. DURBIN[8], R. B. RENDEN[3];
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Abstract: PTEN-induced kinase 1 (PINK1) is a mitochondrial serine/threonine kinase with roles in neuronal plasticity. We previously found that PINK1 activation with kinetin increases cleaved PINK1 (c-PINK1) and promotes dendritic growth through a PKA-BDNF axis in primary cortical neurons (Soman et al., 2021, J Neurosci Res); however, H89 only partially blocked kinetin-induced dendrite elongation, suggesting additional mechanisms. Because calcium/calmodulin-dependent kinase IV (CaMKIV) has been linked to PINK1-related mitophagy (Zhang et al.,

2020, Cell Calcium), we tested whether PINK1 regulates synaptic plasticity through calcium/calmodulin (CaM)-dependent CaMKII/IV signaling.Primary mouse hippocampal neurons were treated with kinetin for 24 h or transfected for 3 d with GFP-tagged full-length PINK1, cleaved PINK1 (DeltaN110), or kinase-dead full-length PINK1 while endogenous PINK1 was suppressed by siRNA. Kinetin increased PINK1 autophosphorylation, CaMKII/IV phosphorylation, cleaved BDNF, dendrite length, spine formation, and calcium transient frequency. CaMKII/IV phosphorylation was assessed by Western blotting, Phos-tag Western assays, and immunocytochemistry. KN93, an inhibitor of CaM-dependent kinase activation, attenuated PINK1/kinetin-induced CaMKII/IV phosphorylation, BDNF, dendrite length, spine formation, and calcium transient frequency in most experiments. Spines were quantified by confocal microscopy in DIV17 GFP-transfected hippocampal neurons.Full-length PINK1 and DeltaN110 c-PINK1, but not kinase-dead PINK1, increased phospho-CaMKII and phospho-CaMKIV immunoreactivity. Endogenous CaMKII or CaMKIV immunoprecipitated from whole 10-month-old mouse brain co-precipitated full-length and cleaved PINK1. Conversely, FLAG- or GFP-tagged full-length and cleaved PINK1 pulled down endogenous CaMKII and CaMKIV in transfected SH-SY5Y cells; kinase-dead PINK1 did not impair binding, suggesting catalytic activity is required for activation but not complex formation. Crystal structure-guided modeling and HPC molecular dynamics showed stable PINK1-CaMKII and PINK1-CaMKIV interactions across 100-ns simulations, with a PINK1-CaMKII velcro patch-like interface and distinct PINK1-CaMKIV contacts.All experiments were repeated in three independent biological replicates using vector, kinase-dead, siRNA, and KN93 controls; spine quantification was blinded to condition. Overall, our data support a PINK1-CaM/CaMKII/IV-BDNF pathway that complements the PINK1-PKA-BDNF axis, and links PINK1 activation to dendritic growth, spine formation, and calcium-dependent neuronal activity.

Disclosures: R.K. Dagda: None. **M. Woodruff:** None. **S. Soman:** None. **M. Barancheshmeh:** None. **C. Aram:** None. **M. Khodabandehloo:** None. **S. Mohammadian:** None. **A. Alishvandi:** None. **R. Durbin:** None. **R.B. Renden:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.03/Web Only

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

Support: Grant-in-Aid for Scientific Research (JP21K07274 to ST)
Grant-in-Aid for Start-up (JP23K19402 to HS)
Grant-in-Aid for Young Scientists (JP25K18967 to HS)

Title: Activity-dependent induction of GPR3 links CREB signaling to NR4A1-mediated presynaptic maturation

Authors: H. SHIRAKI[1], K. HARADA[2], N. SAKAI[3], ***S. TANAKA**[4];
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Abstract: Constitutively active G protein-coupled receptors (GPCRs) regulate intracellular signaling without ligand stimulation. GPR3 is a class A rhodopsin-like GPCR that activates Gαs-dependent cAMP signaling and promotes neurite outgrowth, neuronal survival, and axonal regeneration. However, how inducible GPR3 expression contributes to neuronal differentiation remains unclear.
Using NGF-induced differentiation of PC12 cells, we found that Gpr3 mRNA showed biphasic induction, with an early transient increase followed by sustained late-phase upregulation. NET-CAGE analysis detected rapid nascent transcription around the proximal Gpr3 promoter, approximately 200 bp upstream of the transcription start site. Among NGF-responsive early genes, Gpr3 was strongly induced, whereas no other GPCR showed comparable rapid induction. Promoter reporter assays showed that conserved cAMP response elements (CREs) in the upstream regulatory region contribute to NGF- and forskolin-dependent Gpr3 transcription. The proximal −34 CRE had a major role, and ChIP-qPCR showed stimulus-dependent recruitment of phosphorylated CREB to this region after NGF or forskolin treatment.
We next examined whether induced GPR3 regulates downstream CREB-related transcriptional programs. Gpr3 knockdown suppressed delayed upregulation of Nr4a1, Nr4a2, and Nr4a3 during NGF-induced differentiation, whereas GPR3 overexpression increased these genes without external differentiation stimuli. GPR3 also enhanced Nr4a1 promoter activity through CRE-containing regions. Because NR4A transcription factors are involved in neuronal differentiation, we focused on Synapsin1 (Syn1), a presynaptic vesicle-associated gene. Gpr3 knockdown reduced late Syn1 induction, whereas GPR3 overexpression increased Syn1 mRNA. This increase was abolished by Nr4a1 knockdown, but not by Nr4a2 or Nr4a3 knockdown, suggesting that NR4A1 links GPR3 signaling to Syn1 expression.
Finally, primary cortical neurons from Gpr3 knockout mice showed reduced developmental upregulation of Nr4a family genes and Syn1. Immunocytochemical analysis also revealed fewer SYN1-positive presynaptic puncta in Gpr3-deficient neurons at DIV7 and DIV14.
Together, these findings suggest that GPR3 is not only a constitutively active cAMP-generating receptor but also an inducible component of the CREB-regulated early-response network. By amplifying cAMP-CREB signaling and promoting NR4A1-dependent Syn1 expression, GPR3 may coordinate extracellular cues with neuronal maturation and presynaptic development.

Disclosures: H. Shiraki: None. **K. Harada:** None. **N. Sakai:** None. **S. Tanaka:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.04/D15

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

Support: NIH Grant NS097638
NIH Grant NS129668

Title: Non-neuronal cells modulate synaptogenesis at neuromuscular junctions through EGF-domain proteins

Authors: *S. J. CHERRA, III;
Neurosci., Univ. of Kentucky, Lexington, KY

Abstract: Synaptogenesis is a highly orchestrated process coordinated by interactions between neurons forming the synapse and neighboring non-neuronal cells, like glial cells. Using *C. elegans*, this study investigated how non-neuronal cells restrict synapse formation at the neuromuscular junction. EAT-20 is a transmembrane protein that contains epidermal growth factor (EGF)-like domains. Genetic mutations that impair EAT-20 function result in the formation of extra synapses between cholinergic motor neurons and muscle cells. EAT-20::GFP knock-in animals were created using CRISPR/Cas9 technology to investigate the expression pattern of EAT-20. Near neuromuscular junctions, EAT-20::GFP was observed in epidermal cells adjacent to cholinergic neurites and presynaptic terminals. Interestingly, the density of cholinergic synapses could be reduced to wild type levels by expressing wild type EAT-20 in the epidermis but not in neurons. These findings are consistent with the hypothesis that EAT-20 mediates a signal between the epidermis and cholinergic motor neurons. To identify how EAT-20 restricts synapse formation, candidate signal transduction pathways were screened using genetic mutations. Inhibition of a MAP kinase prevented the formation of extra cholinergic synapses in *eat-20* mutants. Moreover, activation of MAP kinase signaling only in cholinergic neurons increased the number of cholinergic neuromuscular junctions to a similar level as *eat-20* mutants. To investigate how epidermal EAT-20 may influence MAP kinase signaling in cholinergic neurons, candidate receptor proteins were screened. Loss of function mutations in one putative EAT-20 receptor resulted in extra cholinergic synapses, but there were no further increases in synapse density in the double mutants. Finally, disruption of MAP kinase signaling in the putative EAT-20 receptor mutant background reduced cholinergic synapses to wild type levels. This interaction is consistent with EAT-20, its putative receptor, and a MAP kinase coordinating a signal between epidermal cells and motor neurons to constrain synapse formation. Altogether, this study suggests that EGF-like domain proteins may provide direct signaling between non-neuronal cells and neurons to coordinate neural circuit formation.

Disclosures: S.J. Cherra: None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.05/D16

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

Support: NSTC114-2326-B-A49-001
NSTC114-2321-B-001-005
NSTC114 2636-B-A49-001
MOST111-2326-B-A49-001-MY3
NSTC Doctoral Fellowship

Title: Npas4 Regulates Synaptic Development in the Patch/Striosome Compartment and Early Affective Vocalization in Neonatal mice

Authors: Y.-H. LEE[1], H.-Y. KUO[1], S.-Y. CHEN[1], Y.-N. CHANG[1], C. R. GERFEN[2], ***F.-C. LIU**[1];
[1]Natl. Yang Ming Chiao Tung Univ., Taipei, Taiwan; [2]LNP NIMH, Bethesda, MD

Abstract: Early vocal communication, such as isolation-induced ultrasonic vocalization (USV) in neonatal rodents, is critical for infant survival and represents a primary readout of early affective states. The patch/striosome compartment in the striatum has been proposed to serve as a limbic-motor interface integrating emotion and motivation. Developmentally, this compartment undergoes early maturation, during which activity-dependent transcription factors might enable the functional assembly of limbic-striosomal circuits to regulate infant vocal-motor behavior. *Npas4*, an activity-dependent early-response transcription factor, controls the developmental balance of excitatory and inhibitory synaptic activity. Here, we investigated how patch/ striosome compartment-expressing *Npas4* shapes early synaptic development and neonatal vocalization. We found that *Npas4* transcripts were transiently enriched in patch/striosomes at postnatal days (P) 4 and P8, before adopting a homogenous striatal distribution by P14. To investigate its biological function, we generated a patch/striosome-specific *Npas4* conditional knockout. Anatomically, *Npas4* deletion disrupted patch/striosomal synaptic balance, evidenced by a significant reduction in excitatory (Vglut1) and an increase in inhibitory (Vgat) presynaptic terminals. Behaviorally, acoustic and Markov-chain syntactical analyses of isolation-induced USVs revealed a hyper-vocal phenotype at P8, characterized by a significant increase in total USV call numbers and augmented temporal clustering of vocal bouts and sequences. Furthermore, acoustic analysis demonstrated a shift toward more complex syllable types. While the structure of global transition networks was preserved, *Npas4* knockout mice exhibited an elevated sequence entropy rate, indicating greater moment-to-moment structural variability. Our study suggests that *Npas4* shapes the development of limbic-striosomal circuits to provide top-down gating of early affective vocalization in neonates.

Disclosures: Y. Lee: None. **H. Kuo:** None. **S. Chen:** None. **Y. Chang:** None. **C.R. Gerfen:** None. **F. Liu:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.06/D17

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

Title: Hide-and-Seek Genome Editing Reveals the Molecular Mechanism of Axo-Axonic Synapse Assembly

Authors: *Y. OGAWA;
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Abstract: A central question in neuroscience is how neurons establish synapses with both the correct cellular partners and the correct subcellular domains. A striking example is the axo-axonic synapse, in which chandelier cells (ChCs) selectively innervate the axon initial segment (AIS) of cortical pyramidal neurons. Although disruption of these synapses has been implicated in neurodevelopmental and neuropsychiatric disorders, the molecular mechanisms underlying their remarkable specificity remain poorly understood.
To identify molecules that mediate AIS-specific synapse assembly, we previously performed the first subcellular proteomic analysis of AIS membranes and identified Contactin-1 (Cntn1) as a novel AIS-enriched adhesion molecule required for axo-axonic synapse assembly. In addition to Cntn1, AIS proteomic analyses identified multiple AIS-associated cell adhesion and signaling molecules, suggesting that several trans-synaptic signaling systems may contribute to AIS targeting. To identify complementary presynaptic determinants, we analyzed single-cell RNA-sequencing datasets of the mouse cortex and identified a set of ChC-enriched genes encoding candidate trans-synaptic interaction partners for AIS-associated proteins.
Together, these findings support a working model in which complementary AIS- and ChC-enriched adhesion molecules form a combinatorial trans-synaptic code that directs axo-axonic synapse specificity. To facilitate systematic functional interrogation of candidate genes in vivo, we developed the Hide-and-Seek genome editing platform, which enables simultaneous CRISPR-mediated gene manipulation and visualization of axo-axonic synapses. Using Hide-and-Seek, we identified the inhibitory postsynaptic scaffold protein Gephyrin as a critical determinant of axo-axonic synapse assembly in vivo. Ongoing studies integrate AIS proteomics, ChC transcriptomics, and Hide-and-Seek-based functional analyses to define the molecular interactions that establish and stabilize axo-axonic synapses. This work will provide new insight into how synaptic specificity is achieved with cell-type and subcellular precision in cortical circuits.

Disclosures: Y. Ogawa: None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.07/D18

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

Support: Howard Hughes Medical Institute

Title: Glial MerTK mediates synaptic pruning in visual system development

Authors: *D. ARIZANOVSKA, A. GUTU, E. K. O'SHEA;
Janelia Res. Campus, Howard Hughes Med. Inst., Ashburn, VA

Abstract: Synaptic elimination and refinement occur during development and are critical for proper neuronal circuitry formation. Glia, primarily microglia and astrocytes, express receptors that recognize and remove excessive synapses to drive developmental circuit remodeling. Myeloid epithelial reproductive proto-oncogene tyrosine kinase (MerTK), a member of the TAM family of receptor tyrosine kinases, is expressed predominantly by microglia and astrocytes in the central nervous system and plays a key role in many biological functions including cell survival and phagocytosis of apoptotic cells. Recently, global MerTK knockout mice established that MerTK is necessary for synaptic refinement during visual system development. In this model, astrocytes but not microglia were found to drive MerTK-mediated synaptic engulfment in the dorsal lateral geniculate nucleus (dLGN); however, the cell-type specific role of astrocytic versus microglial MerTK in visual system development has not been directly addressed. Here, we use microglial ($Cx3cR1^{Cre}:Mertk^{fl/fl}$) and astrocytic ($Aldh1l1^{Cre}:Mertk^{fl/fl}$) MerTK knockout mice to explore the cell specific functions of glial MerTK. Evaluators were blinded to genotype and condition, and all studies were performed in at least technical duplicate. Following intravitreal injection of the retrograde synaptic tracer cholera toxin B (CTB), we show that astrocytic, but not microglial, MerTK is necessary for the eye-specific segregation of synaptic inputs into the dLGN at post-natal day (P10) in both male and female mice (n=8-11). Conversely, at P30, immunohistochemical analysis shows that ablation of MerTK from microglia leads to increased density of excitatory and inhibitory synapses (n=6-9). This is a time-point where, following a second wave of activity-dependent synaptic pruning, refinement is largely complete. Therefore, our data support a dynamic role for glial MerTK in visual system development, where astrocytic MerTK plays a predominant role in early synaptic pruning and microglia contribute to later refinement.

Disclosures: D. Arizanovska: None. **A. Gutu:** None. **E.K. O'Shea:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

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Program #/Poster #: PSTR120.08/D19

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

Support: JST ERATO JPMJER1801
JSPS KAKENHI 22K21353
AMED Brain/MINDS 2.0 24wm0625207s0101

AMED Brain/MINDS 2.0 24wm0625401h0001
AMED Brain/MINDS 2.0 24wm0625502s0501

Title: Microglia-dependent maturation of retrosplenial circuits contributes to infantile amnesia

Authors: *H. MIZUNO[1], Y. IKEGAYA[1,2];
[1]Grad. Sch. of Pharmaceut. Sci., [2]Inst. for AI and Beyond, The Univ. of Tokyo, Tokyo, Japan

Abstract: Memories acquired during infancy are often forgotten later in life, a phenomenon known as infantile amnesia. Accumulating evidence suggests that infantile memories may persist in a latent form but become inaccessible, implicating postnatal circuit maturation in the regulation of memory persistence. The retrosplenial cortex, particularly the granular retrosplenial cortex, is a key cortical region involved in contextual memory processing and receives prominent input from the subiculum. However, the developmental maturation of subiculum-to-retrosplenial circuits and its contribution to infantile amnesia remain poorly understood. Here, we examined the developmental organization of subicular inputs onto two excitatory neuron types in layer 2/3 of the granular retrosplenial cortex: regular-spiking and late-spiking neurons. Using whole-cell patch-clamp recordings in acute mouse brain slices, we found that subicular inputs undergo distinct, cell-type-specific temporal changes across development. We further investigated whether this refinement depends on microglia-mediated mechanisms and assessed its behavioral relevance using contextual fear conditioning combined with retrosplenial microglial manipulation. Notably, we found that microglial depletion—which preserves infant-like retrosplenial circuitry—significantly modulated infantile amnesia, demonstrating a critical role for microglia-dependent circuit refinement in the transition from infantile to adult memory systems. Together, these findings identify microglia-mediated, cell-type-specific circuit maturation in the retrosplenial cortex as a novel mechanism that regulates memory persistence during early postnatal development.

Disclosures: H. Mizuno: None. **Y. Ikegaya:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

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

Support: NIH Grant R01NS132867
NIH Grant R01NS131557

Title: Heightened Juvenile Sleep Serotonin Signaling Gates Critical Period Experience-Dependent Synaptic Remodeling

Authors: *Z. LIN[1], J. C. SEARS[1,2], K. S. BROADIE[1,2,3,4,5];
[1]Dept. of Biol. Sci., [2]Vanderbilt Brain Inst., [3]Dept. of Pharmacol., [4]Dept. of Cell and

Developmental Biol., Vanderbilt Univ., Nashville, TN; [5]Vanderbilt Kennedy Ctr., Vanderbilt Univ. Med. Ctr., Nashville, TN

Abstract: Synaptic connectivity is remodeled in response to environmental input in critical periods, characterized by temporally-restricted, experience-dependent synapse pruning by glia. In a *Drosophila* brain olfactory critical period model, Or42a olfactory sensory neuron (OSN) synapses in juveniles are pruned based on ethyl butyrate (EB) odorant experience during early life. In all animals, including *Drosophila*, juvenile sleep is elevated during critical periods, suggesting a possible role in this precise connectivity editing mechanism. Sleep is known to be an active regulator of synapse number, regulating proper synaptic strength and connectivity. Therefore, we hypothesized that critical period sleep is required for glia-mediated experience-dependent synapse pruning. Here, we find that juvenile *Drosophila* sleep significantly more than adult *Drosophila*, with elevated sleep primarily in afternoon hours. We discover critical period sleep deprivation blocks EB experience-dependent synaptic pruning during the olfactory critical period. Synapse pruning requires sequential 1) glial infiltration and then 2) glial phagocytosis. Through immunolabeling of the specific glial phagocytes, we find critical period sleep deprivation specifically blocks glial infiltration to targeted synapse pruning sites. We have found previously that directed glial infiltration requires a localized elevation in serotonin (5-HT) signaling and experience-dependent upregulation of the serotonergic 5-HT_{2A} receptor (5-HT_{2A}R). Through labeling 5-HT in the juvenile brain, we find critical period sleep deprivation elevates global brain serotonin level to mask the normal circuit-localized targeted glial infiltration signal. Likewise for 5-HT_{2A}Rs, we find that critical period sleep deprivation blocks the experience-dependent 5-HT_{2A}R upregulation required for glial infiltration. Downstream of the serotonergic signaling, glial phagocytosis pruning is triggered by the Basket (mammalian JNK) signaling cascade. We made a new separation of phases-based activity reporter of kinase (SPARK) biosensor transgenic line to test glial JNK function in this triggering mechanism. We find that critical period sleep deprivation blocks experience-dependent glial JNK::SPARK signaling in glia, which then inhibits glial phagocytosis to prevent synapse elimination. Taken together, we conclude that critical period developmental sleep enables 5-HT_{2A}R signaling-dependent circuit-localized glial infiltration to gate critical period glial phagocytic synaptic pruning for brain circuit connectivity optimization in response to early-life sensory input experience.

Disclosures: Z. Lin: None. **J.C. Sears:** None. **K.S. Broadie:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.10/D21

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

Title: Structured retinal waves shape cortical circuit formation, hierarchy, and retinotopic maps

Authors: *B. SHAKERIFAKHER[1], S. CHANDRA[1], I. R. FIETE[2];
[1]Dept. of of Brain and Cognitive Sci., [2]Ctr. for Learning and Memory, MIT, Cambridge, MA

Abstract: Visual cortical areas form before eye opening, when sensory experience is absent but spontaneous retinal waves provide structured patterns of activity. Retinal waves are necessary for normal development including aspects of retinotopic map refinement (Cang et al., 2005; McLaughlin et al., 2003), however it remains unclear which aspects of cortical organization require the detailed spatiotemporal structure of this activity, rather than activity alone. Here, we study a computational model of early visual system development to test how the spatiotemporal statistics of spontaneous activity shape cortical hierarchy, retinotopy, and circuit motifs.The model consists of a retinal input sheet projecting to an unparcellated cortical sheet corresponding to the visual field, whose synapses form, grow, and prune through an activity- and distance-dependent seek-and-prune rule. Active neurons attempt to form nearby connections, while each neuron is constrained by a budget on incoming and outgoing synaptic projections. Within a neuron, connections compete according to activity and distance, allowing stronger candidate synapses to replace weaker existing ones. We compare structured retinal waves, which propagate across the retina and generate spatially and temporally correlated activation, with randomized activity patterns that preserve overall activity statistics but disrupt wave structure. By varying wave statistics, connection constraints, and activity attenuation across cortical distance, we quantify the time to convergence and number of synaptic prunings until a stable cortical organization emerges, and also quantify feedforward organization, lateral/recurrent connectivity, and map stability.This framework separates permissive effects of activity from instructive effects of activity structure. Preliminary simulations suggest that generic activity can support feedforward hierarchy, whereas structured retinal waves can alter developmental efficiency and bias additional connection motifs. In particular, wave-like correlations may reduce pruning needed to reach stable connectivity and promote lateral or recurrent connections among neurons with related receptive fields. These results suggest that spontaneous activity does more than enable early circuit formation: its spatiotemporal statistics can shape which wiring motifs emerge. The model provides a quantitative framework linking retinal-wave statistics to cortical circuit architecture and may help identify how abnormal early activity patterns contribute to maladaptive development or circuit instability.

Disclosures: B. Shakerifakher: None. **S. Chandra:** None. **I.R. Fiete:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.11/D22

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

Support: NIH Grant R01EY025627

Title: Visual experience drives divergent FMRP-dependent and -independent modes of circuit maintenance in the superficial superior colliculus

Authors: *G. SHARMA[1], A. L. RUSSELL[2], J. W. TRIPLETT[2];
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Abstract: Decades of work have elucidated the mechanisms driving the development and plasticity of neuronal circuits, but how wired circuits maintain their connectivity remains poorly understood. The superficial superior colliculus (sSC) receives topographically organized corticocollicular projections from layer 5 of primary visual cortex (V1CC), which are aligned with the retinocollicular map. Previously, we found that visual map alignment was disrupted in a mouse model of fragile X syndrome (Fmr1-/y), but when these deficits arise is not known. Surprisingly, we found that initial refinement of V1CC axons proceeds normally in Fmr1-/y mice, but terminal zones (TZs) become progressively larger following eye opening, suggesting active maintenance of connectivity mediated by visual experience and fragile X messenger ribonucleoprotein (FMRP). To test this, we deprived wild type (WT), Fmr1-/y, and Fmr1+/- mice of visual experience via eyelid suture beginning at postnatal day 11 (P11) and traced V1CC projections at P45. Consistent with previous results, we observed enlarged TZs in Fmr1-/y sham control mice, which was phenocopied in Fmr1+/- mice. In all groups, visual deprivation led to a significant increase in V1CC TZ size, showing that visual experience is actively required to maintain V1CC refinement. Interestingly, V1CC TZs in deprived Fmr1-/y and Fmr1+/- were significantly smaller than in sham conditions, suggesting distinct modes of experience-dependent maintenance. To explore this possibility, we sutured eyes in all groups at P21, allowing one week of visual experience prior to deprivation. In WT mice, we found TZs were increased in size, though not significantly. In both Fmr1-/y and Fmr1+/- mice, delayed deprivation resulted in significant increases in TZ size, which were larger than those observed in fully deprived mice. Next, we asked if precocious visual experience impacted visual map alignment in each group. Opening eyes at P8 drove premature TZ enlargement in Fmr1-/y mice by P12, confirming that patterned activity, not age, triggers the phenotype in these mice. Interestingly, precocious visual experience accelerated refinement in WT mice, further supporting a role for visual experience in sSC circuit wiring. Together these results demonstrate that visual experience is required for maintenance of visual map alignment in the sSC, which is in part mediated by FMRP. Furthermore, our findings suggest that the onset of patterned vision triggers a phase of circuit assembly driven by FMRP, which is dispensable prior to this.

Disclosures: G. Sharma: None. **A.L. Russell:** None. **J.W. Triplett:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.12/E1

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

Support: NIH Grant U01DC018537

Title: Investigating the Role of Peripheral Tonotopy in Auditory Circuit Development

Authors: K. OWUSU-NYANTAKYI[1], A. SNYDER[1], A. LANGEN[2], W. CHANG[3], C. J. WEISZ[3], M. W. KELLEY[3], *R. BURGER[1];
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Abstract: Tonotopy, the spatial mapping of frequency tuning across populations of neurons, is a key organizing feature of the auditory system. While tonotopy is established in the ear, tonotopic features of auditory processing are recapitulated in most higher order structures. However, the deterministic role of peripheral tonotopic patterning in the development of central auditory structures is poorly understood. In birds, a major functional role of the Nucleus Magnocellularis (NM) is to encode temporal information from acoustic stimuli via phase-locked discharge output to Nucleus Laminaris, the site of binaural coincidence detection for sound localization. In order to maintain temporal precision across the frequency map, NM neurons express tonotopically distributed anatomical and physiological properties that support this function. One such attribute is the distribution of synaptic terminal size and strength from innervating Auditory Nerve Fibers (ANFs). High Characteristic Frequency (HCF) NM neurons are innervated by one or two large endbulb ANF terminals that generate large EPSCs, while Low Characteristic Frequency (LCF) NM neurons are innervated by multiple small synaptic boutons with correspondingly small EPSCs. In this study, we aimed to test whether morphogenic manipulation of cochlear tonotopy influences the development of central auditory circuitry, specifically focusing on patterning of ANF synapse terminal structure and strength in the NM. We applied the morphogen Bmp7 in the early (E5) embryonic chick otocyst to disrupt phenotypic identity in hair cells across the tonotopic axis. Bmp7 specifies low frequency phenotypes in the cochlea. We then labelled the ANFs in E17-18 embryos via electroporation of fluor-tagged dextran into ANFs, which completely filled neurons including their synaptic terminals. We counterstained postsynaptic NM neurons' membranes and nuclei with wheat germ agglutinin (WGA) and 4',6-diamidino-2-phenylindole (DAPI), respectively. Synaptic terminal size was quantified from confocal images using a 3D image segmentation tool. In complementary experiments, we recorded synaptic strength of ANF terminals ipsilateral to control or Bmp7-manipulated ears by measuring evoked unitary EPSC magnitude and kinetics using whole cell voltage clamp. Anatomical and physiological data indicate that central tonotopic gradients of synaptic morphology and strength are reflective of tonotopic organization in both control and manipulated inner ears, suggesting that peripheral organization has a significant and deterministic influence on generation of tonotopic patterns in central circuitry during development.

Disclosures: K. Owusu-Nyantakyi: None. **A. Snyder:** None. **A. Langen:** None. **W. Chang:** None. **C.J. Weisz:** None. **M.W. Kelley:** None. **R. Burger:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.13/E2

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

Support: NIMH R01MH126176

Title: Developmental regulation of synaptotagmin organization in the avian auditory brainstem

Authors: *S. SABBAGH[1,2], S. BEST[2], Y. WANG[2];
[2]Dept. of Biomed. Sci., [1]Florida State Univ., Tallahassee, FL

Abstract: Developing sensory circuits must rapidly acquire mature synaptic release properties to support neural computation. A key component of this maturation is the assembly of presynaptic machinery, including the calcium sensors synaptotagmin (Syt)-1 and -2, which govern the timing and reliability of neurotransmission. How these sensors become differentially distributed across inputs targeting distinct dendritic domains remains unclear. We used the avian brainstem to examine domain-specific presynaptic maturation. Excitatory inputs to bipolar coincidence-detecting neurons innervate segregated dorsal and ventral dendrites, enabling direct comparison of developmental trajectories across computational sub compartments. We quantified Syt1 and Syt2 localization from embryonic day (E) 9, when initial synapses form, through E19, when the circuit is functionally mature. Early in development (E9-11), both sensors were enriched in the ventral domains, indicating asymmetric maturation of presynaptic inputs. This pattern was absent for SV2 (a core synaptic vesicle protein), showing that the asymmetry reflects selective maturation of calcium sensors rather than global vesicle expansion. Syt1 and Syt2 also followed a proximal-to-distal gradient, with stronger proximal labeling that declined distally, suggesting that presynaptic maturation initiates near the soma and extends outward along the dendrite. By E15 and E19, both the domain bias and the proximal-distal gradient disappeared, indicating that these asymmetries are transient developmental features. Across all stages, Syt1 and Syt2 colocalized predominantly with VGluT2-positive excitatory terminals, but were also present in a subset of peri-somatic VGAT-containing inhibitory terminals, revealing a specialized class of inhibitory inputs. Finally, knockdown of an RNA-binding protein FMRP disrupted Syt2 upregulation, delaying the transition toward mature presynaptic states. Together, these findings reveal that presynaptic calcium-sensor organization is shaped by developmental stage, dendritic compartment, local dendritic position, and regulated by FMRP, revealing subcellular specialization of release machinery as a mechanism supporting the emergence of precise sensory computations.

Disclosures: S. Sabbagh: None. **S. Best:** None. **Y. Wang:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.14/E3

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

Support: NIH Grant R00NS124976

Title: Characterizing spatiotemporal dynamics of early-life spontaneous activity across the fly brain

Authors: *T. TRUONG[1], M. KELES[2];
[1]Johns Hopkins Univ., Baltimore, MD; [2]Johns Hopkins Sch. of Med., Baltimore, MD

Abstract: Spontaneous activity is critical for the early-life establishment of neural circuits. In mammalian sensory systems, spontaneous activity is required for precise topographic wiring during heightened periods of plasticity and is known to decline and refine as circuits mature. In contrast, maturation of the invertebrate brain has traditionally been considered largely genetically hard-wired. However, recent studies have documented robust spontaneous activity during neural circuit development. Whether these developmental programs exhibit conserved spatiotemporal dynamics across functionally distinct circuits or instead mature in a modality-specific manner remains unclear. Here, we recorded neural activity in juvenile *Drosophila melanogaster* to characterize the developmental trajectory of spontaneous activity across sensory and associative brain centers. To visualize spontaneous activity, we expressed a genetically encoded calcium indicator (GCaMP) pan-neuronally localized either throughout neurons or to synaptic compartments and performed *in vivo* two-photon calcium imaging across sensory-processing centers in young (1-day-old) and mature (≥5-day-old) flies. In the optic lobe (OL) where visual information is first processed, we found robust, patterned spontaneous activity during development that is significantly reduced in mature flies. Immature OL's exhibited widespread asynchronous activity across columnar neurons. Individual events recruited a high degree of coordination across columns but varied in their temporal coherence, resulting in broad propagating sweeps that differed in their onset and duration. In contrast, mature OL's exhibited markedly reduced spontaneous activity, with most columnar neurons remaining silent during recording. Active neurons were typically confined to smaller, spatially adjacent groups, coordinating with fewer neighboring columns and exhibiting greater temporal synchrony. Together, these findings reveal a developmental shift from broad, dynamically coordinated activity patterns to sparse, localized activity during circuit maturation in *Drosophila melanogaster*. Characterizing these developmental activity patterns in a genetically tractable model provides a foundation for investigating the neurobiological origins and functions of intrinsically generated activity that may be conserved across species.

Disclosures: T. Truong: None. **M. Keles:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.15/E4

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

Support: NIH R01MH135425

Title: Refinement of Intracortical Circuits of Mice Medial Prefrontal Cortex throughout Development

Authors: ***Z. XU**[1], J. KAO[2], P. O. KANOLD[1];
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Abstract: Healthy social cognition and behavior are essential for everyday communication, allowing humans and animals to navigate relationships. Among brain areas associated with such an important function, prelimbic layer 5 (PL L5) of the medial prefrontal cortex (mPFC) serves as a final hub that integrates local inputs and sends commands to downstream regions to initiate social behaviors. The mPFC undergoes a protracted development expanding from adolescence to adulthood with a continued process of myelination and synaptic pruning, yet it remains unknown how its intracortical connectivity matures through this period. Tracking the development of inputs onto PL L5 establishes the baseline knowledge of the maturation of this key structure for cognitive processing, and provides novel insights for future studies into mPFC circuit dysfunctions and associated psychiatric disorders. To investigate the maturation of intracortical inputs onto PL L5, we performed whole-cell patch clamp recordings with laser-scanning photostimulation to spatially map the local inputs onto PL L5 pyramidal neurons of male and female mice at five time points (postnatal week 2, 3, 4, 5, and 9). We found that across ages, PL L5 pyramidal neurons receive more synaptic input from other L5 cells than from other cortical layers. With age, the total amount of intracortical inputs to PL L5 pyramidal neurons decreased from PW2 to PW4. Taking into consideration the spatial input distribution, the input areas and strength from L2/3 to L5 pyramidal neurons decreased from PW2 to the weaning age, PW3. Similar reductions were also observed in the inputs from surrounding L5 neurons to L5 pyramidal neurons, and these reductions extended into PW4. These results showed the profound refinement of intracortical circuits involving mPFC L5 throughout the development from postnatal weeks 2 to 4, which may also, in turn, affect the downstream processing critical to the maturation of social cognition and behaviors. We speculate that disruption by environmental or social stress during such sensitive periods may negatively impact the refinement of mPFC circuits with a prolonged effect extending into adulthood.

Disclosures: Z. Xu: None. **J. Kao:** None. **P.O. Kanold:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.16/E5

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

Support: MH124695

Title: Striatopallidal output regulates the postnatal maturation of prefrontal inhibition

Authors: *M. JANECEK[1], R. PEIXOTO[2];
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Abstract: Prefrontal cortex (PFC) and the basal ganglia are interconnected through a series of cortico-striato-thalamo-cortical (CSTC) loops that support cognitive and motor functions, and whose dysfunction is implicated in multiple neurodevelopmental disorders. In adult mice, striatal spiny projection neurons (SPNs) expressing dopamine 1 receptor (D1-SPNs) and striatopallidal dopamine 2 receptor-expressing (D2-SPNs) play opposing roles in regulating the activity of cortical pyramidal (PYR) neurons. Yet, the contribution of striatal output in the maturation of upstream cortical circuits in development remains poorly understood. We previously found that, in agreement with this classical model, partial focal ablation of D1-SPNs or D2-SPNs induced in the first two postnatal weeks bidirectionally regulates the activity of prefrontal cortical circuits. In the postnatal PFC, inhibitory GABA transmission is mainly provided by two non-overlapping cell-types: early-born somatostatin (SST) and later parvalbumin (PV) expressing interneurons (IN). When investigating the consequences of striatopallidal dysfunction on GABAergic synapse maturation at P15, we observed that whereas SST-PYR synapses were spared, PV-PYR output was markedly reduced following striatopallidal ablation. This line of work left gaps in knowledge in the specific circuitry mediating this inhibitory deficit, in the role of animal state on network activity, and in the timing of when striatopallidal output informs CSTC maturation. To address these, we extend our analysis of population-level Ca^{2+} imaging by considering the state of the network and find that striatopallidal dysfunction exerts strongest effects on PFC activity during quiescence network states. Further, we complete the CSTC loop by testing whether thalamo-cortical feed-forward inhibition (FFI), largely mediated by PV-INs, is similarly affected by striatopallidal dysfunction. Finally, we ask whether PFC inhibitory plasticity is similarly affected by early postnatal and adult ablation of D2-SPNs. We find that striatopallidal dysfunction in adult animals has surprisingly minimal effects on PFC PYR input. Taken together, our findings indicate that striatopallidal output may exert strongest influence over PFC networks in early postnatal development rather than in adulthood, and that its effects are network-state-dependent. Our findings highlight the need to understand how disease-relevant perturbations in CSTC nodes might similarly dysregulate the establishment and maintenance of cortical excitation and inhibition.

Disclosures: M. Janecek: None. **R. Peixoto:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.17/E6

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

Support: NIH R21MH135232-01A1

Title: Hippocampal NMDA Receptor GluN2A Ionotropic Signaling is Required for the Maturation of Spatial Learning and Memory

Authors: *A. E. M. FINDLEY[1], W. SYED[2], J. A. SHANANIER[2], L. B. CLINE[2], T. C. DUMAS[1];
[1]Psychology, [2]George Mason Univ., Fairfax, VA

Abstract: Spatial learning and memory abilities reliant on the hippocampus develop late postnatally across mammalian species. In rodents, behavioral indices of mature spatial learning and memory emerge at roughly three weeks of age. In parallel, the subunit composition of N-methyl-D-aspartate receptors (NMDARs) is also modified such that NMDARs containing GluN2B subunits are replaced by NMDARs containing GluN2A subunits. Molecular manipulations that delay the GluN2B to GluN2A shift delay the maturation of contextual learning and, conversely, advancing the GluN2B to GluN2A shift advances the maturation of contextual learning, illustrating the sufficiency and necessity of the GluN2B to GluN2A shift for mature contextual memory formation. NMDARs produce ionotropic and nonionotropic signals that are regulated by the GluN2 subunits. However, the dependence of hippocampal maturation on ionotropic versus nonionotropic signaling remains unclear. To investigate the importance of ionotropic versus nonionotropic signaling in spatial learning and memory, we tested mice expressing chimeric GluN2 subunits (carboxy terminal domains are swapped between GluN2A and GluN2B) in a modified Barnes maze task at different developmental stages. The task spanned four consecutive days, consisting of a habituation day, two training days including five blocks of four training trials which preceded an immediate probe trial, and concluded with a probe trial twenty-four hours after training. Mice began testing at postnatal day (P) 17-19, 22-24, or 57-59, representing the developmental periods just prior to and after the GluN2B to GluN2A shift, and adulthood. Preliminary results indicate that age-related improvements in spatial learning and memory occur in mice expressing GluN2A-BCTD subunits and wildtypes (WTs), demonstrated by a downward trend in path length to goal as age increases. The GluN2B-ACTD transgenic and GluN2A-KO mice do not show any performance improvement with increasing age. These results suggest that the maturation of spatial learning relies on an increase in GluN2A ionotropic signaling. This study adds a new dimension (ionotropic versus nonionotropic) to the current understanding of the importance of NMDAR signaling for the maturation of spatial learning and memory. Our findings also shine a broader light on the impact of NMDAR dysfunction in numerous complex brain disorders including schizophrenia, autism spectrum disorders, and depression.

Disclosures: A.E.M. Findley: None. **W. Syed:** None. **J.A. Shananier:** None. **L.B. Cline:** None. **T.C. Dumas:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.19/E7

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

Support: R01NS100738
2R01NS100738

Title: Forniceal deep brain stimulation improves memory in Rett syndrome mice by promoting the maturation of adult-born hippocampal neurons

Authors: *Q. WANG[1], B. TANG[1], Z. WU[1], J. TANG[2];
[2]Pediatrics, [1]Baylor Col. of Med., Houston, TX

Abstract: Deep brain stimulation (DBS) is a neurosurgical intervention that delivers electrical stimulation to specific brain targets via implanted electrodes. Although its clinical applications have expanded beyond movement disorders to include cognitive and neuropsychiatric dysfunction, the mechanisms underlying its therapeutic effects remain incompletely understood. Emerging evidence suggests that DBS of hippocampus-connected structures, such as the entorhinal cortex and fimbria-fornix, enhances adult hippocampal neurogenesis (AHN), which may contribute to improvements in learning and memory. However, direct evidence supporting a causal role for AHN in DBS-mediated cognitive benefits is limited, and the effects of DBS on the maturation and circuit integration of newborn neurons remain largely unexplored. Here, we establish a causal link between DBS-induced AHN and hippocampal memory enhancement in a mouse model of Rett syndrome (RTT). Genetic or pharmacological ablation of AHN abolished the beneficial effects of forniceal DBS on contextual fear memory, demonstrating that AHN is required for DBS-mediated cognitive improvement. Furthermore, DBS promoted the maturation and functional integration of newborn dentate granule cells (DGCs), which were essential for memory enhancement. In RTT mice, MeCP2-deficient newborn DGCs exhibited impaired dendritic development and synaptic dysfunction. Forniceal DBS rescued dendritic arborization, synaptogenesis, and long-term synaptic plasticity in these cells. This was likely attributed to the fact that MeCP2 deficiency disrupted the function of the K^+/Cl^- cotransporter KCC2, a key regulator of GABAergic maturation in developing neurons. DBS restored KCC2 function by increasing its expression and activating phosphorylation, thereby normalizing the delayed developmental switch from GABA-induced depolarization to hyperpolarization in newborn MeCP2-deficient DGCs. Collectively, these findings identify enhanced maturation and circuit integration of adult-born neurons as a critical mechanism underlying DBS-induced cognitive improvement and highlight KCC2-mediated GABAergic maturation as a potential therapeutic target in RTT. This work was supported by NINDS R01NS100738 and 2R01NS100738.

Disclosures: Q. Wang: None. **B. Tang:** None. **Z. Wu:** None. **J. Tang:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.20/E8

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

Support: R01MH136990-03
BRFSG-2025-12

Title: Neonatal cholinergic circuits regulate cortical maturation

Authors: *E. D. MENEZES[1], A. S. GUZMAN[2], L. MA[5], D. VALDEMAR[6], T. GODFREY-ANDRADE[3], D. Y. JUNG[7], S. KAUSHALYA[2], J. PREALL[4], J. GELINAS[8], G. POUCHELON[3];
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Abstract: The neocortex underlies our conscious perception of the environment. While cortical development is known to be regulated by sensory experience, whether other factors, such as neonatal brain states, also influence this process remains largely unexplored. Basal forebrain (BF) cholinergic neurons project broadly across the cortex and modulate brain states, including arousal and sleep-wake transitions, in adult mice. Although neonatal awareness is not yet mature, neonates experience distinct brain states that alternate between sleep and wakefulness. Yet whether cholinergic networks are engaged during neonatal brain states and contribute to cortical development remains largely unknown.Here, we investigate how the BF cholinergic system influences neonatal brain states and early cortical maturation using complementary approaches, including electroencephalography (EEG) and electromyography (EMG), chemogenetics, electrocorticography (ECoG), viral circuit manipulations, and single-nuclei transcriptomics. We found that BF cholinergic neurons regulate neonatal sleep and wakefulness as early as postnatal day 5 (P5), coincident with the invasion of their projections into the neocortex, and modulate the characteristic patterns of neonatal cortical activity. Moreover, silencing BF cholinergic inputs profoundly disrupted cortical neuron maturation at both the circuit and molecular levels.Together, these findings identify early-life cholinergic signaling as a key regulator of neonatal brain states and cortical development. More broadly, they expand current models of early cortical development beyond sensory experience and establish neuromodulatory systems as fundamental contributors to cortical maturation.

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Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.21/F1

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

Support: NINDS IRP

Title: Threat memory encoding in basal forebrain cholinergic neurons

Authors: *F. LUO[1], G. WATKINS[4], L. JIANG[5], N. S. DESAI[2], D. A. TALMAGE[1], L. W. ROLE[3];
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Abstract: Distinct populations of basal forebrain cholinergic neurons (BFCN) provide major cholinergic inputs to the basolateral amygdala (BLA) and hippocampus, two critical brain regions for threat memory processing. Cholinergic neurons engaged in associative threat learning in the nucleus basalis/posterior substantia innominata (NBM/SIp) project to the BLA, while those in the medial septum/vertical diagonal band (MS/vDB) innervate the hippocampus & entorhinal cortex. While both of these pathways contribute to threat memory, it remains unclear whether the distinct BFCN populations undergo similar plasticity during associative threat-memory encoding and retrieval.We used an activity-dependent and Cre-dependent (ADCD) viral construct in ChAT-Cre x Fos-tTA/GFP mice to label cholinergic neurons activated during cued threat training and/or reactivated during recall. We examined the electrophysiological properties of NBM/SIp and MS/vDB neurons in three groups: behaviorally naïve controls, mice analyzed 2.5 hours post-recall, and mice analyzed 48 hours post-recall. We found that NBM/SIp and MS/vDB cholinergic neurons exhibit distinct baseline profiles in naïve animals. Following threat memory recall, both populations showed changes in their electrophysiological profiles. Principal component analysis indicated that despite starting from different experience - naïve states NBM/SIp and MS/vDB neurons converge to occupy similar feature space during threat memory recall, consistent with distinct plasticity trajectories. Convergence on the higher excitability states of NBM/SI neurons required changes in 14 of the 18 physiological features, whereas MS/vDB neurons required change in only 10 of the 18 features. Both populations underwent increases in maximum firing rates, reduced firing thresholds, and decreased rheobase. By 48 hours post-recall, multiple physiological parameters of both NBM and MS populations began to relax back to their more experience-naive like states.These findings demonstrate that distinct BFCN populations employ region-specific plasticity mechanisms to support threat memory encoding and retrieval, with both populations converging to a comparable state during active recall despite following different trajectories from their respective baseline states.

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Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.22/F2

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

Title: Investigating the Role of CRD-Nrg1 Signaling in Modulating the Development of Basal Forebrain Cholinergic Neuron Innervation to the Basolateral Amygdala

Authors: *A. CICEU[1], D. FREEMAN[2], C. ZHONG[3], D. A. TALMAGE[4], L. W. ROLE[5]; [1]Natl. Inst. of Neurolog. Disorders and Stroke, Arlington, VA; [2]NIH, Washington, DC; [3]Circuits, Synapses, and Mol. Signaling Section, [5]NINDS, [4]NINDS, Bethesda, MD

Abstract: During brain development, basal forebrain cholinergic neurons (BFCNs) elaborate extensively branched axonal arbors. The regulation of this process has been largely unexplored. We have begun to examine the function of the axonal signaling molecule CRD-Nrg1 in the regulation of BFCN axonal morphogenesis. CRD-Nrg1 is required for survival of spinal cord and brain stem cholinergic motor neurons. Whether CRD-Nrg1 signaling serves a vital role for BFCN development remains unresolved. This gap in understanding has broad implications given that altered CRD-Nrg-1/ErbB4 signaling is associated with increased risk of schizophrenia and neurodevelopmental disorder pathogenesis and may be involved in the premature deterioration of cholinergic neurons in Alzheimer's disease. Consequently, understanding how developmental Nrg1-1/ErbB4 signaling orchestrates BFCN axonal architecture and presynaptic identity could shed light on features of early circuit formation that influence long-term neuronal risk or resilience to neurodegeneration and other forms of dysfunction. To explore the role of Nrg-1/ErbB4 signaling in BFCN development, I am analyzing how the loss of a functional copy of Nrg1 in heterozygous CRD-Nrg1 mutant mice influences the development of cholinergic innervation to the basolateral amygdala, a circuit key to the regulation of conditioned fear memory formation and retention via convergent cholinergic and glutamatergic synaptic transmission. Preliminary data suggest that P70 HET mutants exhibit reduced cholinergic axons within the BLA, with finer analysis revealing a region-specific decrease in the medial BLA subregion. Older HET mutant mice display a remarkable increase in cholinergic axons, which also appear more disorganized in the CRD-Nrg1 heterozygotes. These data underscore an age-dependent cholinergic expression phenotype emergent in heterozygous CRD-Nrg1 mutant animals.

Disclosures: A. Ciceu: None. **D. Freeman:** None. **C. Zhong:** None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.23/F3

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

Title: Investigating the Interaction of CRD-Nrg1 and Acetylcholine in Threat Memory

Authors: *A. GEORGE[1], P. RAJEBHOSALE[2], L. JIANG[2], L. W. ROLE[3], D. A. TALMAGE[4]; [1]NINDS/NIH, Bethesda, MD; [2]NINDS, NIH/ NINDS, Bethesda, MD; [3]NINDS, [4]NINDS, Bethesda, MD

Abstract: Basal forebrain cholinergic neurons (BFCNs) and their synapses are vulnerable to neurodegenerative processes, yet the molecular mechanisms underlying this susceptibility remain poorly understood. Cysteine rich domain-containing Neuregulin-1 (CRD-Nrg1) is a presynaptic transmembrane protein expressed in cholinergic neurons of the brain and spinal cord. CRD-Nrg1 is critical for the development and maintenance of cholinergic synapses at the neuromuscular junction, but its role in central cholinergic circuits remains unclear. Here, we investigated whether reduced CRD-Nrg1 expression alters the number and/or function of BFCNs, focusing on the cholinergic circuit between the nucleus basalis/substantia innominata (NBM/SI) and the basolateral amygdala (BLA). Because activity in the basal forebrain-to-BLA cholinergic circuit is required for conditioned threat learning and recall, this pathway provides a behavioral readout of circuit dysfunction following CRD-Nrg1 reduction. To investigate the importance of CRD-Nrg1 for threat memory, we evaluated the performance of WT mice and mice with heterozygous deletion of CRD-Nrg1 (CRD-Het) in a cued fear conditioning task. While both groups of animals displayed similar defensive behavior during the training session, CRD-Het mice displayed impaired responses (reduced freezing) during the recall session compared to WT mice. We next asked whether reductions in CRD-Nrg1 affect the engagement of the NBM/SI to BLA cholinergic circuit in response to recall of a threat memory. We quantified the number of BFCNs present within the NBM/SI, as well as the number of activated BFCNs, as assessed by Fos expression, in response to threat recall. The distribution of cholinergic neurons throughout the NBM/SI was similar between WT and CRD-Het mice. However, activation of BFCNs in response to threat recall was impaired in CRD-Het mice particularly within a BLA-projecting subregion of the NBM/SI. Furthermore, neuronal spatial organization analysis revealed subregion-specific loss of activation in the NBM/SI BFCNs of CRD-Het mice. Similarly, we found a loss of activation within the anterior BLA in CRD-Het mice compared to WT mice following threat recall. Ongoing studies seek to evaluate the causal relationship between deficits in NBM/SI to BLA cholinergic signaling and reductions in CRD-Nrg1 signaling. We aim to understand the specific contribution of CRD-Nrg1 signaling in BFCNs by performing cholinergic specific knockdown and re-expression of CRD-Nrg1 signaling in WT and CRD-Het mice respectively. These studies identify CRD-Nrg1 as a potential regulator of cholinergic circuit function and threat memory encoding.

Disclosures: A. George: None. **P. Rajebhosale:** None. **L. Jiang:** None. **L.W. Role:** None. **D.A. Talmage:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.24/F4

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

Support: NINDS IRP 1ZIANS009424
NINDS IRP 1ZIANS009416
Brain & Behavior Research Foundation NARSAD 33680

Title: Semilunar Granule Cells Come of Age: Molecular Identity, Developmental Maturation, and Alterations Across Neuropsychiatric Risk Models

Authors: *P. RAJEBHOSALE[1], L. JIANG[2], A. GEORGE[3], N. S. DESAI[4], Y. ZHANG[7], L. W. ROLE[5], D. A. TALMAGE[6];
[2]NINDS, [1]NIH/ NINDS, Bethesda, MD; [3]NINDS/NIH, Bethesda, MD; [4]Circuits, Synapses, and Mol. Signaling Section, [5]NINDS, [6]NINDS, Bethesda, MD; [7]NINDS, NIH, Bethesda, MD

Abstract: The dentate gyrus (DG) contains heterogeneous populations of glutamatergic principal neurons that contribute to hippocampal circuit function. Semilunar granule cells (SGCs) are a rare subtype of DG granule cells, typically comprising less than 5% of the granule cell population. Here, we combined electrophysiological, morphological, and transcriptomic approaches to define SGCs and examine their vulnerability across models of psychiatric disease risk. We found that SGCs exhibit electrophysiological properties and gene expression profiles distinct from typical granule cells. We identified novel molecular markers for this population and, using these markers, observed that SGC abundance increases during postnatal maturation, reaching adult levels between 2-3 months of age. Notably, SGC representation is significantly elevated in Neuregulin-1 (Nrg1) mutant mice. Using these markers, we further identified increased SGC abundance in a mouse model of 22q11.2 deletion syndrome, suggesting convergent alterations in DG cellular composition across distinct genetic risk factors for psychiatric disease. Ongoing studies are evaluating the cellular, morphological, and circuit-level consequences of altered SGC abundance in genetic and environmental risk models, including early-life stress. In parallel, chemogenetic and slice electrophysiological approaches are being used to investigate the contribution of SGCs to DG circuit function and behavior. Finally, comparative analyses in nonhuman primate and human DG tissue are assessing the conservation of SGC molecular and physiological features across species. Together, these findings establish SGCs as a molecularly distinct and developmentally regulated DG cell population and suggest that altered SGC abundance may represent a convergent mechanism linking neurodevelopmental risk factors to hippocampal circuit dysfunction.

Disclosures: P. Rajebhosale: None. **L. Jiang:** None. **A. George:** None. **N.S. Desai:** None. **Y. Zhang:** None. **L.W. Role:** None. **D.A. Talmage:** None.

Poster

PSTR120: Synapse and Circuit Formation, Maturation, and Remodeling

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR120.25/F5

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

Support: This work was supported by funds from the NINDS IRP

Title: Functional imaging analysis reveals heterogeneous acetylcholine release along individual cholinergic axons in mouse ventral hippocampus

Authors: *C. ZHONG[1], N. S. DESAI[2], Y. LI[4], D. A. TALMAGE[1], L. W. ROLE[3];
[2]Circuits, Synapses, and Mol. Signaling Section, [3]NINDS, [1]NINDS, Bethesda, MD; [4]Sch. of life sciences, Peking Univ., Beijing, China

Abstract: Cholinergic projections from the medial septum and diagonal band (MS/DB) to the ventral hippocampus (vHipp) modulate attention, learning, and emotional memory. However, the spatiotemporal dynamics of acetylcholine (ACh) release remain controversial, with ongoing debate between slow volume transmission versus faster synaptic-like signaling. We expressed DIO-ChR2-EYFP in MS/DB cholinergic neurons and red-shifted GRAB-ACh sensors (rACh1.7) throughout vHipp, enabling simultaneous optogenetic activation and real-time imaging of ACh release dynamics in vHipp slices from ChAT-Cre mice. Single optogenetic stimuli (50 ms, 488 nm) evoked focal rACh1.7 response at discrete locations along ChR2-expressing axons, with intervening segments showing minimal signal. ACh signals were spatially restricted within approximately 5 μm of axonal sources, with no detectable signal in background regions lacking cholinergic axons. High-magnification imaging revealed striking bouton-level (~2 μm) heterogeneity: immediately neighboring sites on the same axon showed markedly different release responses to optogenetic stimuli, indicating spatially non-uniform ACh release. To quantify this systematically, we positioned 29 ROIs (3×3 μm each) sequentially along individual cholinergic axons, spanning regions upstream and downstream of the directly illuminated zone (~20×20 μm), plus control ROIs in regions lacking cholinergic axons. Repetitive stimulation (1 Hz, 20 pulses) evoked ACh transients rising in ~100 ms (sensor-limited, indicating actual release kinetics may be even faster) and decaying in 200-300 ms—far faster than traditional neuromodulation timescales. For each ROI, we quantified release probability (Pr, CV^2 analysis) as the fraction of stimuli evoking detectable ACh transients ($\Delta F/F_0$), with background correction. These analyses revealed striking spatial heterogeneity: Pr ranged from <0.02 to >0.10 across ROIs along the same axon, with high-Pr hotspots interspersed among silent or low-probability sites, creating a mosaic pattern of release capacity. ACh release extended into zones upstream and downstream of the illuminated region, indicating bidirectional spreading depolarization along the axonal arbor. Pr declined steeply beyond ~15-20 μm of axonal travel, indicating distance-dependent attenuation of depolarization propagation. These findings reveal discrete spatial organization of ACh release at micrometer and bouton-level resolution, with release probability varying over 5-fold across neighboring sites along individual axons, supporting spatially targeted cholinergic signaling beyond classical volume transmission.

Disclosures: C. Zhong: None. **N.S. Desai:** None. **Y. Li:** None. **D.A. Talmage:** None. **L.W. Role:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.01/F6

Topic: A.09. Development and Evolution

Support: Institutional GF000361
Institutional IS000316

Title: Mapping local proteomic landscape of endoplasmic reticulum in different neuronal types using TurboID-based biotinylation

Authors: *A. S. SOLIMAN[1], K. NEHERIN[2], E. WOLFRUM[3], M. HOYER[2];
[2]Neurodegenarative Sci., [3]Bioinformatics & Biostats Core, [1]Van Andel Inst., Grand Rapids, MI

Abstract: Endoplasmic reticulum (ER) stress and the subsequent unfolded protein response constitute cardinal pathological hallmarks across various neurodegenerative diseases. Moreover, mutations in genes encoding ER proteins, which regulate the architecture of ER network, particularly predispose motor neurons to degeneration, sparing other neuronal types. Hitherto, the molecular underpinnings governing the selective vulnerability of motor neurons to defective ER morphogenesis remain unresolved. Despite the wealth of literature on the general composition of ER, the differences in ER machinery among disparate neuronal populations receive little attention. Herein, we conducted comparative suborganellar ER proteomics of iPSC-derived cortical neurons (iN) and motor neurons (iMN). By leveraging TurboID-based labeling and mass spectrometry, we captured the local ER luminal and membrane proteomes. Compared to controls, we enriched for known ER luminal and membrane proteins in both neuronal types. ER-resident quality control proteins and chaperones are enriched in ER-luminal proteome of iN and iMN. We noticed a higher abundance of specific chaperones (e.g., FKBp10) in iN, whereas other chaperones (e.g., ERP29) predominate in iMN. Likewise, the ER-membrane proteome exhibits neuron-type enrichment for individual ER-phagy and ER-shaping proteins, which modulate ER homeostasis and structure, respectively. Of note, disease-associated ER-phagy and ER-shaping proteins (e.g., FAM134B and REEP1) are significantly more abundant in iMN than iN. Interestingly, iMN-enriched ER-membrane proteome harbors a higher representation of proteins that regulate synaptic vesicle trafficking, in contrast to iN. These findings suggest a specialized interaction between ER and synaptic vesicles in motor neurons. Mapping the proteomic profile of ER in iN and iMN suggest that a neuron-type ER signature possesses variable regulatory influence on ER homeostasis, structural integrity, and neuronal heterogeneity. Therefore, ongoing experiments focus on selecting the top-enriched ER proteins in each neuronal system and comparing their roles in regulating ER. Particularly, we will determine how these proteins facilitate ER architecture and function, besides neuronal morphology and connectivity. Furthermore, we will interrogate the extent to which deleting or overexpressing these proteins disrupts these functions and, hence, sensitizes specific neuronal populations to various disease states. Collectively, this study will introduce the neuron-type-specific regulation of ER and the potential mechanisms underlying neuronal vulnerability and resilience.

Disclosures: A.S. Soliman: None. **K. Neherin:** None. **E. Wolfrum:** None. **M. Hoyer:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.02/F7

Topic: A.09. Development and Evolution

Support: BICAN RRID:SCR_022794

Title: Evolutionary dynamics of gene duplicates: transcriptomic divergence of paralogs across species and brain cell-types

Authors: *V. NIETO CABALLERO[1], F. M. KRIENEN[2];
[1]Princeton Neurosci. Inst., Princeton, NJ; [2]Neurosci., Princeton Univ., Princeton, NJ

Abstract: Brain cells have diversified into an enormous constellation of cell-types through evolution. While single-cell transcriptomic atlases are increasingly detailed and have established homology between species, the mechanisms underlying this diversity remain largely unexplored beyond 1:1 orthologs genes. Similarly, much is still unknown regarding the molecular logic explaining the evolutionary constraints behind uneven patterns of transcriptomic heterogeneity among major neuronal cell classes. Gene duplication is a major driver of evolutionary innovation because one copy can maintain the ancestral function while the other copy can specialize in a new role without breaking the core identity of a cell-type. In this study we aim to investigate evolutionary trends of divergence among paralog pairs expressed in the brain using snRNA-seq data. We focused on the marmoset subcortical cell atlas of 678k cells spanning 212 cell-types (Dan et al., 2026) and a cross-species consensus atlas of 1.8 million cells containing 61 homologous cell-types and three species in the primate basal ganglia (Johansen et al., 2026). To classify the fate of paralogs as dosage amplification/back-up compensation or candidates of neofunctionalization, we quantified divergence among gene duplicates by calculating the correlation of expression and computing their transcriptomic divergence (Farré et al., 2010). Duplicate pairs with higher expression divergence also tend to exhibit higher DNA sequence divergence: when coding sequences change, their expression programs also often diverge, supporting functional differentiation. Using an integration approach that does not rely only on gene orthologs (Tarashansky et al., 2021), we find that paralogs substitution is a widespread event, indicating that orthologs may have lost or changed their functional roles in homologous cell-types. We integrated spatial transcriptomic data and investigated anatomical specificity of gene duplicates across cellular domains. Patterns of specialization often follow an anatomical logic, for example, the calcium-binding proteins CALB1 and their paralog CALB2 have mutually exclusive expression patterns in the subcortex. Our results show that gene duplication is a prevalent mechanism that contributes to the rewiring of gene expression networks and species-specific cellular brain diversity.

Disclosures: V. Nieto Caballero: None. **F.M. Krienen:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.03/F8

Topic: A.09. Development and Evolution

Support: 5R01NS136448-03

Title: Investigating Importin-Mediated Nuclear Transport of Tau

Authors: *T. WILLIAMS[1], M. M. HEFTI[2], B. DOLATYAR[3];
[1]Pathology, The Univ. Of Iowa Neurosci. Grad. Program, Iowa City, IA; [2]Univ. of Iowa, Iowa City, IA; [3]Univ. of Iowa, IOWA CITY, IA

Abstract: Tau is a microtubule-associated protein (MAP) best known for its role in Alzheimer's disease (AD) and related tauopathies. Although the pathological role of tau in AD has been extensively studied, recent evidence points to a critical function of tau during neurodevelopment. Notably, tau is highly expressed in the fetal brain and localizes to the nucleus, where it may regulate gene expression and chromatin organization. However, the mechanisms governing tau nuclear transport and the functional significance of nuclear tau during brain development remain poorly understood. We hypothesize that tau nuclear localization is regulated by importin-dependent transport through the nuclear pore complex.Addressing these gaps will deepen our understanding of tau's physiological roles in the fetal brain and may reveal how disruptions in nuclear tau trafficking affect normal brain development. Human embryonic kidney cells (HEK) were transfected with wild-type human tau (ON3R) and treated with 40μ;M of Importazole. Cells were subjected to subcellular fractionation to isolate nuclear and cytoplasmic extracts, and Western blot analysis was used to assess the nuclear-to-cytoplasmic tau ratio. An approximately 64% of tau level expression was significantly reduced in the experimental condition compared with controls (n=3/group, Student's t-test, $p = 0.0252$). In addition, importin α was successfully immunoprecipitated from cellular fractions, supporting the feasibility of future interaction studies. In conclusion, these findings support a model in which tau nuclear localization is regulated by importin-dependent transport through the nuclear pore complex. Ongoing studies will determine whether tau directly interacts with importins and nucleoporins to facilitate nuclear transport. Characterizing the mechanisms of tau nuclear trafficking may reveal previously unrecognized physiological functions of tau and provide insight into how disruptions in these processes contribute to neurodevelopmental and neurodegenerative disorders.

Disclosures: T. Williams: None. **M.M. Hefti:** None. **B. Dolatyar:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.04/G1

Topic: A.09. Development and Evolution

Support: National Natural Science Foundation of China (32471024)
Natural Science Foundation of Shanghai (24ZR1473700)
Shanghai Pujiang Program (24PJA144)

Title: Molecular and cellular mechanisms underlying maturational heterochrony of the primate cortical sensorimotor-association axis

Authors: *M. LI, S. MA;
Inst. of Neurosci. (ION), Ctr. for Excellence in Brain Sci. and Intelligence Technol. (CEBSIT), Chinese Acad. of Sci., SHANGHAI, China

Abstract: The primate cerebral cortex develops along the sensorimotor-association (S-A) axis, with association cortices exhibiting more protracted structural and functional maturation than primary sensorimotor cortices. Yet the molecular and cellular basis of this maturational heterochrony remains largely unknown. Here, we integrate single-nucleus and spatial transcriptomics with magnetic resonance imaging across neonatal-to-adult primate cortical development to reveal coordinated molecular, cellular, and connectivity changes along the cortical S-A axis. At single-cell resolution, maturational heterochrony was most prominent in supragranular excitatory intratelencephalic neurons. Gene modules revealed that association cortices retain late-embryonic developmental signatures at birth, exhibit delayed completion of neuronal functional programs, and sustain cytoskeletal remodeling, membrane trafficking, and growth cone dynamics that support region-specific axon outgrowth and circuit assembly. Moreover, thalamocortical structural connectivity developed in accordance with the cortical S-A axis. Together, our findings reveal molecular patterns and cellular mechanisms underlying the protracted neurodevelopment of primate association cortices, providing insight into prolonged developmental plasticity and potential susceptibility to neuropsychiatric disorders.

Disclosures: M. Li: None. **S. Ma:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.05/G2

Topic: A.09. Development and Evolution

Support: NSF NeuroNex Grant 2015276

Title: Leveraging primate atlases to identify novel regulatory networks of the macaque cortex

Authors: *C. CARDENAS, L. CACERES, V. E. NIETO CABALLERO, S. DAN, M. DEBERARDINE, F. M. KRIENEN;
Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Cortical cell type diversity varies across regions and species (Krienen et al., 2023; Jorstad et al., 2023; Yao et al., 2023). Although single-cell transcriptomics studies have generated cross-species atlases of subcortical structures and characterizations of a single region across many species (Johansen et al., 2026; Ma et al., 2022), how regulatory programs distinguish cortical areas, and their conservation across primates, remains unclear. Within the common marmoset, recent work identified two opposing gradients of molecular variation across the neocortex, suggesting that divergent gene expression across cortical areas is driven by proximity to the allocortex versus the primary sensory cortex (Huang et al., 2026). In addition to positional identity, cortical areas are distinguished by their rank in a functional hierarchy (Felleman & Van Essen, 1991). To explore the relative contributions of these organizational principles to variation in cell type identity, we generated a Rhesus macaque single-nucleus RNAseq atlas containing 500k cells spanning eight cortical regions positioned along a distributed functional network supporting higher-order visual working memory (Goldman-Rakic, 1988), including the prefrontal cortex, entorhinal cortex, Brodmann area 25, visual area 1 (V1), auditory cortex, anterior cingulate cortex (ACC), posterior cingulate cortex (PCC), and intraparietal sulcus (IPS). Using this atlas as a reference, we annotated whole-brain marmoset and PFC cynomolgus macaque spatial datasets, enabling systematic comparison of cell type spatial distributions across primates. We integrated our data with existing marmoset, cynomolgus macaque, and human multiome datasets to identify compositional differences in cell types. Cross-species multiome analysis revealed cortex-specific gene regulatory network (GRN) candidates with conserved and divergent features across primates. Our results provide a molecular framework for understanding cross-species cortical organization.

Disclosures: C. Cardenas: None. **L. Caceres:** None. **V.E. Nieto Caballero:** None. **S. Dan:** None. **M. DeBerardine:** None. **F.M. Krienen:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR121.06/G3

Topic: A.09. Development and Evolution

Support: NRF RS-2023-00265581
NRF RS-2023-00260454
NRF RS-2024-00353657

Title: Candidate Genes for Human-Specific Cortical Neurogenesis Revealed by Integrative Genomic Analysis

Authors: *J. YUN, J. LEE, S. PARK;
POSTECH, Pohang, Korea, Republic of

Abstract: Despite sharing a highly conserved genome, humans and mice have evolved remarkably distinct brain architectures. While many studies have addressed the molecular basis of this divergence, differences in protein function that emerged during evolution influence human neurodevelopment remains an open question. To investigate this, we constructed a multi-stage computational pipeline in which approximately 720 loss-of-function-intolerant genes (probability of loss-of-function intolerance, pLI > 0.9; gnomAD v2.1.1) were cross-referenced with genes associated with neurodevelopmental and neuropsychiatric disorders. Top candidates were further validated using fetal RNA-seq data by tracking their expression across major stages of the cortical neurogenic lineage. To determine whether these candidates exhibit species-specific functions during cortical neurogenesis, we will perform in utero electroporation of the mouse embryonic cortex with candidate-specific knockdown constructs, followed by rescue with either the human or the mouse form of each candidate. These experiments may provide evidence that human-specific features of the candidate proteins confer distinct functional properties during cortical neurogenesis. Building on these results, we further aim to investigate which structural and functional changes in the candidate proteins underlie their human-specific roles, thereby clarifying how molecular divergence at the protein level contributes to the distinctive features of human cortical development. Collectively, by employing a novel multi-stage filtering approach, this work may shed light on proteins that play previously unrecognized roles in human cortical development, advancing our understanding of the molecular basis of human brain evolution.

Disclosures: J. Yun: None. **J. Lee:** None. **S. Park:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.07/G4

Topic: A.09. Development and Evolution

Title: Neuroendocrine Regulation of Brain Fluid Remodeling During Pregnancy

Authors: *A. MIRMAJLESI[1,2], O. PRUDEN[1,2], S. CANGE[1,2], D. MERCADO[1,2], J. STEARNS[1,2], B. SZEKELY[1,2], R. J. RUSHMORE, III[3,4], C. HELLER[5,6,7], H. ARCINIEGA[1,2]; [1]Rehabil. Med., NYU Grossman Sch. of Med., New York, NY; [2]NYU Langone Concussion Ctr., NYU Langone Hlth., New York, NY; [3]Anat. and Neurobio., Boston Univ. Sch. of Med., Boston, MA; [4]Psychiatry Neuroimaging Laboratory, Brigham and Women's Hosp., Harvard Med. Sch., Boston, MA; [5]Masonic Inst. for the Developing Brain, [6]Dept. of Pediatrics, Univ. of Minnesota, Minneapolis, MN; [7]Dept. of Psychological and Brain Sci., Univ. of California, Santa Barbara, Santa Barbara, CA

Abstract: Maternal brain adaptations may reflect biological changes that prepare the body to support and nurture the developing fetus. Growing evidence suggests that cerebrospinal fluid dynamics (CSF) and endocrine hormones, such as estradiol and progesterone, contribute to immune regulation during pregnancy. To better understand how rising estradiol and progesterone

levels interact with structural changes in the brain, we examined fluid-related structures, such as the ventricular system, choroid plexus (ChP), and perivascular spaces (PVS), during pregnancy. We analyzed open-access data of a 38-year-old healthy female who conceived via in vitro fertilization. The participant completed 26 MRI scans from preconception through 2 years postpartum, with blood samples collected at 19 time points spanning from preconception through week 51 postpartum. Three independent raters segmented the ChP, lateral, third, and fourth ventricles. Global CSF volume was quantified using the ANTsX Deep Atropos protocol, while PVS burden was assessed using the weakly supervised convolutional neural network. Generalized additive models (GAMs) were used to understand the structural trajectories across gestational weeks. The GAMs revealed that the lateral ventricle ($F=5.41$, $edof=3.62$, $p<0.001$), third ventricle ($F=6.13$, $edof=3.71$, $p<0.001$), and CSF ($F=44.0$, $edof=5.0$, $p<0.001$) increased throughout pregnancy, peaking in the third trimester, then decreased within two years postpartum. The ChP and PVS did not have a significant statistical signal from preconception through the first two years postpartum. To better understand how endocrine hormones interact with these regions, we used a GAMs model that adjusted for estradiol and progesterone. After accounting for estradiol and progesterone volume, we found that the hormone changes explain the fluctuations in lateral ventricle volume ($F=1.98$, $edof=6.50$, $p>0.05$). These findings provide insight into fluid-dynamic changes during pregnancy. Given the neuroimmune response occurring during gestation, the remaining fluctuations in CSF and third ventricle volume may be accounted for by other physiological changes during this time. Overall, this work highlights the dynamic relationship between endocrine changes and fluid-related brain structures across pregnancy and the postpartum period.

Disclosures: A. Mirmajlesi: None. **O. Pruden:** None. **S. Cange:** None. **D. Mercado:** None. **J. Stearns:** None. **B. Szekely:** None. **R.J. Rushmore:** None. **C. Heller:** None. **H. Arciniega:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.08/H1

Topic: A.09. Development and Evolution

Title: A modest proposal to account for the migration of the simian primate LGN relative to its position in other mammals

Authors: *P. E. GARRAGHTY;
Indiana Univ. Bloomington, Bloomington, IN

Abstract: In their classic monograph, Sarnat and Netsky (1974) addressed the relative locations of the hippocampal formation (HC) in various species, stating that the HC “is dorsally situated in the forebrain of most animals but becomes displaced ventrally in primates by the development of the neocortex.” Obviously, they could provide no empirical evidence in support of their

assertion, but, just as obviously, there is no clear alternative. Here, a similar argument is presented to account for the location of the primate lateral geniculate nucleus (LGN) relative to its location in non-primate species. To support the argument laid out here, it is essential that one be able to examine brain sections from a wide variety of mammalian species. The roots of the collection used can be traced to Clinton Woolsey in the 1950's, with many contributors along the way. Since 2007, this collection has been curated and maintained at the National Museum of Health and Medicine in Washington D.C. (https://brainmuseum.org/index.html). The major observations are: In all exemplar simian primate mammals (n=5), the HC is confined to the medial temporal lobe, and the LGN is located adjacent to the ventrolateral thalamus (i.e., the mis-named medial geniculate nucleus). It is separated from the rest of the thalamus by the optic tract and probably some caudal fibers in the internal capsule. In all exemplar non-simian primate mammals examined (n=8), the HC extends from the dorsal midline above the brainstem to the temporal lobe, and the LGN is located in the dorsolateral thalamus. In all instances, the optic tract wraps around the lateral surface of the thalamus before turning sharply medial, running between the LGN and the rest of the thalamus. The evolutionary hypothesis set forth here is that the simian primate LGN was sheared off the dorsal lateral thalamus by the expanding cerebral cortex, just as suggested earlier to account for the migration of the simian primate HC. It is further posited that the course of the optic tract, traveling between the LGN and the rest of the thalamus in the more typical mammal enabled this process, as the LGN is tethered to the optic tract and not to the remainder of the thalamus. Thus, it is argued that the migrations of the simian primate HC and LGN were both a consequence of cortical expansion. Did these two structures migrate in tandem? Prosimian primates (n=2) offer the opportunity to turn back the clock a bit. In two exemplar species, the HC retains its "primitive" position, whereas the LGN is clearly displaced ventrally from the dorsolateral thalamus. Thus, the LGN was in the vanguard of the migrations of the HC and LGN during simian primate brain evolution.

Disclosures: P.E. Garraghty: None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.09/H2

Topic: A.09. Development and Evolution

Title: Amygdala Nuclei Across Felidae: A Comparative Analysis of Volumetric and Cytoarchitectural Variation

Authors: *A. K. DORENBUSCH[1], C. SHERWOOD[2];
[1]Anthrop., The George Washington Univ., Washington, DC; [2]George Washington Univ., Washington, DC

Abstract: Felids are a family of mammals characterized by obligate carnivory and diverse ecological niches spanning from solitary ambush hunters to cooperative pursuit predators. Little

is known about interspecies variation in amygdala organization among felids, which is particularly relevant to understanding neural substrates of predation and aggression. The amygdala is a functionally heterogeneous structure composed of cytoarchitecturally distinct nuclei with divergent embryological origins. This study presents an analysis of volumes and neuron numbers from five amygdaloid nuclei (pallial basolateral [ALA, ABL, ABM] and subpallial [CeA, MeA]) across 11 felid species to characterize scaling relationships and evaluate mosaic evolution. Left-hemisphere Nissl-stained sections were used to quantify regional volumes and neuronal numbers using stereology. Phylogenetic generalized least squares (PGLS) regression with maximum-likelihood Pagel's λ examined scaling of amygdala volume and neuron numbers against brain volume, and of each nucleus against the remaining amygdala. Lineage-based regime analysis identified phylogenetic outliers. Results showed that across felid species, amygdala volume and neuron numbers scaled sub-proportionally with brain volume; neuron density decreased significantly in association with brain size enlargement. The ALA dominates the felid amygdala (~50% of both total volume and neurons) and shows sub-proportional scaling. ABM exhibited disproportionate scaling, and MeA was most variable. Felid amygdala organization reflects higher integration of volumetric and neuron number scaling in pallially-derived excitatory nuclei and more pronounced interspecies variation in subpallial inhibitory nuclei scaling, mirroring developmental origins. ALA dominance across Felidae converges with patterns observed in Homo sapiens, positioning felids as a valuable model for amygdala evolution in predatory contexts.

Disclosures: A.K. Dorenbusch: None. **C. Sherwood:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.10/H3

Topic: A.09. Development and Evolution

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National Science Foundation (grants EF-2021785, DRL-2219759)
National Institutes of Health (grants NS092988, AG067419)

Title: A reservoir of non-dividing, late-maturing neurons exists in the amygdala and is expanded in primates

Authors: *M. GHIBAUDI[1,2], N. TELITSYN[2,3], J.-M. GRAÏC[4], C. SHERWOOD[5], L. BONFANTI[3];
[1]Univ. of Pittsburgh, Pittsburgh, PA; [2]Univ. of Turin, Turin, Italy; [3]Univ. of Turin, Grugliasco, Italy; [4]Univ. of Padua, Legnaro, Italy; [5]George Washington Univ., Washington, DC

Abstract: A population of embryonically born, non-dividing neurons has been reported in adult brain regions (e.g. paleo, neocortex) in a wide range of mammals. These cells express immaturity markers (e.g. doublecortin, DCX) and display a protracted developmental timeline. They can either reach maturity, integrating both structurally and functionally into the brain circuitry, or remain in a prolonged, arrested state of maturation for months to years. These neurons are more prominent in species with complex, gyrencephalic brains and in multiple brain regions underlying high cognitive functions. A similar population has been reported in the amygdala of different mammals, however, it is still unclear: (i) whether this population in the amygdala is actively dividing in the adult, (ii) the evolutionary dynamic of late-maturing neurons occurrence in widely different mammals, (iii) the contribution of late-maturing neurons to different amygdala subnuclei and (iv) to what extent these cells persist in old individuals. Using a combination of immunohistochemical, quantitative and phylogenetic analysis, we compared the occurrence, topological distribution and density of late-maturing neurons in the amygdala of eight mammals (from mice to chimpanzee) belonging to different orders, evolutionary clade and with different brain size and complexity, at different ages. We show that late-maturing neurons occur in all eight mammals, being highly prevalent in the amygdala of primates. We demonstrate that late-maturing neurons and dividing cells have different topographical distribution in the amygdala, and co-expression analysis demonstrated that most proliferating cells are oligodendrocyte progenitors. Analysis of the topological distribution of late-maturing neurons in the amygdala showed that they are expanded in the basolateral nuclei, which are highly interconnected to the cerebral cortex and related to complex socio-emotional behaviors. Quantitative analysis revealed that late-maturing neurons stabilize in number through adult and old age, forming a long-lasting reservoir of undifferentiated cells unlike other forms of plasticity that undergo marked age-related reduction (e.g. adult neurogenesis). Together, these results extend the knowledge of mammalian postnatal amygdala development and support the emerging view that a reserve of late-maturing neurons is prominent in the brains of large-brained, gyrencephalic mammals.

Disclosures: M. Ghibaudi: None. **N. Telitsyn:** None. **J. Graïc:** None. **C. Sherwood:** None. **L. Bonfanti:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.11/H4

Topic: A.09. Development and Evolution

Support: NIH IRP, 1ZIA NS003153
Richard Lounsbery Foundation

Title: Evolutionary and ontogenetic architects of the vertebrate dorsal horn

Authors: *D. GOLDBLATT[1], R. B. ROOME[2], F. NICOLA[3], A. RICHARDSON[1], L. LI[1], L. B. SWEENEY[4], C. WYART[5], J. FARRELL[6], A. LEVINE[2];
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Abstract: Neuronal circuit evolution often begins with a common sequence: anatomical expansion, and then molecular subtype diversification. An exquisite example is the spinal cord dorsal horn (sensory/interneuron processing and motor modulation). Over vertebrate evolution, the dorsal horn expanded dramatically from a small region with approx. two dozen known subtypes in zebrafish to a well-developed, laminated structure with over 150 subtypes in mammals. Here, we elucidate the regulatory mechanisms that catalyzed dorsal horn expansion and cell type specialization using evolutionary genetics, comparative vertebrate development, and circuits/behavioral neuroscience. First, we are using multiomic analyses to examine dorsal horn formation in zebrafish. Surprisingly, both anatomical expansion and molecular diversification appear to persist through adulthood. We predict that this juvenile/adult "metamorphosis" may support mature fin development and function. Next, the adult diversification we observed in zebrafish is reminiscent of late dorsal horn neurogenesis in mammals, which generates two thirds of all spinal cord interneurons (dIL family). Is there a common mechanism of dIL diversification? In mammals, we show that deletion of a transcription factor family, *Zic1-5*, profoundly perturbs dIL subtype composition, causing aberrant gait. Ongoing experiments are disentangling (1) how *Zics* differentially drive morphological expansion (progenitor proliferation) from post-mitotic specialization, and (2) whether *Zics* and their regulatory elements are conserved ontogenetic diversifiers across species. Looking ahead, *Zic* manipulations may offer a path to modulate the ontogenetic and evolutionary complexity of cell types in the dorsal horn, and to subsequently relate innovations in form with improvements in spinal circuit function.

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Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.12/H5

Topic: A.09. Development and Evolution

Support: The Nemours CP Program
Swank Foundation

Title: Comparative Proteomic Analysis of Skeletal Muscle Tissue in Spastic Cerebral Palsy

Authors: B. ROMERO CARPIO[1], K. ROBINSON[2], V. PARASHAR[1], M. SHRADER[3], R. E. AKINS[3], ***M. BATISH**[1];
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Abstract: Spastic Cerebral Palsy (CP) is a complex, childhood-onset motor disability disorder known to involve genetic and environmental risk factors. Accumulating data further suggest that epigenetic pathways (e.g. DNA methylation, and non-coding RNAs) play important roles in CP, particularly in the peripheral manifestations of the movement disorder. However, the molecular and cellular mechanisms contributing to motor dysfunction in CP remain largely unknown. While genomic and transcriptomic studies have been performed extensively, there is a lack of proteomic studies in CP field. Proteomics is essential for pinpointing the central hubs within the disease network and prioritizing key pathways and genes. Therefore, we aim to compare proteomic profiles of skeletal muscle tissue from control and individuals with CP.Total protein was isolated from erector spinae muscle biopsies (n=3) under an IRB-approved protocol. Tissue lysis was performed using 8M urea/5% SDS for complete protein solubilization. Protein concentration was quantified by BCA assay, and the protein was subjected to trypsin digestion in preparation for mass spectrometry analysis. To identify differentially expressed proteins, candidates with a fold change greater than or less than 1.5 and *a p*-value less than 0.05 were considered. Proteins identified in at least two replicates within one of the two groups and quantified by at least two unique peptides were included. Differential expression of the candidate proteins was validated using qRT-PCR, immunofluorescence, and ELISA. Enrichment analysis was performed to identify associated biological processes.Principal component analysis (PCA) revealed a clear separation of proteomic profiles between CP and controls. A total of 283 proteins were significantly downregulated in CP skeletal muscle relative to the control group. These proteins were involved in key molecular functions, including metal ion binding, myosin light chain binding, dipeptidyl-peptidase activity. In contrast, 45 proteins were upregulated in CP skeletal muscle compared to controls. The functions associated with these upregulated proteins primarily included long-chain fatty acid transmembrane transporter activity, ubiquitin protein ligase activity, long-chain fatty acid-CoA ligase activity. Validation assays confirmed the dysregulation of key target proteins.This approach identified a unique proteomic “fingerprint” that clearly differentiates CP muscle from healthy tissue. Furthermore, our evidence suggests that motor dysfunction is driven by significant structural and molecular changes within the muscle itself, rather than by neurological signals alone.

Disclosures: B. Romero Carpio: None. **K. Robinson:** None. **V. Parashar:** None. **M. Shrader:** None. **R.E. Akins:** None. **M. Batish:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.13/H6

Topic: A.09. Development and Evolution

Support: Cerebral Palsy Program at Nemours
Swank Foundation

Title: The Regulatory Role of circNFIX and RNA-Binding Proteins in Spastic Cerebral Palsy Muscle Development

Authors: *B. M. ROMERO CARPIO[1], K. ROBINSON[2], V. PARASHAR[1], M. SHRADER[2], R. E. AKINS[3], M. BATISH[1];
[1]Univ. of Delaware, Newark, DE; [2]Nemours Children's Hlth., Wilmington, DE; [3]Nemours Children's Hlth. Syst., Wilmington, DE

Abstract: Spastic cerebral palsy (CP) is the most common motor disability disorder, characterized by persistent muscle stiffness and contractures. These musculoskeletal deformities often worsen over time, highlighting the urgent need for timely interventions and therapeutic targets. Unfortunately, the molecular and cellular mechanisms leading to motor dysfunction in spastic CP remain largely unknown. Our recently published work revealed that a specific circular RNA derived from the NFIX gene (circNFIX) regulates the expression of MEF2C, a muscle-specific transcription factor, by sponging microRNA miR373-3p. Given high-level expression of circNFIX, it is plausible that it has more functions than just miRNA sponging. Another functionally relevant role of circRNAs is to bind/sponge RNA-binding proteins (RBPs) or to serve as a scaffold for the formation of protein complexes, and both roles for circNFIX are yet to be characterized in muscle development. We sought to identify RBPs that interact with circNFIX and to characterize their roles in satellite cell-derived myoblasts (SC-MBs) and myotubes (SC-MTs).SC-MBs were isolated from skeletal muscle biopsies of individuals with spastic CP and control subjects (CN), collected under an approved IRB protocol. The SC-MBs were validated by the expression of PAX7 and MYF5 and cultured and differentiated into myotubes. To identify RBPs, we utilized CARPID (CRISPR-assisted RNA-protein interaction detection method) using two guide RNAs (one targeting the backsplice junction of circNFIX and the other on the region of linear NFIX). Identified RBP expression was validated by qRT-PCR, immunofluorescence (IF), and Western blot, while the interactions themselves were verified using IF and the circFISH technique.Differential RBP enrichment was found when comparing circNFIX to its linear counterpart. After evaluating biological replicates and performing statistical analysis, 26 RBPs showed higher enrichment with circNFIX in MBs, whereas 9 RBPs were more enriched with circNFIX in MTs. The biological processes associated with RBPs enriched for circNFIX mainly involve mRNA 3’-end processing via stem-loop binding and cleavage in MB, alongside protein-containing complex assembly in MT. Using IF and circFISH, we demonstrated that circNFIX exhibited significantly higher colocalization with the identified RBP compared to linear NFIX. Knockdown of circNFIX led to the upregulation of the RBP.As a highly expressed and stable circRNA, circNFIX has a potential to impact multiple muscle development pathways affected in CP. Identifying these pathways will pave the way for future therapeutic targets for spastic CP.

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Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.14/H7

Topic: A.09. Development and Evolution

Title: Subventricular zone radial glial cells maintain inhibitory neuron production in the human brain

Authors: *L. JIA;
Tsinghua university, Beijing, China

Abstract: The number and diversity of inhibitory neurons (INs) increasedsubstantially during mammalian brain evolution. However,the generative mechanisms of the vast repertoire of humanINs remain elusive. We performed spatial and single-celltranscriptomics of human medial ganglionic eminence (hMGE),a pivotal source of cortical and subpallial INs, and built thetrajectories of hMGE-derivedcells during brain development.We identified spatiotemporally and molecularly segregatedprogenitor cell populations fated to produce distinct IN types.We uncovered an evolutionarily distinct progenitor cell type inthe hMGE subventricular zone that maintained the productionof INs and glial cells throughout human brain development.Our findings reveal evolutionarily distinct features of IN generationand shed light on the distinct mechanisms underlying humanbrain development.

Disclosures: L. Jia: None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.15/H8

Topic: A.09. Development and Evolution

Title: An evo-devo framework for neuronal scaling in amniote brains: supply constraints in the developing brain

Authors: *L. XU[1], W. ZHANG[1], Y. DANG[1], X. LI[1], L. JIA[1], L. LI[1], S. HERCULANO-HOUZEL[2], D. MI[1];
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Abstract: The number of neurons follows clade-specific scaling laws across amniote species, exhibiting vast diversity in neuronal density and, consequently, cell size, despite the extreme evolutionary conservation of neuron-specific coding and regulatory DNA sequences. The developmental and evolutionary mechanisms underlying neuronal scaling, however, remain poorly understood. Based on the physical properties of capillary supply and neuronal excitability

in both the developing and the adult brain, we propose a self-limiting, self-organized theoretical evo-devo framework to account for how neurons come to have diverse cell sizes both within the same brain and across different species. The dynamic process of postnatal brain development results in an ever-thinning capillary bed, which provides negative feedback to brain growth and terminates when the upper limit of inter-capillary distance is reached. In support of this theory, several predictions of this model are confirmed by experimental data from mice and humans, including electrophysiological and morphological data. These findings support the notion that neuronal scaling in evolution emerges not solely from cell-type-specific genetic programs but also from conserved physical and energetic constraints that operate during brain development.

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Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.16/Web Only

Topic: A.09. Development and Evolution

Title: Effect of gestational arsenic exposure on oxidative biomarker, and antioxidant response in liver mouse offspring male

Authors: *L. A. RAMOS;
Inst. Nacional De Psiquiatría Ramón De La Fuen, Mexico City, Mexico

Abstract: Effect of gestational arsenic exposure on oxidative biomarker, and antioxidant response in liver mouse offspring male

Velázquez-Juárez Jacqueline[1], Navarro-Mabarak C[2], Silva-Adaya D[3,4], Petrosyan P[5], León-Olea M[1], Gonsebatt ME[5], Ramos-Chávez LA[1*]
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Abstract: Arsenic (As) is a ubiquitous semimetal and neurotoxic contaminant with global relevance. As can cause multi-organ cancer, neurotoxicity, specifically in children. The metabolism of As leads to a cellular pro-oxidant state, decreasing glutathione levels, the putative mechanism of As toxicity. Additionally, it exist an antioxidant response to counteract the pro-

oxidative substances like As. We explore the effects of As exposure on oxidative biomarkers and antioxidant proteins in the liver of offspring, a main tissue that metabolize As. Animals were exposed to 20 mg/L of As in the drinking water of their parents, during gestational development and continued until postpartum day 90. The offspring animals were sacrificed at day 1, 15 and 90. Lipid peroxidation, MTT, GSH-transports' (xCT, EACC1, and LAT1) were evaluated. Preliminary results suggest an increase in the lipid peroxidation, and MTT. However, we observed early antioxidant GSH transported-related and metal response, and a decrease in chronic exposure in liver mouse offspring male.
Keywords: Arsenic, gestational, oxidative damage, mouse.

Disclosures: L.A. Ramos: None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.17/I1

Topic: A.09. Development and Evolution

Support: NSF Award# 2437511

Title: Distribution of Parvalbumin-Expressing GABAergic Interneurons in the Telencephalon of Zebrafish Shows Similarities to Mammalian Basket Cells

Authors: V. WILLIAMS[1], D. WEBSTER[1], ***T. MUELLER**[2];
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Abstract: Due to its genetic tractability, zebrafish (*Danio rerio*) has become an important model for studying the cellular and genetic basis of human neurological disorders. To this day, however, we do not fully understand how the zebrafish forebrain relates to that of mammals. In the latter, parvalbumin-expressing (PV+) GABAergic interneurons constitute a major class of fast-spiking inhibitory neurons, including basket cells that provide perisomatic inhibition onto principal neurons in cortical and amygdaloid circuits. Whether analogous PV+ interneuron populations exist in the zebrafish telencephalon remains an open question. Here, we describe the distribution of PV+ GABAergic interneurons in the adult zebrafish forebrain using dual-label immunohistology against parvalbumin and GABA. We find that PV+/GABA+ double-labeled neurons are predominantly concentrated in the central zone of the dorsal telencephalon (Dc), which we consider a part of the dorsal pallium comparable to the mammalian neocortex. The distribution of these newly identified GABAergic PV+ interneurons within Dc resembles that of GABAergic basket cells in mammals. These results suggest that conserved GABAergic PV+ inhibitory neurons in the vertebrate pallium are present in zebrafish. These results are critical for using zebrafish as a model for human neurological disorders.

Disclosures: V. Williams: None. **D. Webster:** None. **T. Mueller:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

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Program #/Poster #: PSTR121.18/I2

Topic: A.09. Development and Evolution

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European Federation of Pharmaceutical Industries and Associations
AUTISM SPEAKS
Autistica
Simons Foundation Autism Research Initiative
King's College London

Title: Neonatal serotonin associated with social-emotional difficulties in South African children and adolescents: A prospective birth cohort study

Authors: *C. PHAM[1], K. C. O'REILLY[3], E. LOTH[1], L. SHUFFREY[4], P. SPRINGER[5], H. ODENDAAL[6], W. FIFER[7], B. OAKLEY[1], D. RAKESH[2], G. M. ANDERSON[8], J. VEENSTRA-VANDERWEELE[7], D. MURPHY[1];
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Abstract: The serotonin (5-HT) system plays an important role in neurodevelopment, with links to social-emotional difficulties (SED) in children. Early life environmental factors (ELF) influences the emergence of SED. However, the combined impact of ELF and 5-HT on later SED is unknown. We investigated the prospective associations between (i) cord blood and placental 5-HT and SED at 5-16 years; (ii) ELF and 5-HT; and (iii) ELF and SED and whether 5-HT mediated these associations. Umbilical cord blood (n=283) and placental 5-HT (n=89) were quantified by a high-performance liquid chromatography-fluorometric method in a population-derived South African birth cohort, *Safe Passage Study*. ELF (sociodemographic, prenatal and birth domains) were collected by questionnaires, clinical assessment and extracted from medical records. SED (Internalising Problems, Peer Problems and Emotional Symptoms) were measured

by caregiver-reported Strengths and Difficulties Questionnaire at age 5-16 years (n = 1,960). Prospective associations were examined by multivariable regression analyses adjusted for covariates. Indirect effects of ELF on SED through 5-HT were examined using counterfactual-based mediation analysis. Increased cord blood 5-HT was associated with decreased Internalising Problems (β = -0.55, 95% CI (-1.06, -0.05); p = 0.03), particularly Peer Problems (β = -0.32, 95% CI (-0.60, -0.05); p = 0.02) following adjustment for child's sex, child's age at assessment, presence of clots, birth weight, maternal prenatal anxiety, maternal prior depression history and Afrikaans language at home. Indirect effects of ELF and SED partly mediated by increased cord blood 5-HT levels included gestational diabetes mellitus, increased smoking frequency in trimester three and prematurity. Modest associations were detected for placental 5-HT and Emotional Symptoms. Cord blood serotonin was inversely associated with SED, and partially mediated the associations between some prenatal health and lifestyle factors and SED. Further work is required to elucidate the role of maternal and fetal serotonergic pathways and social-emotional and behavioural development.

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Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

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Title: Human-specific regulation of cerebellar synapse development and connectivity by zona pellucida glycoprotein 2

Authors: *S. KIM[1], N. SESTAN[2];
[1]Neurosci., Yale Univ. Sch. of Med., NEW HAVEN, CT; [2]Neurosci., Yale Univ. Sch. of Med., New Haven, CT

Abstract: The cerebellum plays a critical role in motor control, attention, and cognition, with its outputs targeting motor and cognitive regions of the thalamus and cerebral cortex. Cortical excitatory projection neurons regulate cerebellar activity via glutamatergic pontine neurons, which form mossy fibers that synapse with granule and Golgi neurons in the cerebellar cortex.

Abnormal development or dysfunction of this circuitry is linked to ataxia and neuropsychiatric conditions such as attention-deficit hyperactivity disorder, autism spectrum disorder, schizophrenia, and other cognitive disorders. The human cerebellum has undergone substantial expansion and prolonged postnatal development, raising the possibility that additional molecular mechanisms evolved to refine synapse formation under increased circuit complexity. To investigate the evolutionary diversification of the primate cerebellum, we performed single-nucleus transcriptomic and chromatin accessibility profiling of the adult cerebellar cortex in humans, chimpanzees, macaques, and marmosets. This analysis revealed that human-specific transcriptomic and regulatory features are strongly enriched for synapse-related pathways. Notably, among genes with human-specific expression, we identified enrichment of zona pellucida glycoprotein 2 (ZP2) and several of its potential interactors, a gene family previously characterized exclusively for roles in gamete interaction. Functional analyses demonstrated that ZP2 expression in human granule cells is induced by pontine mossy fiber input and accumulates at cerebellar glomeruli, a specialized synaptic structure, where it suppresses the formation of excitatory and inhibitory synapses. In cerebellar cell cultures, recombinant ZP2 reduced synaptic protein abundance and suppressed neuronal electrophysiological activity. In vivo validation using human ZP2 knock-in mice confirmed that sustained ZP2 expression limits glomerular synapse formation and reduces glial engagement during postnatal circuit refinement. In humans, granule cell numbers are greatly expanded relative to pontine inputs, making it more difficult to establish precise synaptic connectivity. We propose that ZP2 contributes to this refinement by constraining synapse formation and neuronal activity in the expanded human cerebellar circuit. Together, these results identify ZP2 as a novel human-specific regulator of cerebellar synapse and circuit formation, revealing the unexpected co-option of a reproductive protein for neural circuit refinement during human cerebellar evolution.

Disclosures: S. Kim: None. **N. Sestan:** None.

Poster

PSTR121: Comparative Anatomy and Cellular and Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR121.20/I4

Topic: A.09. Development and Evolution

Support: NIH Grant R01NS095654

Title: Broad evolvability of intercellular communication and neuronal function inferred from systematic gene age analysis

Authors: *V. LURIA;
Yale Univ., New Haven, CT

Abstract: The invention of novel modes of intercellular communication was fundamental for the emergence of complex multicellular organisms. The evolutionary origin of signaling pathways

and their components, however, has remained mysterious. We developed a strategy for evaluating the evolutionary age of protein-coding genes. By building and optimizing databases with deep genomic and proteogenomic coverage at many taxonomic nodes, by determining optimal sequence search length for discovering distant relatedness, and by comparing similarity detection algorithms with different sensitivities, our method evaluates with improved accuracy the age of proteins as small as 40 amino acid residues in length. Compared with synteny-based gene age evaluation, our method also has the advantage of being insensitive to gene duplication. We find that evolutionary change of protein sequences is constrained by structural preservation requirements. When applied to protein ligands and receptors in all canonical human signaling pathways, this analysis shows that ligands are markedly younger evolutionarily and more complex than their cognate receptors. When applied to PsychENCODE genes expressed in multiple human brain regions and associated with major human psychiatric disorders (autism spectrum disorder, bipolar disorder andschizophrenia), this analysis shows that the proportion of genes differentially expressed or differentially spliced is higher for evolutionarily ancient genes than for young genes, and that 78 genes, including CYP26B1, are common to these three disorders. We propose that these features of signaling pathways and neuronal function have important implications for the evolvability of novel regulatory interactions and of novel cell types such as neurons in multicellular organisms.

Disclosures: V. Luria: None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.01/I5

Topic: B.03. Ion Channels

Support: Defense Threat Reduction Agency (DTRA) Grant CB11458

Title: Efficacy of neostigmine against tetrodotoxin intoxication in mouse hemidiaphragm preparations

Authors: *A. S. CHEN, H. G. STEIER, M. F. STONE, A. WANG, C. R. SCHULTZ, L. W. KABUI, R. MCFARLAND, L. A. LUMLEY, M. ADLER;
Neurosci. Dept., U.S. Army Med. Res. Inst. of Chem. Def. (USAMRICD), Aberdeen Proving Ground, MD

Abstract: Tetrodotoxin (TTX), commonly found in certain species of pufferfish, is one of the most powerful neurotoxins known, as it is about 1000 times more toxic than cyanide to humans. Historically, cases of human TTX poisoning are reported to be linked to the ingestion of TTX-containing marine organisms. TTX blocks voltage-gated Na^+ channels, leading to the inhibition of the generation and propagation of action potentials in nerve and muscle cells. Symptoms of intoxication include paresthesia, muscle weakness, and flaccid paralysis, which can develop

within 30 minutes to 4 hours of exposure. In severe cases, TTX poisoning can result in respiratory failure, hypotension, cardiac arrythmia, loss of consciousness, and death. There is no known antidote available, and treatment often focuses on respiratory support. Neostigmine is a cholinesterase inhibitor, which prevents the breakdown of acetylcholine at neuromuscular junctions and synapses, leading to enhanced muscle contraction and parasympathetic stimulation. Neostigmine is FDA-approved for administration after surgical procedures to reverse the effects of neuromuscular blockade in patients recovering from general anesthesia and restore muscle function, thereby enhancing airway safety and reducing the risk of complications such as respiratory depression or airway obstruction during recovery. Neostigmine has been used off-label to treat sporadic cases of TTX intoxication in humans. Its efficacy, however, has not been established since there are limited to no animal preclinical studies and controlled human clinical trials. In the current study, an ex vivo mouse phrenic nerve hemidiaphragm preparation was used to evaluate neostigmine as a treatment against TTX-intoxication. Supramaximal isometric twitch tension was elicited by phrenic nerve stimulation in the presence of TTX alone, neostigmine alone, or neostigmine following TTX exposure. Hemidiaphragm muscles were first intoxicated with TTX to produce a ~50% inhibition of twitch tension. Addition of 1 μM neostigmine to TTX-intoxicated muscles restored tensions to control levels within 5 minutes, and tensions remained potentiated at nearly 80% of control even 2 hours after addition of neostigmine. These results are encouraging in that neostigmine, an FDA-approved drug, rapidly reversed TTX-induced muscle paralysis.

Disclosures: A.S. Chen: None. **H.G. Steier:** None. **M.F. Stone:** None. **A. Wang:** None. **C.R. Schultz:** None. **L.W. Kabui:** None. **R. McFarland:** None. **L.A. Lumley:** None. **M. Adler:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.02/I6

Topic: B.03. Ion Channels

Support: NIH R01MH124351 (FL)
NIH R01MH132226 (FL)

Title: CKB-Nav1.6 Coupling Confers Resilience Through Plasticity and Reward-Seeking Motivation

Authors: *N. A. GOODE[1], A. K. SINGH[3], Z. HAGHIGHIJOO[1], Y. MARMOL CONTRERAS[4], T. BAUMGARTNER[5], A. VENKATESH[1], J. SINGH[7], H. TEIMOURI[2], A. THOMAS[8], L. KOFF[9], J. DI RE[8], W. K. RUSSELL[1], G. GOLOVKO[10], F. H. DO MONTE[11], T. A. GREEN[12], F. LAEZZA[6], G. AQUINO-MIRANDA[13];
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Abstract: Neuropsychiatric disorders (NDs) are prevalent and debilitating conditions whose global burden continues to increase. Although genetic, environmental, and epigenetic factors contribute to disease susceptibility and progression, the molecular mechanisms governing vulnerability and resilience, and their influence on maladaptive versus adaptive neuronal plasticity, remain incompletely understood. To address this gap, we conducted differential proteomic profiling of the voltage-gated sodium channel Nav1.6 complex, a critical regulator of medium spiny neuron (MSN) excitability in the nucleus accumbens (NAc), using a rat model of resilience and vulnerability to reward-related dysfunction (n = 24; 6 males and 6 females per condition). This analysis identified creatine kinase B (CKB) as a previously unrecognized Nav1.6-interacting protein that was selectively enriched in resilient animals. Through an integrated approach combining computational modeling, biophysical and in vitro interaction assays, structure-guided peptide engineering, and patch-clamp electrophysiology, we established that CKB forms a functional protein-protein interaction (PPI) with the Nav1.6 C-terminal domain. Mechanistically, CKB overexpression suppressed Nav1.6-mediated sodium currents and reduced channel availability under both basal and repetitive activation conditions. In contrast, disruption of CKB-Nav1.6 coupling with a rationally designed tethering peptide abolished these effects (n = 12 per group). In vivo, targeted manipulation of CKB expression within the NAc bidirectionally regulated MSN excitability, with CKB overexpression promoting a resilience-associated phenotype characterized by reduced neuronal firing, enhanced axonal firing fidelity, and expanded Nav1.6 localization at the axon initial segment. Notably, in socially isolated, vulnerability-prone rats, CKB overexpression prevented maladaptive MSN hyperexcitability, an effect that was eliminated following molecular uncoupling of the CKB-Nav1.6 complex. These neuroprotective adaptations were accompanied by enhanced incentive motivation and greater response vigor during reward-seeking behavior (n = 10 per group). Collectively, these findings identify CKB-Nav1.6 coupling as a previously unrecognized signaling mechanism that promotes neuronal resilience and adaptive plasticity, highlighting protein-protein interaction-based modulation of ion channel complexes as a promising therapeutic strategy for neuropsychiatric disorders.

Disclosures: N.A. Goode: None. **A.K. Singh:** None. **Z. Haghighijoo:** None. **Y. Marmol Contreras:** None. **T. Baumgartner:** None. **A. Venkatesh:** None. **J. Singh:** None. **H. Teimouri:** None. **A. Thomas:** None. **L. Koff:** None. **J. Di Re:** None. **W.K. russell:** None. **G. Golovko:** None. **F.H. Do Monte:** None. **T.A. Green:** None. **F. Laezza:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Co-Founder of IonTX. **G. Aquino-Miranda:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.03/I7

Topic: B.03. Ion Channels

Support: NIH Grant R01MH095995 (FL)
NIH Grant 1R01MH111107 (FL, JZ)

Title: Targeting IKK2 reveals a druggable pathway regulating Nav1.7 function in human sensory neurons

Authors: *A. K. SINGH[1], N. A. GOODE[1], J. SINGH[1], A. PAL[2], C. A. LUPASCU[3], M. MIGLIORE[3], S. YUAN[2], F. LAEZZA[1];
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Abstract: Neuropathic pain remains difficult to treat, in part because signaling pathways that acutely regulate nociceptor excitability are incompletely defined. Nuclear factor κB (NF-κB) signaling is broadly implicated in inflammation, neurodegeneration, and chronic pain, yet its direct, nontranscriptional control of ion channel function remains poorly understood. We tested whether IKK2 (IKKβ), the principal catalytic driver of the IκB kinase complex, regulates Nav1.7, a tetrodotoxin-sensitive sodium channel that is essential for nociceptive excitability and strongly linked to neuropathic pain. Using an in-cell split-luciferase complementation assay, pharmacological inhibition, and whole-cell patch-clamp electrophysiology in human iPSC-derived sensory neurons, we interrogated the IKK2-Nav1.7 signaling axis and evaluated its functional dependence with AAV-shIKK2-mediated silencing. Bay 11-7082 disrupted the IKK2/Nav1.7 interaction in the complementation assay with an IC50 of 347 nM. Patch-clamp recordings of pharmacologically isolated Nav1.7 currents showed that Bay 11-7082 altered peak current density, fast inactivation kinetics (τ), voltage-dependent activation, steady-state inactivation, long-term inactivation, and use-dependent cumulative inactivation. Importantly, AAV-shIKK2-mediated silencing abolished the Nav1.7 current modulation produced by Bay 11-7082, demonstrating that IKK2 is required to maintain Nav1.7 channel function in sensory neurons. Consistent with disease relevance, IKK2 expression was reduced in a gp120-driven mouse model of HIV-associated pain, supporting disruption of this signaling pathway in pathological pain states. Together, these findings identify IKK2 as a critical nontranscriptional regulator of Nav1.7 and establish the IKK2-Nav1.7 axis as a druggable signaling node governing nociceptor excitability, with translational relevance for neuropathic pain.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR122.04/I8

Topic: B.03. Ion Channels

Support: NRF Grant RS-2018-NR031058
NRF Grant RS-2025-25436785

Title: Modulation of $Na_v1.7$ currents by amphiphiles

Authors: *R.-E. KIM[1,2], J. CHOI[1,2];
[1]Col. of Pharm., The Catholic Univ. of Korea, Bucheon-si, Korea, Republic of; [2]Integrated Res. Inst. of Pharmaceut. Sci., Bucheon-si, Korea, Republic of

Abstract: Voltage-gated sodium channel $Na_v1.7$ is a key regulator of nociceptor excitability and a genetically validated target for non-opioid pain modulation. While current $Na_v1.7$ inhibition strategies predominantly focus on direct pore blockade, voltage-sensor modulation, or the disruption of intrinsic protein-protein interactions, membrane-embedded ion channels can also be regulated by local lipid-protein interactions. Building upon our previous finding that polysorbate 80 inhibits $Na_v1.7$ currents, we sought to determine whether this amphiphilic suppression stems from nonspecific bulk membrane perturbation or a more selective mechanism involving the channel-lipid interface. Using whole-cell patch-clamp electrophysiology, we first validated a stable HEK293-$Na_v1.7$ platform designed to retain transient-transfection-like gating properties while improving experimental consistency. This platform enabled quantitative assessment of $Na_v1.7$ current density, voltage-dependent gating, and amphiphile sensitivity. To determine whether current suppression was associated with global membrane-order changes, we employed Laurdan generalized polarization (GP) imaging. While a reference cholesterol-depleting agent (MβCD) produced detectable GP shifts, confirming assay sensitivity, polysorbate 80 treatment did not produce a detectable bulk GP change. This suggests that $Na_v1.7$ inhibition is not explained solely by global membrane disorder. Further structural control experiments revealed that hydrophilic components alone failed to reproduce the inhibitory effect, whereas multiple non-ionic amphiphiles reduced $Na_v1.7$ current. Notably, cholesterol depletion produced an opposite functional effect, increasing $Na_v1.7$ current. Together, these findings suggest that amphiphilic $Na_v1.7$ inhibition may not be solely attributable to generic bulk membrane perturbation. Instead, the results point toward the possibility that $Na_v1.7$ is modulated by compound-specific amphiphilic architecture, which may involve interactions at the channel-associated lipid environment or the local membrane-channel interface. By integrating electrophysiological and membrane-order imaging platforms, this work highlights the importance of considering noncanonical lipid-protein interactions in $Na_v1.7$ modulation, offering a potential conceptual starting point for targeting nociceptor excitability in pain therapeutics.

Disclosures: R. Kim: None. **J. Choi:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.05/J1

Topic: B.03. Ion Channels

Support: Eli Lilly Sponsored Research Agreement SPO 317357

Title: Non-Toxic HSV-1-Mediated NaV1.7 Knockdown for the Targeted Treatment of Chronic Neuropathic Pain

Authors: *N. MAHINPARVAR[1], M. KLUKINOV[1], P. MCNEAL[2], L. DEMSEY[2], T. VO[2], D. C. YEOMANS[1];
[1]Anesthesia, Stanford Univ., Stanford, CA; [2]Alice L.Walton school of medicine, Bentonville, AR

Abstract: Background: Chronic neuropathic pain affects over 20% of adults worldwide, yet current treatments provide incomplete relief and are limited by adverse effects. The voltage-gated sodium channel NaV1.7, highly expressed in dorsal root ganglion (DRG) nociceptors, is a validated target for pain modulation. Recombinant herpes simplex virus type 1 (HSV-1) vectors undergo retrograde transport to the DRG following peripheral administration, enabling targeted gene delivery to pain-sensing neurons. While CRISPR-dCas9- and AAV-based gene-silencing approaches have shown analgesic efficacy, their translational complexity remains a hurdle. We evaluated a single-vector HSV-1 platform employing short hairpin RNA (shRNA) to achieve targeted NaV1.7 knockdown in DRG neurons. Methods: A replication-defective HSV-1 vector encoding NaV1.7-targeting shRNA and an mCherry reporter was generated using a BAC-based platform. In vitro validation was performed to assess transgene expression and cytotoxicity prior to in vivo studies. Adult rats received intradermal hindpaw injections of HSV-NaV1.7, scrambled-shRNA HSV, or vehicle. Lumbar (L4-L6) and thoracic DRGs were harvested for immunohistochemical and immunofluorescence analyses of vector transduction and NaV1.7 expression. Safety was assessed by histological examination and clinical observation. Behavioral studies using von Frey and Hargreaves assays are ongoing. All tissue analyses were performed in a blinded manner. Results: In vitro studies demonstrated robust mCherry expression and efficient vector transduction without detectable cytotoxicity. Following hindpaw administration, mCherry fluorescence was observed exclusively in L4-L6 DRG neurons, consistent with retrograde transport, whereas no signal was detected in thoracic DRG controls. Quantitative immunohistochemical and immunofluorescence analyses demonstrated a marked reduction in NaV1.7 protein expression in HSV-NaV1.7-treated DRG neurons compared with scrambled-control and vehicle-treated groups. Histological evaluation revealed no evidence of neuroinflammation, tissue pathology, or adverse local effects. Conclusion: These findings demonstrate that a replication-defective HSV-1 vector can safely deliver NaV1.7-targeting shRNA to lumbar DRG neurons via retrograde transport, resulting in localized suppression of NaV1.7 expression in vivo. Successful targeting of nociceptive sensory neurons and a favorable preliminary safety profile support further development of this single-vector platform as a targeted gene therapy approach for chronic neuropathic pain. Behavioral efficacy studies are ongoing.

Disclosures: N. mahinparvar: None. **M. Klukinov:** None. **P. McNeal:** None. **L. Demsey:** None. **T. Vo:** None. **D.C. Yeomans:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.06/J2

Topic: B.03. Ion Channels

Title: A Validated hNav1.9 Screening Cascade for Pain Discovery

Authors: *A. M. RUSH, G. D. SMITH, K. L. PUDDEFOOT, S. TOKAR, A. S. HAWORTH, C. M. HODGSON, T. D. M. HILL, A. JINAT, E. B. STEVENS, G. S. CLARK;
Metrion Biosci. Ltd, Cambridge, United Kingdom

Abstract: Nav1.9 is a key target for pain drug discovery due to its nociceptor-specific expression and the genetic association of *SCN11A* with human pain disorders. We have generated a monoclonal hNav1.9 CHO cell line and developed a robust, reproducible high-throughput (384-well) assay using the Qube platform (Sophion Biosciences) with multi-hole acquisition. The Qube 384 assay was used to screen a panel of Nav inhibitors exhibiting a range of potencies against hNav1.9. Calculated IC_{50} values (μM) were as follows: A-803467 (3.51), amitriptyline (18.0), ICA-121431 (>30), lidocaine (460), TC-N 1752 (0.2), tetracaine (11.5), tetrodotoxin, TTX (18.7), and VX-548 (14.1). Assay robustness was validated across two independent experiments using a randomised spiked-plate approach with TC-N 1752 (10-point concentration-response curve, 0.5 log dilutions from 30 μM). The amplitude and variability of DMSO test wells were comparable to DMSO control wells, and screening hits were identified at >30% inhibition. The spiked TC-N 1752 concentration-response curve showed good agreement across runs and with historical data, and was consistent with the concentration-response relationship observed in control wells. In addition, Qube assays were developed for rat and cynomolgus Nav1.9 orthologues, alongside selectivity assays spanning hNav1.1-hNav1.8. Multiple Nav1.9 screening campaigns have been successfully completed, identifying novel chemical matter. Collectively, these assays constitute a fully validated Nav1.9 screening cascade to support Nav1.9 discovery programmes.

Disclosures: A.M. Rush: A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **G.D. Smith:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **K.L. Puddefoot:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **S. Tokar:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **A.S. Haworth:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **C.M. Hodgson:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **T.D.M. Hill:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **A. Jinat:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **E.B. Stevens:** A.

Employment/Salary (full or part-time):; Metrion Biosciences Ltd. **G.S. Clark:** A. Employment/Salary (full or part-time):; Metrion Biosciences Ltd.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR122.07/J3

Topic: B.03. Ion Channels

Support: U01NS113868
U01DK116311
OT2OD023854
1R01DK141890

Title: Tetrodotoxin-insensitive $Na_V1.8$ is essential for the conduction of action potentials in a subset of human and murine vagal nerve fibers

Authors: *S. NAIR[1], T. TAYLOR-CLARK[2];
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Abstract: Action potential conduction along nerve fibers is dependent on voltage-gated sodium channels (Na_V1s). The vagus nerve, which consists of both afferent and efferent fibers, controls a variety of functions of visceral organs. This requires transmission of information in the form of action potentials along these vagal nerve fibers. The nine isoforms of pore-forming Na_V1 ion channels show diverse expression patterns in vagal neurons. Nerve terminal and neuronal soma studies from multiple labs have shown the critical role that these isoforms play in vagal action potential (AP) generation. Our lab had previously published that multiple Na_V1 isoforms contribute to AP conduction in the rodent vagus nerve, with $Na_V1.7$ playing a critical role in ~70% of fibers. Here, we investigated the role of tetrodotoxin-resistant $Na_V1.8$'s role in vagal AP conduction. We tested two structurally different $Na_V1.8$-selective pharmacological blockers, A803467 (A80) and PF01247324 (PF24) and their effects on electrically-evoked C-fiber compound action potentials (CAPs) along mouse and human vagus nerves. Human vagus nerves were dissected from de-identified lung tissue provided by Lifelink Foundation. Tetrodotoxin (300nM) completely abolished both mouse and human vagal CAPs. Despite TTX completely blocking CAPs, both A80 and PF24 caused a concentration-dependent decrease in the C-fiber CAPs of mouse and human vagi (>50% inhibition). To test the role of $Na_V1.8$ in the reduction of CAPs by A80 and PF24, we conducted experiments using vagus nerves of $Na_V1.8$ knockout mice (B6.129(Cg)-Scn10atm2(cre)Jwo/TjpJ): here, 1uM A80 significantly decreased vagal CAPs, indicating a substantial non-$Na_V1.8$ inhibition by A80; whereas PF24 had no effect on these nerves, indicating its selectivity for $Na_V1.8$. In further studies of wildtype mice, PF24 only caused a minor decrease in the CAP following incubation with $Na_V1.7$-selective blocker PF-05089771, indicating that $Na_V1.8$-dependent block affects vagal fibers sensitive to $Na_V1.7$-dependent inhibition. These data suggest that axonal TTX-sensitive Na_V1s(in particular $Na_V1.7$)

and TTX-R $Na_V1.8$ cooperate to conduct APs along the vagus nerve. Inhibition of $Na_V1.8$ could be a potential therapeutic strategy to treat diseases affecting vagally-innervated organs of the viscera.

Disclosures: S. Nair: None. **T. Taylor-Clark:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

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Program #/Poster #: PSTR122.08/J4

Topic: B.03. Ion Channels

Support: NIH R43NS125749

Title: State-Dependent Drug Block of an in-vitro Sodium Channel on Simulated Neuronal Activity Evaluated Using a Real-Time Dynamic Clamp System

Authors: *M. W. NOWAK[1], B. K. PANAMA[2], L. KORBEL[1], L. NILSSON[1], R. L. RASMUSSON[2,1], G. C. L. BETT[2,1];
[1]Cytocybernetics, Buffalo, NY; [2]Jacobs Sch. of Med. and Biomed. Sci., SUNY at Buffalo, Buffalo, NY

Abstract: Aberrant Na^+ channel behavior underlies many neurological disorders (e.g., chronic pain or epilepsy) due to increased neuronal activity. Drug development targeting ion channels using conventional patch-clamp electrophysiology has proved difficult since static approaches do not always assess the emergent behavior of neuronal activity or accurately predict a drug's efficacy. We used a Cybercyte dynamic clamp system to input an *in vitro* cloned ion channel current into an *in silico* neuron. This method can be used to assess the effects of drugs targeting the cloned ion channel current with neuronal activity of an *in silico* neuron as the read-out. For these studies, we used a HEK-293 cell line stably expressing NaV1.2 (provided by Dr. A. George, Northwestern University) to input the expressed NaV1.2 current into an *in-silico* neuron, generated with the dynamic clamp system run in Synthetic Cell Mode. Electrophysiological recordings were performed using either the whole-cell ruptured or perforated patch clamp configuration. TEA was included in the bath solution to block K^+ currents. The NaV1.2:HEK-293 cell line expressed NaV1.2 with a peak current density of -67.1±7.5 pA/pF at -20 mV with $V_{1/2}$ for activation and inactivation of -30.7±0.4 and -52.8±0.6 mV, respectively (n=34). The *in silico* neuron had a 5 pF capacitance and consisted of published HH models of NaV1.6 and IKv and a linear passive leak current (E_{rev} = -60 mV). The RMP for the *in silico* neuron was -61±1 mV. Capacitance compensation and leak current correction were applied when NaV1.2 current was input into the *in silico* neuron. Single evoked APs (stimulus = 200 pA, 0.5 ms) in the absence of NaV1.2 current had a peak amplitude of -10±6 mV and no AHP. The addition of NaV1.2 current resulted in APs with a more physiological morphology having a peak of +22±6 mV (peak NaV 1.2 current = -339±53 pA), a well-defined AHP (peak at -68±2 mV, amplitude =

6±1 mV) and an APD_{50} of 2.9±0.2 ms (n=7). By adjusting the *in silico* neuron channel composition, spontaneous APs were elicited with similar morphology as evoked APs. This platform was be used to interrogate the effects of known state-dependent NaV1.2 blockers on AP morphology and activity in the *in silico* neuron. Adding a real ion channel current to a dynamic clamp-generated *in silico* neuron can facilitate predictive screening of cloned patient-specific ion channel mutations expressed in real cells to identify desired effects on AP behavior, in conjunction with higher-throughput methods, such as automated patch-clamp recordings. This work was funded by NIH R43NS125749 and Cytocybernetics.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.09/J5

Topic: B.03. Ion Channels

Support: NIH Grant HL161160

Title: A transgenic rat model which expresses TdTomato under control of the Scn11a (NaV1.9) gene

Authors: K. BRANDT[1], P. HEROLD[1], N. MORRIS[1], G. M. HOLMES[2], N. M. GRAZIANE[1], M. FARBANIEC[3], *V. RUIZ-VELASCO[1];
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Abstract: The voltage-gated Na^+ channel $Na_V1.9$, which is encoded by the Scn11a gene, is expressed primarily in small diameter, peripheral nociceptive neurons. $Na_V1.9$ channels are known to contribute to setting the resting membrane potential and to play a major role in neuropathic and inflammatory pain. A transgenic rat encoding TdTomato under the control of the Scn11a gene was generated and characterized in this study. The presence of the recombinant transgene in both homozygous and heterozygous-positive offspring was verified by PCR reactions showing amplification of the insert sequence in the genomic DNA. Heterozygotes were distinguished from homozygotes based on the presence of a PCR amplicon specific for the wild-type SCN11a gene lacking tdTomato. Expression of the tdTomato protein was verified through Western blotting experiments showing $Na_V1.9$ in all rats, but only tdTomato was present in transgenic rats. TdTomato was observed within cell bodies and fibers of dorsal root ganglia (DRG), trigeminal ganglia (TG), and nodose ganglia (NG) isolated from both male and female

rats. We also observed that expression of TdTomato was dependent on supplementing the media with growth factors (NGF, GDNF, CNTF) as expression of the fluorophore disappeared within 5 days without growth factors. Confocal microscopy images also showed TdTomato expression throughout the myenteric ganglia of the gut. We failed to observe any overt TdTomato signal in brain regions. $Na_V1.9$ currents were recorded employing the whole-cell patch-clamp technique with external recording solutions containing tetrodotoxin (TTX) and the selective $Na_V1.8$ blocker A-803467 (3-10 μM), using a series of command pulses from a holding potential of -90 mV. The peak of the I-V current was between 0 to +5 mV.Preliminary behavioral assays (i.e., von Frey, tail-flick, and hot plate assays) revealed no significant genotype-dependent differences across all behavioral measures, suggesting that the transgenic animals do not exhibit altered baseline mechanical sensitivity or thermal nociception. Overall, these initial studies indicate that this new transgenic rat model may serve as a valuable resource to identify and study the role of $Na_V1.9$ channels in nociceptive neurons in several pain model systems.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.10/J6

Topic: B.03. Ion Channels

Support: NIH Grant R01MH095995 (FL)
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Title: A brain-permeant small-molecule modulator of the FGF14/Nav1.6 complex reprograms reward-encoding medium spiny neuron excitability in the nucleus accumbens

Authors: A. K. SINGH[1], C. ZHANG[1], Z. HAGHIGHIJOO[1], H. TEIMOURI[2], G. AQUINO-MIRANDA[4], J. SINGH[1], H. CHEN[3], M. LIJFFIJT[5], F. H. DO MONTE[6], J. ZHOU[3], ***F. LAEZZA**[1,5,7];
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Abstract: Anhedonia is a core symptom of major depressive disorder (MDD) that remains inadequately treated, in part because the molecular mechanisms controlling reward-circuit excitability are not well defined. Protein-protein interactions involving voltage-gated sodium (Nav) channels represent an emerging therapeutic entry point for precision control of neuronal

firing. In nucleus accumbens (NAc) reward-encoding medium spiny neurons (MSNs), the fibroblast growth factor 14 (FGF14)-Nav1.6 complex regulates firing output during motivational states. To therapeutically target this signaling node, we used a multimodal discovery pipeline integrating medicinal chemistry, cheminformatics, split-luciferase complementation assays, molecular docking, and patch-clamp electrophysiology to evaluate ~50 analogs derived from compound 1028 and its parent scaffold 7605. Prior studies identified compound 1028 as a selective brain-permeant modulator of the FGF14/Nav1.6 interface that shifts Nav1.6 inactivation, enhances reward-encoding MSN firing, and restores motivation in operant tasks. Structure-guided screening of the analog series resolved two mechanistic classes defined by predicted hydrogen-bond interactions with FGF14 residues R117 or E152, two critical hotspots within the interface. R117-interacting compounds, represented by 1028-like analogs, were predicted to act as positive allosteric modulators, whereas E152-interacting compounds, represented by 7605-like analogs, were predicted to act as negative allosteric modulators. Among the latter, compound CZ0251 robustly inhibited FGF14/Nav1.6 complex assembly in the complementation assay (27.86% of maximal signal at 100 nM; $n = 8$; $p < 0.0001$) and markedly suppressed FGF14-enhanced Nav1.6 currents in patch-clamp recordings, with an estimated IC50 of 166 pM and ~84% efficacy. In addition, CZ0251 modulated cue-driven reward seeking through the FGF14/Nav1.6 signaling axis. Ex vivo NAc MSN slice studies are ongoing to define the impact of CZ0251 on reward-circuit excitability, and pharmacokinetic profiling together with in vivo behavioral testing will further evaluate its translational potential. These data identify the FGF14/Nav1.6 complex as a druggable regulator of reward-circuit function and support a first-in-class therapeutic strategy for anhedonia and other reward-processing deficits in MDD.

Disclosures: A.K. Singh: None. **C. Zhang:** None. **Z. Haghighijoo:** None. **H. Teimouri:** None. **G. Aquino-Miranda:** None. **J. Singh:** None. **H. Chen:** None. **M. Lijffijt:** None. **F.H. Do Monte:** None. **J. Zhou:** None. **F. Laezza:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); IonTX Inc..

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

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Program #/Poster #: PSTR122.11/J7

Topic: B.03. Ion Channels

Support: NIH P20GM103408
FY26 ISU HERC

Title: Ion Channel Gating of an Epilepsy-Associated hNaV1.2 Variant: Implications forNeuronal Dysfunction

Authors: *S. HANIYYAH, J. R. GROOME;
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Abstract: Voltage-gated sodium channels are essential for the initiation and propagation of action potentials in neurons. The human sodium channel NaV1.2 is critical for neuronal excitability, with mutations in this channel linked to neurological disorders including developmental encephalopathic epilepsy (DEE). Despite its clinical relevance, there is not yet a consensus on how DEE mutations affect sodium channel behavior. To investigate this further, wild-type NaV1.2 and the D1598N mutation were expressed in Xenopus oocytes by messenger RNA injection, with each also expressed in an inactivation deficient background. Channel activity was then recorded using cut open oocyte voltage clamp electrophysiology. Voltage-clamp protocols were applied to characterize the probability and kinetics of activation, entry into fast inactivation from the closed or open states, and recovery from inactivation. Igor Pro was used to compare gating properties between wild-type and the variant channels. Wild-type NaV1.2 channels exhibited rapid voltage-dependent activation and inactivation, with the D1598N variant slowing fast inactivation as a gain-of-function effect. Characterizing DEE mutations and their effects on sodium channel function can offer new insight to support the development of more specifically targeted therapeutic interventions for infantile epilepsy. Research was supported in part by an Institutional Development Award (IDeA) from the National Institute of General Medical Sciences of the National Institutes of Health number P20GM103408 and by FY26 HERC award to J Groome.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

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Topic: B.03. Ion Channels

Support: 5R01DA053261-05

Title: Dopaminergic signaling and mitochondrial gene adaptations in the dorsal dentate gyrus are associated with extinction of cocaine-associated memories

Authors: *S. M. FEEHAN[1], L. PASSARELLI-ROBERTS[2], J. WALSH[2], C. MADDOX[3], M. BIN IBRAHIM[4], V. LUNA[2], A. M. RAJADHYAKSHA[5];
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Abstract: Context-associated memories formed during drug use are major contributors to craving and relapse in substance use disorders (SUDs). While the dorsal hippocampus is known to regulate contextual memory formation, the mechanisms underlying the extinction of drug-associated memories remain incompletely understood. The dorsal dentate gyrus (dDG) has

emerged as a critical brain region for extinction learning, particularly through dopaminergic signaling mechanisms. Previous work from our laboratory demonstrated that excitatory granule cells in the dDG expressing dopamine D1 receptors (D1Rs) require functional $Ca_v1.2$ L-Type calcium channels to successfully extinguish cocaine conditioned place preference (CPP). However, dopamine (DA) dynamics during extinction learning, the source of DA, and downstream molecular adaptations remain unclear. To address these questions, we used *in vivo* fiber photometry and a DA-specific biosensor to monitor DA levels in the dDG during cocaine CPP in mice. Because DA input to the dorsal hippocampus is proposed to arise from the locus coeruleus (LC) and ventral tegmental area (VTA), we are used chemogenetics to identify the specific circuit recruited in the dDG during extinction learning. In parallel, to identify the underlying molecular adaptations, we conducted single nucleus RNA sequencing that revealed that mice that successfully extinguish cocaine CPP display selective upregulation of various mitochondrial genes in the dDG. These genes code for proteins involved in the formation of Complex I, Complex IV, TIM Complex, and TOM Complex of mitochondria. Notably, these transcriptional adaptations were absent in animals that failed to extinguish as well as following only the acquisition of cocaine CPP. Quantitative PCR validated extinction-specific mitochondrial gene upregulation in an independent cohort. Together, these studies will provide new insight into circuit and molecular mechanism underlying extinction-related plasticity relevant to SUD vulnerability.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

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Topic: B.03. Ion Channels

Support: NIH Grant DA053261
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Title: Circuit-specific Cacna1c loss in mouse prelimbic cortex differentially regulates sociability and anxiety

Authors: *M. BIN IBRAHIM, S. FEEHAN, E. ZAMORA-RAMIREZ, S. KHANDESHI, W. LE, J. WALSH, A. M. RAJADHYAKSHA;
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Abstract: L-type calcium channels (LTCCs) are essential for neuronal excitability, and perturbations in their function have widespread behavioral consequences. *CACNA1C*, encoding the LTCC subtype $Ca_v1.2$, has consistently emerged as a neuropsychiatric risk gene. As certain psychiatric-associated *CACNA1C* polymorphisms reduce its expression, preclinical $Ca_v1.2$

knockout models provide a useful tool to investigate neurobiological mechanisms underlying altered behavior. Previous studies show that deleting $Ca_v1.2$ in the prelimbic cortex (PL), a region involved in social behavior, produces robust sociability deficits, mirroring social impairments observed across neuropsychiatric disorders. As the PL projects to multiple brain regions associated with valence and motivation, we aim to uncover the neurocircuitry through which $Ca_v1.2$ loss drives social behavioral deficits. Using a combinatorial viral knockout strategy, $Ca_v1.2$ loss in PL neurons projecting to the nucleus accumbens (NAc; PL→NAc), a region involved in social reward processing, results in sociability deficits without affecting anxiety-like behaviors. In contrast, deletion of $Ca_v1.2$ in PL projections to the basolateral amygdala (BLA; PL→BLA) leads to intact sociability but elevated anxiety-like behavior. In all, these findings highlight the utility of projection-specific approaches for dissecting psychiatric-associated behaviors. Future work will characterize $Ca_v1.2$ knockouts in other PL outputs to further ascertain the specificity of PL→NAc circuitry in mediating social deficits. We will also expand on downstream consequences of PL→NAc $Ca_v1.2$ deletion in the NAc, focusing on the cell-type selectivity of PL→NAc projections and their functional impact. Overall, we aim to uncover neuronal processes by which circuit-specific $Ca_v1.2$ loss perturbs sociability, linking cortical excitability to social behavioral outcomes. This work will guide future molecular and circuit-level investigations aimed at understanding how dysfunction of this neuropsychiatric risk gene contributes to disease-relevant behavioral phenotypes.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

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Program #/Poster #: PSTR122.14/K2

Topic: B.03. Ion Channels

Title: Phase Separated ERM Proteins Organize Calcium Signaling Subdomains at Neuronal Endoplasmic Reticulum Plasma Membrane Junctions

Authors: *H. DENG[1], C. TAYLOR[2], M. ZHANG[3], X. WU[3], K. SHEN[4];
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Abstract: Endoplasmic reticulum-plasma membrane junctions (ER-PM junctions, EPJs) are membrane contact sites that coordinate lipid exchange and Ca^{2+} signaling in excitable cells, yet the molecular organization of neuronal EPJs remains poorly understood. Using endogenous protein tagging and serial section transmission electron microscopy in *C. elegans* neurons, we found that neuronal EPJs form extensive patch like domains arranged in a striking soccer ball like pattern across the neuronal soma. Distinct calcium signaling modules occupy separate EPJ

subdomains. The store operated calcium entry (SOCE) components ORAI-1 and STIM-1 form large patch like condensates, whereas the calcium induced calcium release (CICR) machinery, including the Voltage Gated Calcium Channel EGL-19, Junctophilin JPH-1, and Ryanodine Receptor UNC-68, assembles into smaller puncta positioned adjacent to ORAI-1/STIM-1 domains. A forward genetic screen identified the conserved ERM family proteins FRM-4 and FRM-1 as key organizers of EPJ architecture. FRM-4 and FRM-1 localize to EPJs, undergo liquid-liquid phase separation, and organize peri junctional F-actin networks. Loss of FRM-4 and FRM-1 disrupts EPJ subdomain organization, reducing both ORAI-1/STIM-1 enrichment and EGL-19/JPH-1/UNC-68 puncta. Conversely, FRM-4 overexpression promotes ORAI-1/STIM-1 accumulation while suppressing CICR puncta, suggesting that FRM-4 condensates spatially partition distinct calcium signaling modules within EPJs. Functionally, FRM-4 and FRM-1 are required for normal sound-evoked calcium responses in vivo. Notably, human homologs of FRM-4 and FRM-1, including FRMD3, FRMD5, and EPB41L1, have been implicated in neurological disorders but have not previously been linked to EPJs. We found that FRMD3 and FRMD5 also localize in a characteristic EPJ soccer ball like pattern, suggesting an evolutionarily conserved role in EPJ organization. Together, our findings identify FRM-4 and FRM-1 as master regulators of neuronal ER-PM junction architecture and reveal a phase separated subdomain organization that spatially coordinates calcium signaling complexes at neuronal EPJs.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

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Program #/Poster #: PSTR122.15/K3

Topic: B.03. Ion Channels

Title: Modulation of N type Ca^{2+}current by G beta-gamma: The role of PIP_2

Authors: *M. D. NEGRETE RUIZ[1], E. M. CASTRO RODRÍGUEZ[2], H. CRUZBLANCA-HERNANDEZ[1];
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Abstract: In superior cervical ganglion (SCG) neurons, the N-type Ca^{2+} current (ICaN) is inhibited by the Gβγ dimer *via* voltage-dependent (VD) mechanism. This occurs following stimulation of the α2-adrenergic (α2-AR), somatostatin (SS) type 2 (SSTR2), vasoactive intestinal peptide (VIP), or the muscarinic M4 receptors. We reported (Soc. Neurosci.Abstr. 2024) that pharmacological blockade of PIP_2 synthesis, with the PI4-K inhibitor phenylarsine oxide (PAO), attenuated the adrenergic modulation of ICaN, that is attenuated the inhibitory effect of NE (20 μM) on ICaN by ~ 60 %; and ii) decreased the prepulse facilitation coefficient (FC) in the presence of NE from 2.2 ± 0.24 in control cells (n =11) to 1.2 ± 0.04 in PAO-treated cells (n = 11). In this work, the role of PIP_2 in the adrenergic regulation of ICaN was further

characterized and extended to the modulation of ICaN by SS and VIP. The VD-inhibition of ICaN was studied measuring the prepulse facilitation protocol, under two different pharmacological strategies: i) inhibiting the synthesis of PIP_2 with PAO or wortmannin (Wmn); and ii) sequestering PIP_2 by dialysis with poly-L-lysine (PLL, 3 kD). Consistent with the effects of PAO, Wmn treatment (20 μM; 8 min), significantly decreased the adrenergic inhibition of ICaN, reducing it from 54.7 ± 3.8% (n = 6) in control cells to 15.9 ± 3.8% in treated neurons. Likewise, Wmn reduced the FC in the presence of NE from 1.7 ± 0.01 to 1.1 ± 0.05 (n = 6). On the other hand, the PIP_2 scavenger significantly reduced current density, which decreased from 40.4 ± 4.3 pA/pF (n = 11) in cells dialyzed with standard internal solution to 19.0 ± 2 pA/pF (n = 9). In contrast to PAO, PLL slightly reduced the magnitude of α2-AR-mediated inhibition from 73.8 ±3.5% to 66.2 ± 3.6%. However, PLL markedly disrupted the VD inhibition of ICaN, as FC was reduced from 2.2 ± 0.24 to 1.3 ± 0.12. In addition, when analyzing the regulation of ICaN by SS or VIP, similar results were found to those described above for the adrenergic cascade. The FC with SS (500 nM) and VIP (1 μM) were attenuated from 1.8 ± 0.1 (n =8) to 1.26 ± 0.07 (n = 8) and from 1.6 ± 0.07 (n = 7) to 1.21 ± 0.06 (n = 6), respectively. Finally, PAO slowed down the kinetics of re-inhibition by NE or SS from τ = 63.5 ms (n= 6) to τ = 77.3 ms (n = 5), and from τ = 41.8ms (n = 7) to τ = 62.4 ms (n = 6), respectively. We suggest that PIP_2 is required for Gβγ binding to CaV2.2 channels.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

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NS135807
MH082174
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GM144303
GM129376
MH134119
IK6BX005753
HL121059

Title: A Unifying Mechanism for Synaptic Amyloid beta Toxicity. Beta Adrenergic Potentiation of the Ca2+ Channel CaV1.2 by Amyloid beta

Authors: *P. BARTELS[1,3], S. ROUGE[1], J. SCRIPTER[5], Z. ZENG[4], J. L. PRICE[1], C.-Y. CHEN[2], J. A. GRAY[4], Y. XIANG[6], M. M. NAVEDO[7,2], M. C. HORNE[9], M. HRUSKA[10], J. W. HELL[8];
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Abstract: Soluble amyloid-β (Aβ) oligomers are key initiators of Alzheimer's disease (AD), but how they acutely perturb ion channel-dependent synaptic signaling and plasticity remains incompletely understood. Using cell-attached single-channel recordings from cultured hippocampal neurons, we show that Aβ rapidly potentiates L-type Ca^{2+} channel CaV1.2 by increasing channel open probability, primarily via a reduction in mean closed time with no change in mean open time. This effect develops within seconds and requires β2-adrenergic receptor (β2AR) signaling, as β2AR antagonists completely prevent Aβ-induced changes in $Ca_V1.2$ gating. Mechanistically, Aβ hijacks a β2AR-cAMP-PKA cascade to enhance $Ca_V1.2$ function via phosphorylation of serine 1928 (S1928); neurons expressing the nonphosphorylatable S1928 mutant exhibit no Aβ-dependent modulation of $Ca_V1.2$. At excitatory synapses, brief Aβ exposure drives rapid recruitment of Ca^{2+}-permeable AMPA receptors (CP-AMPARs) to postsynaptic sites, accompanied by increased miniature EPSC amplitude and accelerated decay kinetics, consistent with altered ion channel and receptor composition at the synapse. Pharmacological inhibition of β2AR or $Ca_V1.2$ abolishes these effects, indicating that pathological Ca^{2+} influx through dysregulated $Ca_V1.2$ channels is the proximal trigger for maladaptive synaptic remodeling. In acute hippocampal slices, Aβ impairs long-term potentiation in a $Ca_V1.2$- and S1928-dependent manner, linking channel-level dysregulation to circuit-level plasticity deficits. With chronic Aβ exposure, β2AR-$Ca_V1.2$ hijacking disrupts postsynaptic nanostructure, reduces dendritic spine density, and increases neuronal vulnerability, whereas uncoupling β2AR from $Ca_V1.2$ or preventing S1928 phosphorylation fully rescues these structural and functional phenotypes. These findings identify neuromodulatory hijacking of $Ca_V1.2$ as a central ion channel mechanism by which Aβ drives pathological Ca^{2+} signaling, receptor remodeling, and synaptic failure in early AD.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

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Program #/Poster #: PSTR122.17/K5

Topic: B.03. Ion Channels

Support: Maryland Stem Cell Research Fund Post-Doctoral Fellowship
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Title: CACNA1A Mutations Affect the Structure, Function, and Trafficking of $Ca_V2.1$ Channels

Authors: *H.-O. KAISER[1], M. MACPHEE[1], E. GUDMUNDSSON[2], I. E. DICK[2], A. S. KARLS[1], A. A. KRAMER[2];
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Abstract: $Ca_V2.1$ is a voltage-gated calcium channel that is expressed throughout the nervous system where it mediates synaptic transmission by facilitating neurotransmitter release. The *CACNA1A* gene encodes $Ca_V2.1$, a monomeric channel. The pore-forming region of $Ca_V2.1$ is composed of four repeats (RI-RIV) of six alpha helices (S1-S6) and a large intracellular C-terminus. Individuals with mutations in *CACNA1A* present with a wide range of symptoms, including episodic ataxia, familial hemiplegic migraine, seizure, and neurodevelopmental disorder. The heterogeneity of phenotypes reflects region-specific changes of $Ca_V2.1$ expression, particularly in the cerebellum and cerebral cortex. Historically, mutations in *CACNA1A* have been classified as gain-of-function, loss-of-function, or mixed effects, but the mechanisms underlying the different channel functions are not well understood. Mutations in *CACNA1A* have been identified across the entire channel. Here we will focus on four mutations that are specifically found in RIII S3 (D1317E), S4 (T1356I), and RIV S4 (R1667P, Q1674Sfs). The S3 helix stabilizes the pore, and the S4 is the voltage sensor: studying mutations in regions essential for proper channel activity is critical to better understand the diversity of *CACNA1A*-related disorders. We characterized the effect of each mutation on channel function, confirmation, and expression pattern. Electrophysiological studies demonstrated mutation-specific shifts in current density and activation. Predictive modeling using AlphaFold2 and ChimeraX was employed to investigate structural changes induced by each mutation. The resulting models found altered hydrogen bonding in the pore-forming region of the channel. For example, increased hydrogen bonds, as predicted with D1317E, might make the channel more difficult to open; decreased bonds, predicted with R1667P, might be more favorable for activation. Preliminary studies show that $Ca_V2.1$ channels expressed in HEK293 cells are suitable for examining channel trafficking capability. Taken together, this work supports the idea that distinct biophysical signatures seen with each mutation are driven by a combination of factors, including structural and trafficking changes, thus providing new insights into the pathological mechanisms of $Ca_V2.1$ dysfunction.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

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Program #/Poster #: PSTR122.18/K6

Topic: B.03. Ion Channels

Title: Reduction in Ca^{2+}conductance of voltage-gated calcium channels alters their abundance and retention at active zones

Authors: *C. SOOD, J. T. LITTLETON;
MIT, Cambridge, MA

Abstract: Active zones (AZs) are specialized presynaptic sites where voltage-gated Ca^{2+} channels (VGCCs) accumulate to mediate Ca^{2+} influx that triggers synaptic vesicle (SV) fusion and neurotransmitter release. A major determinant of SV release probability (P_r) and synaptic output is the amount of presynaptic Ca^{2+} influx, which is correlated with the abundance of VGCCs at release sites. To understand how VGCCs traffic, accumulate and recycle at AZs, we are using the Drosophila neuromuscular junction to characterize how the abundance of Cacophony (Cac), the sole AZ-localized VGCC in Drosophila, is set and regulated at individual release sites. Previous studies from the lab have found that during AZ maturation, AZs accumulate Cac to a capped upper limit, in contrast to the core AZ scaffold Bruchpilot (BRP), whose AZ abundance increases given extended developmental time. The upper limit of AZ Cac abundance is determined by its delivery and turnover generating a heterogeneous distribution across AZs correlating to AZ size and synaptic output. Cac delivery is rate-limited by its accessory subunit α2δ, confining individual Cac channels to single AZs and promoting their turnover. In vitro studies in other models have suggested Ca2+ conductance properties may regulate VGCC trafficking and synaptic abundance. Whether channel conductance also regulates in vivo VGCC trafficking and synaptic abundance is less clear. To assay if alterations in Ca^{2+} conductance provides additional layers of control for Cac abundance and turnover at AZs in vivo, we generated GFP and photoconvertible mMaple-tagged Cac conductance mutants (cac^{F} and cac^{NT27}) to compare their AZ dynamics to wildtype channels. We find that heterozygotes and homozygotes of cac conductance mutants display increased AZ abundance of both the mutant and wildtype channels. Using FRAP and half-life determinations, we find alterations in Cac AZ abundance in the conductance mutants tracks with increased synaptic delivery and reduced protein turnover of the mutant channels. Lastly, to characterize VGCC transport properties and AZ dynamics, we have employed living imaging of post-golgi Cac vesicles using a UAS driven full length Cac tagged with multiple mNeonGreens at the C-terminus (UAS-Cac-3xNG). In combination with motorneuron specific Gal4 lines, these tagged channels, can provide general and neuron specific rules for Cac trafficking, allow for genetic perturbations to identify regulators of Cac dynamics and provide valuable insights to the lifecycle of VGCCs.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.19/K7

Topic: B.03. Ion Channels

Support: Emory URC Research Award 00160763

Title: Functional mapping of neuropsychiatric disease variants at scale in human neurons

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Abstract: Due to the recent advances in sequencing technologies and genetic testing, the discovery of new disease variants has now vastly outpaced their functional annotation, resulting in the accumulation of variants of unknown significance (VUS), now reaching 1.2M listed in ClinVar, which pose a significant challenge to both providers and patients. Multiplexed assays of variant effects (MAVE) are uniquely positioned for tackling the challenge due to their ability to assess variant impact at scale. Traditional MAVEs often favour scalability and feasibility over physiological relevance of the cellular context, which remain a major roadblock for MAVEs geared towards resolving neuropsychiatric disease variants. To tackle this challenge, we describe the first human neuronal MAVE, testing its feasibility on the cross-disorder risk gene *CACNA1C,* which encodes for the pore-forming subunit of Cav1.2 calcium channel and is associated with both rare, severe neurodevelopmental disorders and common neuropsychiatric disorders such as schizophrenia. We introduced a prime editing library covering 1770 *CACNA1C* variants and 300 controls to our undifferentiated WTC11-PE7-iNGN2 line, which provides stable expression of prime editor 7 (PE7) and doxycycline inducible expression of neurogenin-2 (iNGN2), to create the CACNA1C mosaic line (Ca1C). Representation of variant classifications across four batches were comparable to the initial variant library of *CACNA1C* pegRNAs with all 9000 pegRNAs captured in each batch. The WTC11-PE7-iNGN2 cells were then treated with doxycycline to transition into progenitor cells and finally bonafide cortical glutamatergic neurons (MAP2+ SLC17A6+ CACNA1C+). To establish a scalable, artifact-free readout of Cav1.2 function in human neurons amenable for genotyping, we adopted a TurboID-based calcium recording system called Calcium-activated Split-TurboID (CaST). Towards this, we transfected human cortical neurons with a hSyn-CaST construct to validate the feasibility and resolution of our readout. Brief stimulation of CaST+ neurons with 67mM *KCl* showed higher levels of biotinylation compared to control neurons, as a read out via fixed-cell FACS. These results suggest that fixed-cell FACS provides the resolution needed to separate neurons in an activity dependent manner using CaST. Our work indicates that multiplexed prime editing can create the *CACNA1C* mosaic line whose variant composition is representative of real-world variant classification. Ca1C cells can also be differentiated into neurons allowing us to study variants at scale in highly specialised cells.

Disclosures: J. Belanger-Bienvenue: None. **F. Birey:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.20/K8

Topic: B.03. Ion Channels

Support: NIH Grant GR5271591

Title: Spatial distribution of Cacna1a mRNA splice isoforms in the developing mouse cerebellum and other brain regions

Authors: *A. SALAZAR[1], M. SISTI[2], D. LIPSCOMBE[3];
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Abstract: Alternative mRNA splicing drives protein diversity essential to support cell-specific physiology. The Cacna1a gene encodes the α1 subunit of CaV2.1 (P-type) voltage-gated calcium channels. Cacna1a is upregulated during development and CaV2.1 channels are principal mediators of action potential-evoked excitatory neurotransmission throughout the brain. In the cerebellum, CaV2.1 is highly enriched in Purkinje Cells (PCs) where it contributes to essential processes including synaptic transmission, activity-dependent maturation and competitive input pruning. We confirm and expand prior reports of a developmental change in Cacna1a splice isoform expression in cerebellum. Mutually exclusive e37a and e37b encode a critical EF-hand domain in the proximal C-terminus of CaV2.1, but only e37a confers Ca2+-dependent facilitation (Chaudhuri et al., JNeuroSci, 2004). We show a progressive switch in mouse cerebellum from e37b-Cacna1a dominating at P0 to e37a-Cacna1a dominating by P28, assessed using qPCR to track bulk changes and RNA-probes to resolve spatial information. Widely used single-cell RNA sequencing methods provide incomplete information about Cacna1a splice isoforms; they are optimized for transcripts < 5 kb and larger cells like PCs are fragile and susceptible to damage during cell isolation. To map spatial and temporal expression of Cacna1a splice isoforms in brain, we utilize a custom RNA-based duplex in-situ hybridization assay to distinguish e37a- from e37b-Cacna1a mRNAs. Using knockin mice which only express either e37a- or e37b-Cacna1a we confirm probe specificity and visualize e37 splice isoforms in PCs of the cerebellum. We were able to discriminate isoforms that differ by < 40 bases. But as the visual signals are chromogenic, signal deconvolution in heterogeneous and dense tissue layers - like the cerebellum - is challenging. Existing methods rely on cell-border detection and puncta counting software which work well in monolayer cultures. We developed a Python-based pipeline combining manual region of interest selection with automatic threshold detection and duplexed chromogenic vector assignment. By this method we effectively separate and sum independent probe contributions to the chromogenic signal, to quantify relative isoform abundance in situ. We are applying this analysis pipeline to map spatial and temporal distribution of Cacna1a isoforms in brain and other regions of the nervous system. In addition, this analysis pipeline should be helpful to resolve cell-specific expression patterns of splice isoforms of other ion channels and membrane protein transcripts across tissues.

Disclosures: A. Salazar: None. **M. Sisti:** None. **D. Lipscombe:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.21/L1

Topic: B.03. Ion Channels

Support: NIH Grant R01NS055251

Title: Splicing factors that regulate Cacna1a splicing in cerebellum

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Abstract: Voltage-gated CaV2 channels mediate calcium entry at pre- and post- synaptic sites in response to membrane depolarization. The Cacna1a gene encodes pore-forming α1 subunits of CaV2.1 in central and peripheral nervous systems. CaV2.1 dominates in regulating transmitter release at many synapses, particularly in the adult brain. Single point mutations and CAG expansions in Cacna1a cause several neurological disorders in humans.Cacna1 genes generate multiple mRNAs through alternative pre-mRNA splicing; a critical step in protein optimization for cell-specific functions. In this study we investigate splicing regulation of Cacna1a and, in particular, mutually exclusive exons e37a and e37b which encode the EF-hand domain in the proximal C terminus of CaV2.1. Using knock-in mouse models that constitutively express either only e37a (Cacna1ae37a+/+) or only e37b (Cacna1ae37b+/+) we show that e37a-containing Cacna1a is essential for viability, whereas e37b-containing Cacna1a contributes to more subtle aspects of motor function.Building on earlier reports, we show that exon choice during pre-mRNA is strongly influenced by development in cerebellum and other brain regions. At P0 the vast majority of Cacna1a mRNAs contain e37b but by P28 most Cacna1a mRNAs contain e37a. These findings motivated us to identify the splicing factor(s) regulating this switch in exon expression. The closely related Cacna1b gene contains homologous e37a and e37b, and e37a is enriched in nociceptors but not, as far as we know, developmentally regulated. Cell-specific expression of e37a of Cacna1b is controlled by a co-transcriptional mechanism involving cell-specific hypomethylation of e37a gDNA permitting CTCF binding and exon recognition (Lopez-Soto & Lipscombe, 2020). ChIP-seq data showed CTCF binding to Cacna1a gDNA close to e37a, but manipulating CTCF levels did not alter Cacna1a e37a/e37b splicing.Here, we present evidence that the neuronal RNA-binding protein CELF4 (CUGBP Elav-like family member 4), critical for prenatal mammalian neocortical synaptic development, is a strong candidate for controlling Cacna1a exon choice (e37a or e37b) during development. CELF2 and CELF4 bind Cacna1a pre mRNA within the e37a locus based on the POSTAR3 (Zhaoet al., 2022) database. We used shRNA, iRNA, and cDNA overexpression in neuronal cell lines to manipulate expression levels of CELF2 and CELF4. CELF4, but not CELF2 knockdown lead to a 3-fold increase in Cacna1a e37a inclusion relative to control. Our data also suggest that CELF4 mRNA levels are reduced during development in cerebellum consistent with it acting as a repressor of e37a inclusion early in development.

Disclosures: M.S. Sisti: None. **A. Salazar:** None. **S. Sakhabutdinov:** None. **D. Lipscombe:** None.

Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: B.03. Ion Channels

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SFARI Autism Rat Consortium 4551

Title: Scn2a haploinsufficiency induces cortical hyperexcitability and increases seizure susceptibility in Long-Evans rats

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Abstract: Genetic variation in *SCN2A* is a major risk factor for neurodevelopmental disorders, including developmental epilepsies, autism spectrum disorder (ASD), and intellectual disability. *SCN2A* encodes the voltage-gated sodium channel $Na_V1.2$, which in mature neocortex, is expressed primarily in excitatory neuron dendrites. Loss-of-function (LoF) variants that suppress or eliminate $Na_V1.2$ function are associated with intellectual disability and ASD, and, in an estimated 20-30% of children, epilepsy with onset after the first 3 months of postnatal development. Our goal here is to understand how loss of $Na_V1.2$ in excitatory neurons affects seizure susceptibility. Long-Evans rats heterozygous for the *Scn2a* gene have been developed as a model for studying effects of $Na_V1.2$ loss. We find that these animals exhibit spontaneous seizure events as assayed by multi-site electroencephalogram (EEG) recordings from the cortical surface. Specifically, we observed an increase in spike-wave discharges (SWDs) in *Scn2a*$^{+/-}$ rats relative to wild type littermate controls. These SWDs occurred most frequently during periods of rest and were acutely attenuated by ethosuximide. SWDs are thought to result in part from increased synchrony of cortical neuron firing. We observed increased excitability of cortical pyramidal cells *ex vivo*, measured by increased AP frequency for any given somatic current injection stimulus. This increased cellular excitability may give rise to increased synchronous firing. Hyperexcitability in these cortical cells appears to be due to two mechanisms: first, the loss of $Na_V1.2$ in dendrites leads to a lack of depolarization-dependent engagement of dendritic voltage-gated potassium channels. As such, neurons do not repolarize as effectively between APs, priming them for subsequent activity. Second, these neurons have increased input

resistance, and further electrophysiological analysis suggests that potassium channel function in dendrites is reduced. Thus, direct interactions between $Na_V1.2$ and dendritic potassium channels, and long-term changes in dendritic potassium channel function due to heterozygous loss of $Na_V1.2$, may increase seizure burden in rat models. This work aims to establish a mechanistic link between loss of $Na_V1.2$ and seizure generation, providing a new model to understand *Scn2a* loss-of-function related epilepsies and evaluate therapeutics.

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Poster

PSTR122: Voltage-Gated Sodium and Calcium Channels

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR122.23/L3

Topic: I.02. Perception and Imagery

Title: Infrared Photons Generated by Voltage-Gated Sodium Channel Dynamics: A Hypothesis for Cooperative Electrodynamic Interactions at the Axon Initial Segment

Authors: *D. S. GUPTA;
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Abstract: Voltage-gated sodium (NaV) channels are essential for neuronal excitability and action-potential generation, yet the electrodynamic consequences of voltage-sensor motion remain largely unexplored. Here, we propose a biophysically grounded hypothesis in which transient electromechanical dynamics of NaV-channel voltage sensors give rise to weak cooperative electrodynamic interactions at the axon initial segment (AIS). Specifically, we consider the behavior of conserved arginine gating charges within the S4 voltage-sensor segment as they traverse the hydrophobic constriction site (HCS) and charge-transfer center (CTC) during membrane depolarization. Under subthreshold conditions, local electrostatic and π-cation interactions may transiently stabilize intermediate states of S4 motion, permitting brief reversible excursions ("micro-reversals") of gating charges within the confined high-field environment of the HCS.Based on known structural properties of the voltage-sensing domain and experimentally characterized vibrational modes of the arginine guanidinium group, we propose that these micro-reversal dynamics may generate transient oscillating dipoles capable of weak electromagnetic emission in the mid-infrared range. Because NaV channels are densely organized within the AIS and occupy a subwavelength volume relative to the predicted emission wavelength, subsets of emitters may experience similar local electric fields, orientations, and transition frequencies. Under these conditions, transient phase alignment and weak field-mediated coupling among neighboring emitters could, in principle, support cooperative emission exhibiting qualitative features consistent with Dicke-type behavior. The proposed mechanism does not require long-

lived quantum coherence, sustained entanglement, or quantum computation. Rather, it represents a testable framework linking established NaV-channel biophysics to experimentally accessible electromagnetic observables. We derive order-of-magnitude estimates for charge acceleration, photon emission, and cooperative enhancement, and outline specific experimental predictions, including time-locked mid-infrared emission, nonclassical photon statistics, dependence on AIS organization, and sensitivity to pharmacological or genetic perturbation of NaV-channel function. Together, these predictions provide a framework for evaluating whether transient cooperative electrodynamic interactions play a role in feature integration, perceptual awareness and voluntary motor control.

Disclosures: D.S. Gupta: None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: B.07. Network Interactions

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Charles University Grant Agency (GAUK), No. 224226
Programme Johannes Amos Comenius (OP JAK) under the project MSCA Fellowships CZ - UK3

Title: Class-specific modulation of single-unit activity during cortical ripples in macaque primary visual cortex

Authors: *K. STUDENIčOVÁ, A. MORALES-GREGORIO, K. KORVASOVÁ;
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Abstract: Cortical ripples, brief high-frequency (80-150 Hz) oscillatory bursts in the local field potential, have been linked to memory, attention, and sensory processing, yet their generating mechanisms and cell-type specificity remain poorly understood. We characterize spontaneous ripples in the primary visual cortex (V1) of three macaque monkeys during wakeful rest, recorded with multiple Utah arrays implanted in parallel, across both eyes-open and eyes-closed conditions. Ripple-band power was anticorrelated with delta-band activity during eyes-closed periods, consistent with sleep-related up/down state dynamics, and co-occurred with elevated population spiking across both vigilance states.
Spike sorting combined with waveform-feature classification revealed distinct single-unit classes: Narrow and Medium Biphasic units (putative Layer 4); Wide units (broadly distributed); Triphasic and Positive-polarity units (putative deep layers). These classes showed markedly different coupling to ripple-band activity. Putative Layer 4 and Wide units were strongly up-modulated during periods of elevated ripple-band power and exhibited robust sinusoidal phase-locking near the oscillatory trough, consistent with a local excitatory-inhibitory generating

circuit. Positive-polarity units showed near-complete phase selectivity with a distinctly non-sinusoidal rhythmicity, which we reproduced with a leaky integrate-and-fire model driven by sinusoidal input — suggesting these units inherit the rhythm rather than generate it. Triphasic units were only weakly modulated and showed little phase selectivity, consistent with a non-somatic, likely axonal origin.
The same coupling patterns held during natural image viewing: preferred phases and firing-rate modulation were preserved across all unit classes, implying that a single underlying circuit is recruited in both spontaneous and evoked states. Together, these results reveal a cell-type-specific organization of spiking during cortical ripples and point to a candidate generating mechanism in early visual cortex built around Layer 4 circuitry with complementary deep-layer output.

Disclosures: K. Studeničová: None. **A. Morales-Gregorio:** None. **K. Korvasová:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.02/L5

Topic: B.07. Network Interactions

Support: TRR/CRC 418 Project C05

Title: Ketamine-induced changes of excitation-inhibition balance and neural variability follow a cortical hierarchy

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Abstract: Neural variability is increasingly recognized as a fundamental feature of brain function, reflecting the dynamic range and flexibility of neural systems. Previous work suggests that excitation-inhibition (E:I) balance can play a critical role in shaping neural variability, yet the spatial organization of this relationship across the human cortex remains poorly understood. In particular, it is unclear whether the coupling between neural variability and E:I balance differs across cortical hierarchies and functional networks.To address this question, we analyzed 64-Channel EEG data from a within-subject, placebo-controlled study in which 25 healthy participants received racemic ketamine (target plasma concentration: 0.15 µg/ml), propofol (0.5 µg/ml), or placebo. Ketamine, an NMDA receptor antagonist, is widely used as a pharmacological model of schizophrenia and has been proposed to alter cortical E:I balance. MNE source-reconstructed EEG data were parcellated using the 100-region, 7-network Schaefer atlas. The aperiodic component of the source-projected EEG power spectrum (1-50 Hz) was used as a proxy for regional E:I balance and analyzed along the sensory-to-association (SA) axis for cortical hierarchy. We here report on task-free as well as peri-task data while subjects executed

an auditory decision making task using dichotically presented trains of clicks.Resting-state analyses revealed ketamine-related alterations in spectral exponents that varied systematically along the sensory-to-association axis, with stronger shift in the E:I balance toward excitation observed in lower-level sensory regions. Building on these findings, we examine trial-by-trial fluctuations in pre-stimulus spectral exponents during the task to characterize the stability of cortical states across conditions and cortical hierarchy levels. We further quantify post-stimulus neural response variability across trials, allowing us to assess how cortical regions respond to sensory input under ketamine, propofol and placebo and how it changes in different hierarchies. Finally, we investigate whether pre-stimulus E:I balance is associated with subsequent response variability, linking spectral exponents with task-evoked neural dynamics across the cortical hierarchy.By linking pharmacologically induced alterations in E:I balance to patterns of neural variability, this work provides new insights into the hierarchical regulation of cortical dynamics and their perturbation under NMDA receptor blockade.

Disclosures: J. Kunze: None. **J. Student:** None. **S. Tune:** None. **C. Nau:** None. **J. Obleser:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

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Program #/Poster #: PSTR123.03/L6

Topic: B.07. Network Interactions

Title: Prefrontal neural oscillations during sleep are modulated by rice-memolin

Authors: *T. NAGAHIRO[1], S. IIJIMA[2], K. WATANABE[2], K. TAKEDA[2], Y. IKEGAYA[2,3], N. MATSUMOTO[2,3];
[1]The Univ. of Tokyo, Bunkyo-ku, Tokyo, Japan; [2]Grad. Sch. of Pharmaceut. Sci., [3]Inst. for AI and Beyond, The Univ. of Tokyo, Tokyo, Japan

Abstract: Sleep is essential for memory consolidation, orchestrated through dynamic interactions between the medial prefrontal cortex (mPFC) and other regions via distinct neural oscillations. These oscillations are key physiological signatures of memory consolidation and can be influenced by exogenous substances. Rice-memolin, a rice bran-derived pentapeptide, ameliorates cognitive decline, potentially by modulating the cholinergic system via α7 nicotinic acetylcholine receptors. Given the critical role of the cholinergic system in memory and sleep, we hypothesized that rice-memolin alters sleep-related neural activity.
To test this, we investigated local field potentials (LFPs) and electrocardiograms (ECGs) in mice. Electrodes were implanted into the mPFC and dorsal hippocampus to record LFPs, and wire electrodes were placed on the pectoralis muscle for ECG monitoring. Rice-memolin or vehicle was orally administered for 3 consecutive days, and physiological signals were recorded in home cages. Sleep states were defined by periods of immobility. To distinguish rapid eye movement (REM) from non-REM (NREM) sleep, the delta-to-theta power ratio was calculated

from non-overlapping windows of hippocampal LFPs.
Spectral analysis revealed that rice-memolin significantly attenuated mPFC theta power during REM sleep. During NREM sleep, overall mPFC LFP power was significantly attenuated, and beta and high-gamma oscillation power significantly decreased. Despite these alterations, rice-memolin did not affect cardiac or autonomic function. Heart rate, heart rate variability, and indices of parasympathetic and sympathetic activity remained unchanged across all sleep states. These findings demonstrate that rice-memolin modulates cortical network dynamics in a frequency-specific manner during sleep. By acting on α7 nicotinic acetylcholine receptors, rice-memolin may fine-tune the excitatory-inhibitory balance required for gamma-oscillation generation. Furthermore, the reduced theta power may reflect altered communication within prefrontal-hippocampal networks. These sleep-related oscillatory changes may contribute to the procognitive effects of rice-memolin.

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Poster

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Topic: B.07. Network Interactions

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Title: Directional and lateralized theta dynamics during verbal working memory in human medial temporal lobe

Authors: D. CHOI, ***H.-B. HAN**;
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Abstract: The medial temporal lobe (MTL) is known to orchestrate large-scale neural networks via theta oscillations, contributing to both memory encoding and retrieval. However, how verbal working memory in humans is regulated by the dynamic neural activity of MTL subregions remains poorly understood. To address this, we analyzed intracranial EEG recordings from the hippocampus, amygdala, and entorhinal cortex of patients with epilepsy performing a Sternberg memory task. We found that theta-rhythmic information flow within MTL subregions followed opposing directional gradients depending on task phase: a posterior-to-anterior direction during encoding and an anterior-to-posterior direction during retrieval. Inter-hemispheric Granger causality analysis further revealed that this effective connectivity was predominantly directed from the left hemisphere to the right, consistent with the verbal nature of the Sternberg task and

the well-established left-lateralization of language processing. Supporting this, theta burst analysis demonstrated that bursts in the left hemisphere were more strongly modulated by task demands than those in the right. Together, these findings suggest that the MTL network reflects cognitive load through left-lateralized theta bursts for verbal working memory, with its leading hub fluidly adapting to phase-specific memory demands.

Disclosures: D. Choi: None. **H. Han:** None.

Poster

PSTR123: Oscillations and Synchrony

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Topic: B.07. Network Interactions

Support: NINDS Grant T32NS115656
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Title: Thalamocortical mechanisms of delta oscillations in a mouse model of Angelman syndrome

Authors: *D. P. MONTGOMERY, J. KINNAMAN, M. S. SIDOROV;
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Abstract: Angelman syndrome (AS) is a neurodevelopmental disorder caused by loss of function of the maternal *UBE3A* gene. Elevated delta (1-4 Hz) power during wake is a near-ubiquitous feature of the disorder in both children with AS and *Ube3a*$^{m-/p+}$ mice, and has been linked to behavioral deficits in both species. However, despite the prevalence of the delta phenotype and its potential use as a translational biomarker, little is known about its underlying circuit-level mechanisms. Typically, delta oscillations occur during NREM sleep and are thought to be generated by interactions between thalamic and cortical circuits: increased activity of thalamic reticular nucleus (TRN) neurons inhibit thalamic relay neurons, shifting those neurons into burst-mode firing to rhythmically drive cortex at the delta frequency. Whether a similar mechanism drives delta oscillations observed during wake in Angelman syndrome remains unknown. To investigate this, we recorded local field potentials and single unit activity simultaneously in primary visual cortex (V1) and either the lateral geniculate nucleus (LGN) or TRN of wild-type and *Ube3a*$^{m-/p+}$ mice. We found that elevated delta power in *Ube3a*$^{m-/p+}$ mice was driven by increased time spent in delta episodes rather than greater power within episodes. While LGN burst firing was slightly elevated in *Ube3a*$^{m-/p+}$ mice, this increase was explained by the increased time spent in delta oscillations, with no genotype difference in burst rates within delta episodes. TRN bursting was unexpectedly *impaired* in *Ube3a*$^{m-/p+}$ mice, arguing against the TRN as the driver of elevated delta. In cortex, fast-spiking (putative PV+) interneuron firing rates were reduced, and LGN bursts evoked stronger cortical responses, consistent with weakened feedforward inhibition lowering the threshold for thalamocortical delta recruitment.

Together, these results suggest that cortical inhibitory dysfunction, rather than thalamic circuitry, represents the primary driver of the AS delta phenotype. These findings establish a mechanistic framework linking circuit-level changes to a defining EEG signature of AS, laying the groundwork for future circuit-informed therapeutic strategies.

Disclosures: D.P. Montgomery: None. **J. Kinnaman:** None. **M.S. Sidorov:** None.

Poster

PSTR123: Oscillations and Synchrony

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Program #/Poster #: PSTR123.06/M1

Topic: B.07. Network Interactions

Support: VA Merit Award I01 BX004500
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NIH R21 MH125242

Title: The role of the basal forebrain on brain-wide oscillatory and connectivity dynamics during olfactory decision-making in mice

Authors: E. B.-L. MANESS[1], M. MACIVER[1], J. T. MCKENNA[2], *J. M. MCNALLY[3]; [1]Psychiatry, VABHS/Harvard Med. Sch., West Roxbury, MA; [2]Research/Psychiatry, VA Boston/Harvard Med. Sch., West Roxbury, MA; [3]VABHS, Harvard Med. Sch., West Roxbury, MA

Abstract: The ability to flexibly attend and respond to an unpredictable environment requires precise coordination of distributed brain networks across conscious states. In olfactory cognition, chemosensory information must travel from primary sensory neurons to regions involved in higher-order cognition and behavior. Recent studies suggest that the basal forebrain (BF) is central to controlling shifts in network activity and facilitating transitions between inattentive and attentive states. To characterize the role of the BF in time- and performance-dependent changes in oscillatory activity and brain-wide connectivity, mice (n = 11) were outfitted for multi-site local field potential recording and trained in a self-initiated olfactory discrimination Go/No-Go task during which they are required to retrieve reward following the presentation of a "Go" odor and refrain from reward retrieval when the "No-Go" odor is delivered. Task-associated electrophysiological data reveal robust suppression of high-frequency neural activity (high gamma, 60-200 Hz) prior to and during attentional effort in the BF as well as across all other recorded brain regions, including those associated with olfaction (olfactory bulb (OB)), attention and salience (prelimbic cortex (PrL) and anterior insula (AI)), and memory (retrosplenial cortex and hippocampus). In contrast, lower-frequency oscillations (delta, 1-4 Hz; theta, 4-8 Hz; alpha, 8-12 Hz; beta, 12-30 Hz; and low gamma, 30-60 Hz) showed region-, time-, odor-, and behavior-dependent enhancements across the attentional time span. BF-centered connectivity analysis revealed transient task-related network modulation that was significantly

associated with behavioral accuracy and interacted with cortical activity (notably AI, OB and PrL signals) in predicting performance outcomes. By revealing intra-regional rhythmic signatures and between-region coordination underlying signal-driven attention - with particular focus on BF-mediated regulation of distributed cortical and limbic network states - these findings suggest that maintaining exteroceptive awareness in support of goal-directed and adaptive behaviors requires synchronized activation of cortical and subcortical networks.

Disclosures: E.B. Maness: None. **M. MacIver:** None. **J.T. McKenna:** None. **J.M. McNally:** None.

Poster

PSTR123: Oscillations and Synchrony

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Program #/Poster #: PSTR123.07/M2

Topic: B.07. Network Interactions

Title: Neural Oscillatory Dynamics and Interoceptive Awareness Following Nadamay Meditation Training

Authors: *C. KAUSHAL[1], K. MEGHA[2];
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Abstract: Neural Oscillatory Dynamics and Interoceptive Awareness Following Nadamay MeditationTrainingAbstract Background: Nadamay Meditation, a contemplative practice derived from the Nada Yoga tradition,emphasizes sustained attention to sound as a pathway toward progressively refined states of awareness.While meditation-related changes in neural oscillations have been reported across several contemplativetraditions, the neurophysiological mechanisms underlying Nadamay Meditation remain largely unexplored.We investigated whether eight weeks of Nadamay Meditation modifies frontal EEG oscillatory activity andinteroceptive awareness relative to active and passive control conditions.Methods: Eighty-two healthy adults participated in a single-blind, three-arm randomized controlled trialand were assigned to Nadamay Meditation, Indian classical music listening, or mind-wandering controlgroups. Participants completed baseline and post-intervention assessments of frontal EEG power spectraldensity (PSD), dispositional mindfulness using the Mindful Attention Awareness Scale (MAAS), andinteroceptive awareness using the Multidimensional Assessment of Interoceptive Awareness (MAIA).Results: Linear mixed-effects analyses revealed significant group-by-time interactions for frontal thetapower, $F(2, 28.25) = 4.50$, $p = .020$, $\eta p^2 = .45$, and frontal alpha power, $F(2, 26.68) = 3.38$, $p = .049$.Participants practicing Nadamay Meditation demonstrated significantly greater increases in both oscillatorybands compared with active and passive controls. Meditation training was also associated with substantialimprovements in dispositional mindfulness ($d = 0.87$) and selective enhancement across four MAIAsubscales reflecting increased awareness, trust, and regulation of bodily sensations. In contrast, controlgroups exhibited fewer and less consistent changes across neural and self-report

measures.Conclusions: These findings provide evidence that Nadamay Meditation produces training-specificmodulation of frontal theta and alpha oscillatory dynamics accompanied by improvements in interoceptiveawareness. The observed pattern suggests enhanced internal attentional regulation and embodiedawareness, supporting the hypothesis that sound-based contemplative training engages neural mechanismsrelevant to consciousness and self-regulation.**Keywords:** Nadamay Meditation, Nada Yoga, EEG oscillations, theta power, alpha power, interoception,mindfulness, consciousness

Disclosures: C. Kaushal: None. **K. Megha:** None.

Poster

PSTR123: Oscillations and Synchrony

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Program #/Poster #: PSTR123.08/M3

Topic: B.07. Network Interactions

Support: 5R01NS121316-03
5T32AG071745-05

Title: AMNESIA: Amelioration of biomarkers of Memory with Neuromodulation, Electrophysiological recordings demonstrate recovery of SWRs after Injury and during Aging

Authors: *M. S. STEN[1], L. FRAYSER[2], J. O'LEARY[1], D. CHAPMAN[5], S. VICINI[6], J.-Y. WU[3], M. P. BURNS[4];
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Abstract: Background:
Memory deficits occur in patients with traumatic brain injury (TBI) and aging. The hippocampus uses synchronized brain firing patterns called sharp wave ripples (SWRs) to consolidate memories. Truncating SWRs causes memory impairments. However, how TBI and aging changes SWRs remains unknown. In this study, we aim to investigate how TBI and aging influence SWRs, and if non-invasive brain stimulation (tDCS) rescues TBI or age-associated SWR changes.
Methods:
tDCS was delivered using the Soterix animal transcranial stimulator (20 minutes per day, for 3 consecutive days). For the aging study, naïve controls (n=7, ages 4-8 months, 3 males+4 females) were compared to aged mice (n=6, ages 23-24 months, 2 males+4 females) and aged mice who received 3 days of tDCS (n=8, ages 21-24 months, 4 males+4 females). For the TBI study, we used controlled cortical impact (CCI, 1.5 mm depth) mice at 1 month post-injury. TBI mice were divided into sham (C57BL/6, n=4, ages 7 months, females) or received 3 days of TDCS (n=2, ages 6 months, males). Mice were euthanized 24 hours after the final tDCS

treatment.
Results:
We found that aged mice have SWRs with shorter average duration (80.83±4.221ms) compared to young mice (124.9±14.3ms). The number of ripple cycles per SWR were also significantly decreased in aged (13.36±0.6957) vs young mice (18.42±1.493). These phenotypes were both completely restored by 3d of tDCS treatment (duration: 135.3±11.58ms; ripple cycles: 19.61±1.164).
Similarly, we found that CCI also caused a significant reduction in SWR duration (86.71±10.60ms) compared to the naïve controls (124.9±14.30ms). The number of ripple cycles per SWR were also significantly decreased in CCI mice (13.95±1.160) vs controls (18.42±1.493). These phenotypes were both completely restored, and even extended by 3d of tDCS treatment (duration: 251.2±30.57ms; ripple cycles: 32.76±2.655).
Conclusion:
Collectively, these data demonstrate a novel mechanism for cognitive impairments experienced by both TBI and aged animals. Our future goals are to elucidate the mechanisms by which tDCS causes the restoration of SWR architecture in aged and TBI mice.

Disclosures: M.S. Sten: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder. **L. Frayser:** None. **J. O'Leary:** None. **D. Chapman:** None. **S. Vicini:** None. **J. Wu:** None. **M.P. Burns:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Patent holder.

Poster

PSTR123: Oscillations and Synchrony

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Program #/Poster #: PSTR123.09/M4

Topic: B.07. Network Interactions

Support: NIDC of the NIH
CTSI

Title: Developmental mechanisms underlying neural hyperexcitability in tuberous sclerosis complex

Authors: *N. HARUNANI[1], B. MCNALLY[2], A. MCGRATH-CONWELL[4], J. SMITS[6], M. POWERS[7], N. RYCHAGOV[4], K. F. RAAB-GRAHAM[3], J. MAIER[5];
[1]Translational Neurosci., [3]Physiol. and Pharmacol., [2]Wake Forest Sch. of Med., Winston Salem, NC; [4]Wake Forest Univ. Sch. of Med., Winston-Salem, NC; [5]Translational Neurosci., Wake Forest Univ. Sch. of Med., Winston salem, NC; [6]Univ. of Texas, Austin, TX; [7]Univ. of Texas at Dallas, Dallas, TX

Abstract: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by loss of function in either TSC1 or TSC2 genes, leading to constitutive/hyperactive mTOR signaling. TSC is a multiorgan disease characterized by benign tumors and cysts throughout the body. In the brain, it is associated with epilepsy, autism spectrum disorder, and cognitive impairments collectively termed as TSC-associated neuropsychiatric disorders (TAND). These symptoms have been linked with cortical hyperexcitability, which is observed in both human patients and animal models. Excitation-inhibition (E/I) balance is established during early postnatal development with the maturation of inhibitory circuits. Disruptions in the maturation of inhibitory circuitry may contribute to cortical hyperexcitability and the early emergence of TSC-associated symptoms. However, the developmental circuit mechanisms underlying this dysfunction remain poorly understood. Identifying early circuit abnormalities may provide critical insight into developmental windows for therapeutic intervention in TSC. We hypothesized that hyperexcitability in TSC arises from altered developmental maturation of inhibitory circuitry. To test this hypothesis, we recorded spontaneous and odor evoked neural activity from the prefrontal cortex of awake mice with a neuron-specific cKD of TSC1 (nTSC1(+/-) and wild-type (WT) mice across early postnatal development (P10-P26). Following brief isoflurane anesthesia and electrode implantation, neural recordings were obtained in these awake animals. Odor stimuli (amyl acetate; 1% saturated vapor) were delivered orthonasally using constant-flow air dilution olfactometry. Neural activity was analyzed using MATLAB, Kilosort4 spike sorting, and spectral analysis approaches. nTSC1(+/-) mice exhibited increased spontaneous network activity, elevated neuronal firing rates, and enhanced odor-evoked responses beginning at PND 10. In addition, TSC mice showed increased gamma oscillatory power, which demonstrates early cortical hyperexcitability in line with our hypothesis. Notably, putative PV interneurons also displayed elevated firing rates. These findings argue against reduced inhibitory neuron activity or excessive autoinhibition as primary drivers of network dysfunction. Instead, they suggest that hyperexcitability may arise from an impaired developmental GABAergic switching that contributes to abnormal circuit activity in TSC.

Disclosures: N. Harunani: None. **B. McNally:** None. **A. McGrath-Conwell:** None. **J. Smits:** None. **M. Powers:** None. **N. Rychagov:** None. **K.F. Raab-Graham:** None. **J. Maier:** None.

Poster

PSTR123: Oscillations and Synchrony

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Topic: B.07. Network Interactions

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R21 MH126072
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Title: Traveling waves reflect spatiotemporally structured input ensembles along the cortical depth

Authors: *L. YAN[1,2], M. P. MORTON[3], A. S. NANDY[4], M. JADI[1];
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Abstract: Traveling waves (TWs) are widely observed in the brain and attributed multiple functional roles, yet their neural basis remains unclear. Using translaminar recordings in macaque visual cortex, we observed local field potential (LFP) TWs modulated by sensory experience. Slow LFP TWs were associated with suppressed spiking compared to periods without TWs. Although no TWs were observed in multi-unit activity envelope (MUAe), LFP TWs periods were associated with increased depth synchrony of MUAe. Crucially, TW speeds predicted population response dynamics: faster waves were associated with larger MUAe responses, whereas slower waves correlated with weaker responses. We propose a computational framework in which LFP TWs reflect spatiotemporally structured synaptic inputs, while MUAe reflects their leaky integration within the cortical columns. By providing a mechanistic account of TWs in the cortical depth, this framework dissociates LFP TWs from propagating spiking activity and instead links them to the temporal alignment of inputs.

Disclosures: L. Yan: None. **M.P. Morton:** None. **A.S. Nandy:** None. **M. Jadi:** None.

Poster

PSTR123: Oscillations and Synchrony

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Topic: B.07. Network Interactions

Support: NIH R01 NS128901
NIH R01 NS146078
NIH R34 NS137454

Title: State-Dependent Theta-Phase Modulation of Inter-Areal Communication through Single-Cell Voltage Dynamics

Authors: *Y.-Y. SHAN[1], M. HU[1], N. HAKAM[1], J. REIMER[1,2];
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Abstract: Anatomical connectivity between brain areas remains largely stable over behavioral timescales, yet the functional interactions shift rapidly across spontaneous behaviors and task demands. How the brain dynamically reconfigures communication across states without changing its underlying wiring remains a central question in systems neuroscience. The Communication through Coherence (CTC) framework proposes that coherent neuronal oscillations support routing by aligning excitability windows between source and receiver populations such that inputs arriving during depolarized phases are transmitted more effectively. However, CTC has not been tested at single-cell resolution. Prior work has relied predominantly on extracellular recordings, which conflate single-cell phase with population field potentials. Here, we used the genetically encoded voltage sensor, FORCE1s, and two-photon mesoscopy to simultaneously record voltage activity from individual layer 2/3 pyramidal cells (L2/3 PCs) in mouse primary visual cortex (V1) and higher visual areas (HVAs) during spontaneous behavior. We found that V1 and HVA PCs exhibited brain-state-dependent inter-areal theta-band (4-8 Hz) synchrony that was most prominent during low arousal. V1-HVA spike coupling between individual PCs was enhanced when their theta oscillations were phase-aligned. To further test whether postsynaptic theta phase influences responses to inter-areal input, we are optogenetically activating V1 PC axon terminals while imaging FORCE1s activity in HVA L2/3 PCs. Together, our findings support a model in which theta-phase synchrony may contribute to state-dependent inter-areal communication at single-cell resolution.

Disclosures: Y. Shan: None. **M. Hu:** None. **N. Hakam:** None. **J. Reimer:** None.

Poster

PSTR123: Oscillations and Synchrony

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Thrasher Research Fund
Rosamund Stone Zander Translational Neuroscience Center
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Charles H. Hood Foundation

Title: Bursty to rhythmic: developmental trajectories of neural oscillations in typical development and Down syndrome

Authors: H. CHUNG[1], W. W. AN[1], M. TSOU[1], C. A. NELSON[1,3], *C. L. WILKINSON[2,3]; [1]Boston Children's Hosp., Boston, MA; [2]Boston Children's Hosp., Brookline, MA; [3]Harvard Med. Sch., Boston, MA

Abstract: Transient changes in spectral power in the theta/alpha range (4-12 Hz) are observed in early childhood in typical development (TD), with studies reporting a gradual shift in peak frequency between 6-to-10Hz. Recent findings report transient double peaks (5.5 and 9.5Hz) at 2-4 months, with the higher 9.5Hz peak disappearing by 6 months. In Down syndrome (DS), double peaks in this range persist, suggesting atypical development in oscillatory dynamics. Power spectral peaks are thought to reflect neural oscillatory activity; however, peaks may arise from either irregular (bursty) or sustained (rhythmic) activity. Thus, transition from double- to single-peaks may reflect a change of transient to mature circuitry, a process potentially altered in DS. This study characterizes the developmental changes and differences in rhythmic properties in TD and DS children. We analyzed resting-state EEG data in TD (n=607; 2-to-44 months) and DS (n=77, 18-to-45 months) children. Lagged coherence (LC) was computed to explore the rhythmicity of the signal across 2-40Hz, in 0.2Hz steps from 1-to-3 lags. In TD, Generalized Additive Mixed Models revealed a three-way interaction between age, frequency, and lag index (edf = 100.69, $p < .001$), indicating that frequency-specific patterns of oscillatory properties change significantly across development (Figure1A). Rhythmic posterior alpha emerged ~6-9 months onward, with peak frequency and LC magnitude increasing with age. Distinct peaks at 5 and 9.5Hz were observed between 2-to-4 months, decaying rapidly across lag indices, reflecting bursty activity. In contrast, in DS, double peaks remained bursty throughout childhood (Figure1B). These findings imply two independent transient oscillations with distinct rhythmic properties present early in TD, both of which decrease as mature rhythmic alpha emerges. In DS, an incomplete transition to rhythmic oscillatory alpha dynamics may reflect altered thalamocortical circuit maturation, given the role of thalamocortical loops in generating and sustaining alpha oscillations.

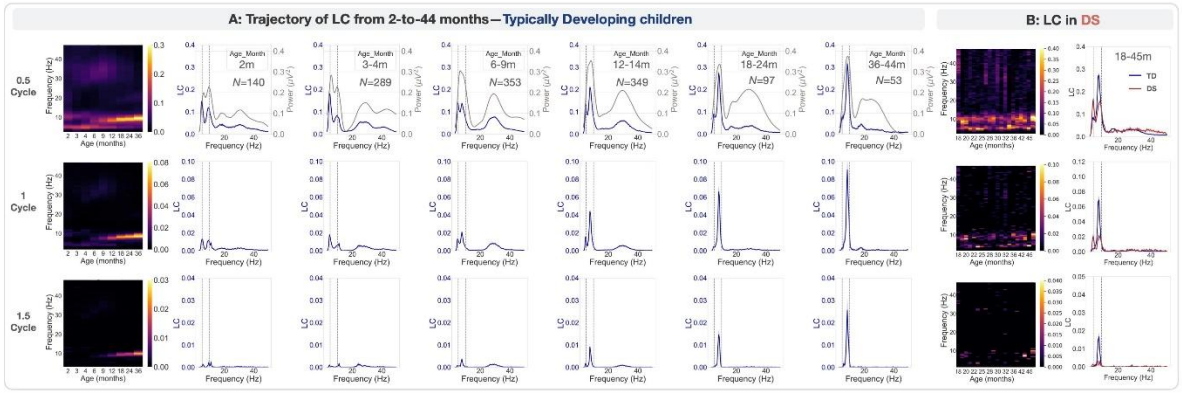


Figure 1. Developmental trajectory of lagged coherence (LC) in typically developing (TD- A) children and Down syndrome (DS- B).
(A) LC across frequency (2-40 Hz) and age (2-44 months) in TD children, shown at three lag indices (0.5, 1.0, and 1.5 cycles; rows). Left heatmaps display LC as a function of age and frequency at each lag index. Line plots show mean LC (blue) and power spectra (grey) at six age windows (2, 3–4, 6–9, 12–14, 18–24, and 36–44 months). At 0.5 cycles, double peaks at ~5.5 and ~9.5 Hz are visible in early infancy, both decaying rapidly across lag indices, reflecting bursty activity. From 6-9 months onward, a single peak between 6-9 Hz emerges and persists to 1.5 cycles, reflecting the developmental consolidation of rhythmic alpha oscillations. (B) LC in DS, shown alongside TD data (blue) for comparison. Heatmaps and line plots (red) indicate that double peaks at ~5.5 and ~9.5 Hz persist beyond toddlerhood, with both peaks remaining bursty across all lag indices and no evidence of rhythmic alpha consolidation comparable to TD.

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Poster

PSTR123: Oscillations and Synchrony

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Program #/Poster #: PSTR123.13/N4

Topic: B.07. Network Interactions

Title: Neuromodulatory dynamics of the infraslow oscillation during the psychedelic state and NREM sleep

Authors: *J. GUENZA-MARCUS[1], D. A. MCCORMICK[2];
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Abstract: During sleep, neural dynamics are dominated by internally generated network rhythms. A striking example of this is the infraslow oscillation (ISO; <0.1 Hz), a physiological oscillation with a period of between 30 and 100 s observed during NREM sleep that presents as an oscillatory constriction and dilation of the pupil in sleeping mice. The ISO is evolutionarily conserved across species (Bergel et al., 2026) and is known to coordinate multiple physiological processes during sleep, including thalamocortical rhythmogenesis, autonomic activity, and vascular dynamics, suggesting that it reflects a fundamental organizing rhythm of brain state (Bergel et al., 2026). Recently, our lab has demonstrated that the ISO can be pharmacologically induced with the phenethylamine psychedelic DOI (2,5-dimethoxy-4-iodoamphetamine), as well as by the 5-HT2a agonist psychedelics 4-AcO-DMT and 25C-NBOH, in the awake state (Vickers et al., bioRxiv, 2026). Separately, we have also shown pupil diameter, as an indicator of arousal, to exhibit high coherence with the cortical axonal activity of norepinephrine (NE) and acetylcholine (ACh) projections from the locus coeruleus and basal forebrain, respectively, during spontaneous waking behavior (Collins et al., 2023). Here, we aimed to determine the extent to which NE and ACh shape the ISO in the psychedelic state and sleep. We used fiber photometry to record thalamic NE and ACh concentration with genetically-encoded GRAB sensors (GRAB-NE1h and GRAB-ACh3.0) in mice during sleep and DOI-induced psychedelic states. Preliminary recordings from NE (n = 4) and ACh (n = 4) cohorts indicate that thalamic neuromodulatory tone is organized at ISO timescales during the psychedelic state, such that both NE and ACh are elevated in thalamus during the pupil peak and decrease during the pupil trough of the ISO. Furthermore, the onset of the ACh rise at the beginning of pupil dilation prior to the peak appears to occur at 5.50 +/- 0.58 s prior to that of NE, and declines at 8.75 +/- 1.20 s before the decline of NE during pupil constriction after the ISO peak. Ongoing stimulation experiments will test the necessity and sufficiency of ascending thalamic NE and ACh inputs towards the emergence of the ISO across the brain, including cortex. Together, these experiments provide insight into the role of neuromodulators in the generation and propagation of the ISO and show great promise in furthering our understanding of the mechanisms underlying the pro-neuroplastic effects of psychedelics.

Disclosures: J. Guenza-Marcus: None. **D.A. McCormick:** None.

Poster

PSTR123: Oscillations and Synchrony

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Topic: B.07. Network Interactions

Support: CREST JPMJCR1864
KAKENHI 21H04423

Title: Awake cortex shapes traveling-wave information routing and neural synergy

Authors: *K. MISAWA, N. MUKAI, Y. MAKIHARA, Y. KOMURA;
Grad. Sch. of Human and Envrn. Studies, Kyoto Univ., Kyoto, Japan

Abstract: Theories of consciousness hypothesize that perceptual experience arises from global cortical communication, yet the neural substrate mediating inter-areal information transfer remains uncertain. Large-scale traveling waves describe how neural activity flows across the cortex, but whether information flows the same way is unknown. We investigated whether neural flow and informational flow coincide, and how this depends on conscious state. Using an ultra-thin, multi-channel sheet ECoG array covering nearly the whole cortex, we recorded visual-evoked responses to LED stimulation under awake and isoflurane-anesthetized conditions. Traveling waves were extracted from broadband signals using the generalized-phase method, and directional information flow was quantified by transfer entropy (TE). Simulations showed that consistent phase delays, the signature of a traveling wave, need not imply informational flow (TE) in the same direction. However, in vivo, cortical traveling waves serve as an effective vehicle for information transfer. The awake waves displayed more widespread and diverse motifs than anesthetized waves. To see how information flow aligns with the wave, at each electrode we plotted TE to its eight neighbors against their direction relative to the wave, forming a tuning curve analogous to neuronal tuning, which we call informational tuning. TE peaked along the wave direction in both states (V-test, $p < 0.05$), and this tuning was sharper in the awake state, where late motifs were more selective than all others, including anesthetized ones. Furthermore, we used the pairwise neural activities to compute “synergy” based on the mathematics of Partial Information Decomposition (Williams & Beer, 2010; Wibral et al., 2017; Mediano et al., 2025), revealing higher synergy in the networks during wakefulness than under anesthesia.The neuro-informational framework introduced here offers a promising approach to elucidate how neural signal propagation translates into directional information flow across the cortex, and how the dynamics support consciousness and diverse cognitive functions.

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Poster

PSTR123: Oscillations and Synchrony

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Program #/Poster #: PSTR123.15/N6

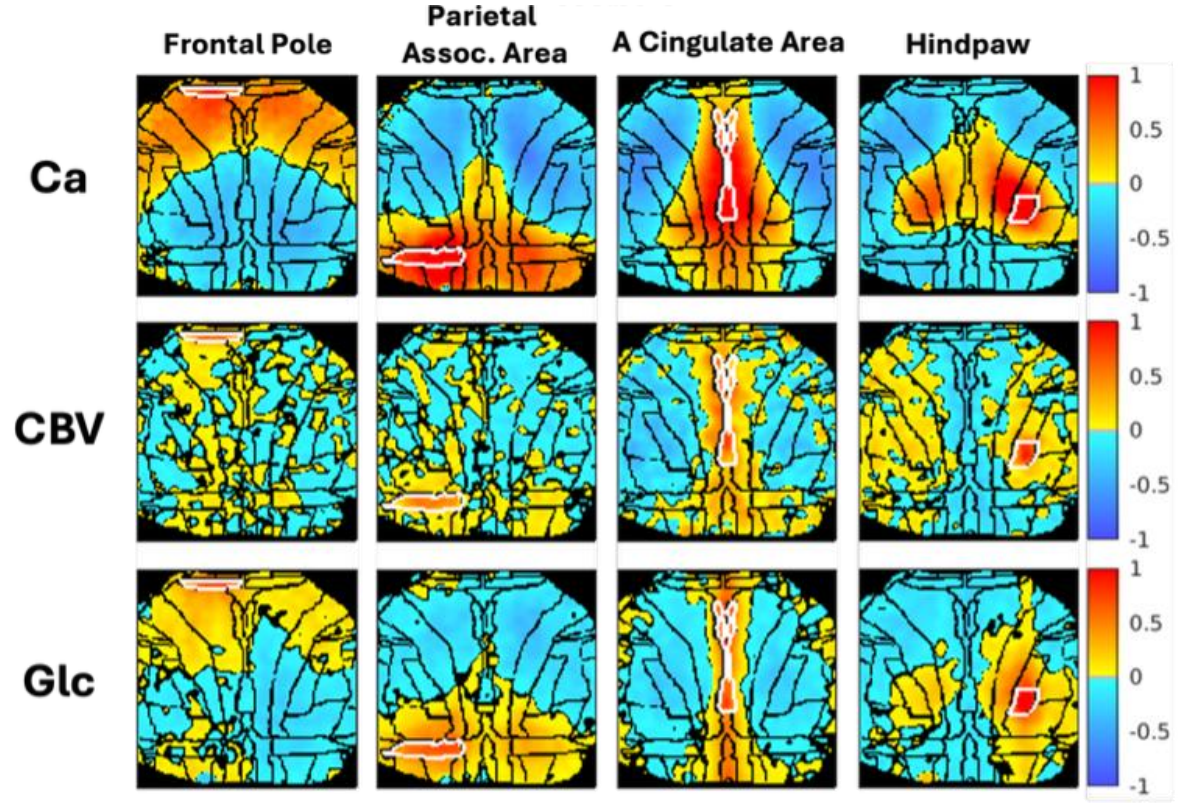
Topic: B.07. Network Interactions

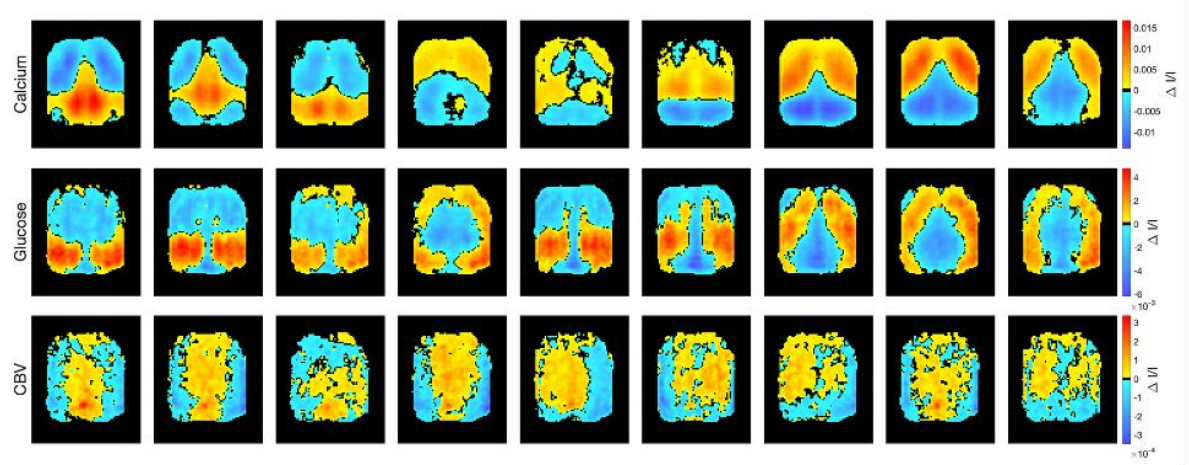
Support: R01-MH067528
R01 NS100106
R01-AG084681
R21- AG085366

Title: Dissecting the neurometabolic and neurovascular contributions to brain network at rest

Authors: *B. CHANG[1], J. V. VERHAGEN[2], P. HERMAN[3], F. HYDER[1];
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Abstract: While neurovascular coupling (NVC) and neurometabolic coupling (NMC) provide the foundation for functional brain imaging with fMRI and PET methods, their contributions to brain networks remain unexplored. We simultaneously measured fluctuations in neuronal activity (neurodynamics), glucose uptake (glucodynamics), and hemoglobin (hemodynamics) to assess NMC and NVC in resting mouse brain. Using an in-house multiplexed optical system designed for whole cortex imaging in mice through implanted cranial window, we measured neurodynamics (red fluorescence of Ca^{2+} signaling), glucodynamics (green fluorescence of 2NBDG, a glucose analog), and hemodynamics (near-infrared absorbance) in Thy-1jRGECO1a mice following a bolus 2NBDG injection. Seed-based analysis at four selected regions (**Figure A**) demonstrates strong network patterns of activity that emerge across neurodynamics and glucodynamics. In contrast, network patterns of hemodynamics are much weaker, hinting at strong NMC and weaker NVC. These network couplings hold up across multiple trials and across 5 mice. Hierarchical clustering of the cortical image series showed close correspondence between neurodynamics and glucodynamics, while hemodynamics displayed more global patterns (**Figure B**). These findings indicate that glucodynamics follows neurodynamics more stringently than hemodynamics, suggesting that NMC and NVC are both critical for functional imaging in health and disease.





Disclosures: B. Chang: None. **J.V. Verhagen:** None. **P. Herman:** None. **F. Hyder:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); FH is the founder of InnovaCyclics, a biotech startup developing NextGen MRI contrast agents..

Poster

PSTR123: Oscillations and Synchrony

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Topic: B.07. Network Interactions

Support: NSF 2515404
NSF 2332744
NSF 2318139
NIH-NINDS 1R01NS130759

Title: Characterizing spike-time to local field potential phase coupling in human-derived brain assembloids

Authors: *J. P. MOLER[1,2], S. MIRSADEGHI[1,2], J. HSIEH[1,2], F. SANTAMARIA[1,2];
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Abstract: Understanding how neuronal signals propagate across spatial scales requires the characterization of both single-cell activity and population-level phenomena. Here we used multi-electrode extracellular recordings to investigate the relationship between spiking and local field potentials (LFPs) in 16 human-derived brain assembloids, produced from 4 lines of healthy donors. The assembloids were generated by fusing cortical and ganglionic eminence organoids at 60 days in vitro (DIV), and all recordings were performed after at least 120 DIV and 60 days post-fusion. All data was processed using an analysis platform developed in-house. We used the local coefficient of variation (CV_2) of inter-spike intervals to characterize units as Regular (CV2 < 0.8), Poisson (0.8 < CV_2 < 1.2), or Bursting (CV_2 > 1.2). We found 27 ± 5.70 SEM units per organoid with a total of N_{Tot} = 435 units. From this total, our classification showed that 13.3% were Regular, 67.8% were Poisson, and 18.9% were Bursting. For every unit, we calculated the pairwise phase consistency value to determine spike-phase coupling (SPC) with 5 different LFP bands: Delta (0.5-4 Hz), Theta (4-8 Hz), Alpha (8-12 Hz), Beta (12-30 Hz), and Gamma (30-150 Hz). We found that 76.3% of Poisson units were phase-coupled with Gamma. Regular units showed an even distribution of SPC across LFP bands, though some showed overlap in phase-coupling with neighboring bands. By contrast, 72.9% and 63.5% of Bursting units showed phase-coupling with Delta and Gamma, respectively. For the Poisson units, the stochastic firing patterns indicate heterogeneous afferent connectivity, while their phase-coupling with Gamma suggests their firing is modulated by network activity. The homogeneous spread of SPC for Regular units might indicate a band-specific link with LFP generation. Interestingly, Bursting units were coupled with Delta and Gamma, suggesting an underlying LFP phase-phase coupling, possibly due to slow-timescale mechanisms that affect fast-timescale signaling. Overall, these findings show distinct spike-LFP relationships between different neural populations in human-derived brain assembloids.

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Poster

PSTR123: Oscillations and Synchrony

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Program #/Poster #: PSTR123.17/N8

Topic: B.07. Network Interactions

Title: Individual Oscillation Differences Between Reported Mind-Wandering in Resting State EEG Data

Authors: *E. R. SCHULZ[1], T. KANG[3], E. ZATORSKI[2], R. GRAHAM[4];
[1]Psychology, Texas State Univ., San Marcos, TX; [2]Texas State Univ., Kyle, TX; [3]North Dakota State Univ., Fargo, ND; [4]Psychology, Texas State Univ. San Marcos, San Marcos, TX

Abstract: The interruption of a stream of consciousness when attention shifts from external tasks to internal thoughts- known as Mind Wandering (MW)- is an occurrence marked by its variability across individuals. The present study aims to identify and compare neural patterns associated with these individual differences by examining oscillatory power changes across brain regions in individuals with high and low MW during eyes-open (EO) and eyes-closed (EC) conditions. These conditions provide insight into the activation of specific regions within the default mode network (DMN) during individual MW.To test this, 51 college students completed the Four-Factor Mind Wandering Questionnaire (4FMWQ) and were grouped into high MW (scores ≥ 33) and low MW categories. Students' resting-state EEG data were pooled from two separate studies that included the 4FMWQ. The averages across 64 channels were squared, log-transformed, and clustered by electrode within nine topographic regions for each frequency band and condition. A mixed factorial ANOVA was used to compare factors within clusters and between high and low MW groups. Data analyses are ongoing, and results will be discussed in relation to current MW literature, with additional planned analyses (e.g., theta-beta ratio) examining the strength of DMN engagement during MW periods.

Disclosures: E.R. Schulz: None. **T. Kang:** None. **E. Zatorski:** None. **R. Graham:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.18/O1

Topic: B.07. Network Interactions

Title: Stable spatiotemporal configurations and recurrent phase gradient representations in human electrocorticography

Authors: *M. DEXHEIMER[1], S. COLE[1], H. SHAH[2], D. J. KRUSIENSKI[1];
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Abstract: Cortical oscillatory activity is not spatially stationary, it propagates across the cortex as traveling wavefronts, observed across neuroimaging modalities, species, and behavioral contexts. Despite growing evidence for the role of these phenomena in information transfer and cognition, the temporal evolution of spatiotemporal activity in intracranial recordings remains poorly characterized. Specifically, how long do stable propagating states persist, how abruptly do they transition, and do they recur as recognizable spatiotemporal patterns? Here we address these questions using a data-driven pipeline applied to human electrocorticographic (ECoG) recordings from eight epilepsy patients undergoing clinical evaluations. These patients were each implanted with 8x8 electrode arrays, and the analyzed recordings were conducted during a verbal working memory task. We apply singular value decomposition to instantaneous phase gradient vector fields, projecting the resulting low-dimensional representation into high-dimensional score space. Moment-by-moment Euclidean distances in this space quantify the rate of spatiotemporal reconfiguration, revealing that cortical activity evolves through intermittent periods of stability punctuated by rapid state transitions. Dwell time distributions follow an exponential decay, consistent with dynamics previously reported in EEG and MEG analyses, here demonstrated in intracranial recordings. During stable periods, phase gradient fields exhibit coherent propagating structure consistent with traveling wavefronts. Applying agglomerative hierarchical clustering and UMAP visualization to stable-period gradient representations, we identify a landscape of recurring spatiotemporal configurations that exceeds statistical surrogate tests. This landscape forms a continuum with regions of elevated recurrence, preferred spatiotemporal states revisited throughout the recording. Critically, the relative occupancy of these states shows subtle but consistent modulation across task conditions. This work provides a characterization of spatiotemporal dwell-and-transition dynamics in human ECoG and expands our understanding of how propagating cortical activity is organized in time.

Disclosures: M. Dexheimer: None. **S. Cole:** None. **H. Shah:** None. **D.J. Krusienski:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.19/O2

Topic: B.07. Network Interactions

Title: Spectrolaminar characterization of the primate cortical neuronal microcircuit

Authors: A. ABDALTAWAB[1], A. NILAJAGI[2], H. NEJAT[4], A. BASTOS[5], M. BABAEI[6], ***D. MENDOZA-HALLIDAY**[3];
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Abstract: Cortical rhythms follow a conserved laminar motif across cortical areas: gamma (γ) power is strongest in superficial layers, whereas alpha/beta (αβ) power peaks in deep cortex,

suggesting a canonical laminar architecture for rhythm generation. Yet it remained unclear how many separable rhythms compose this motif, what defines each spectrolaminar component (SLC), and whether these components reveal how the canonical circuitry is organized across layers, and neuronal populations. To address this, we analyzed baseline local field potential (LFP) and spiking activity from 118 laminar macaque recordings across 13 cortical areas. We then developed a model that decomposed the spectrolaminar motif into discrete SLCs superimposed on a shared aperiodic background. Three SLCs captured the motif with high explained variance ($R^2 = 0.90$): superficial delta/theta (δθ) and γ rhythms, and a dominant deep αβ rhythm with greater amplitude and laminar spread. These SLCs preserved their laminar organization across cortical areas while differing in area-specific spectral tuning. They were also organized into superficial and deep compartments: LFP phase synchrony was stronger within than across compartments, even after controlling for channel proximity. Despite this compartmentalization, phase-amplitude coupling linked superficial γ and δθ rhythms with deep αβ activity across compartments. Neuronal synchrony showed a compartmental structure matching the SLCs, peaked among superficial units, and was remarkably higher among narrow-spiking pairs. We then asked how SLCs relate to neuronal activity using spike-field pairwise phase consistency. Superficial γ and δθ rhythms synchronized strongly with superficial neuronal firing, with γ synchrony strongest among narrow-spiking units. In contrast, deep αβ activity synchronized with neurons across the cortical column, consistent with its broader laminar extent. Spike phase preference varied with SLC depth, occurring near the trough of superficial SLCs and near the peak of deep αβ. Finally, spike synchrony to SLCs was correlated with pairwise spike synchrony, with δθ coupling emerging as the strongest contributor. Together, these findings show that the spectrolaminar motif reflects three interacting cortical rhythms with a preserved canonical laminar architecture linking cortical rhythms and neuronal populations through distinct field-field, spike-spike and spike-field coupling patterns.

Disclosures: A. Abdaltawab: None. **A. Nilajagi:** None. **H. Nejat:** None. **A. Bastos:** None. **M. Babaei:** None. **D. Mendoza-Halliday:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.20/O3

Topic: B.07. Network Interactions

Support: PAPIIT-UNAM-DGAPA IN217225

Title: Heterogeneity of Astrocyte network dynamics in the brain

Authors: *M. ZAHAR PÉREZ[1,2], A. RIVERA-VILLASEÑOR[3], R. OLIVARES-MORENO[5], G. ROJAS-PILONI[6], J. J. GUTIÉRREZ-LEDEZMA[4], O. PEREZ[7], M. LÓPEZ-HIDALGO[8]; [1]Univ. Nacional Autónoma de México, Ciudad de México, Mexico; [2]Inst. de Fisiología Celular, Ciudad de México, Mexico; [3]Lab. de Interacciones Neuro-Gliales, Inst. de Neurobiología,

UNAM, Querétaro, Mexico; [4]Inst. de Neurobiología, UNAM, Queretaro, Mexico; [5]Neurobiología del desarrollo y neurofisiología, Lab. A-13, Univ. Nacional Autonoma De Mexico, QUERETARO, Mexico; [6]Univ. Natl. Autonoma Mexico, Queretaro, Mexico; [7]Escuela Nacional de Estudios Superiores Juriquilla, UNAM, Queretaro, Mexico; [8]UNAM, Queretaro, Mexico

Abstract: Astrocytes respond to neuronal activity through intracellular calcium signaling, providing a reliable readout of underlying network dynamics. While calcium dynamics in individual astrocytes have been extensively characterized, the population-level functional organization of astrocytic networks remains poorly understood. Here, we characterize the functional connectivity and topological structure of spontaneous astrocyte activity across three brain regions using calcium imaging and graph theory.Male C57BL/6J mice (3 months old) were injected with AAV5-GFAP-GCaMP6f into the prelimbic cortex (PrL), secondary somatosensory cortex (S2), and hippocampus. Spontaneous calcium imaging was performed in anesthetized animals using a one-photon miniscope. Signals were preprocessed by correcting photobleaching drift via rolling mean baseline subtraction, and activity events were detected by thresholding the corrected signal to generate binary activity series per astrocyte. Functional connectivity was assessed using Jaccard similarity corrected for chance co-activation through surrogate analysis, yielding statistically validated networks without arbitrary threshold selection. Temporal network reconfiguration was quantified using sliding-window correlation analysis. Network topology was characterized by graph-theoretic metrics including degree, centrality, efficiency, clustering coefficient, and modularity, and community structure was identified with the Louvain algorithm. Additionally, the temporal evolution of astrocytic network dynamics was modeled using discrete linear dynamical systems to identify attractor states and characterize state transitions across brain regions.Our analyses reveal differences in calcium activity patterns across PFC, S2, and hippocampus, suggesting region-specific astrocytic network organization. These results provide a basis for characterizing how astrocyte network topology and dynamics vary across brain regions, and whether these differences reflect distinct contributions to local neural computations.

Disclosures: M. Zahar Pérez: None. **A. Rivera-Villaseñor:** None. **R. Olivares-Moreno:** None. **G. Rojas-Piloni:** None. **J.J. Gutiérrez-Ledezma:** None. **O. Perez:** None. **M. López-Hidalgo:** None.

Poster

PSTR123: Oscillations and Synchrony

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.21/O4

Topic: B.07. Network Interactions

Support: NIH Grant T32DK138894
NIA Grant AG078116

Title: Reorganizing Astrocytic Neurovascular Control through Enhanced Insulin Receptor Signaling

Authors: T.-H. LU, R.-L. LIN, S. SIMS, *O. THIBAULT;
Pharmacol. and Nutritional Sci., Univ. of Kentucky, Lexington, KY

Abstract: Brain insulin resistance contributes to neurovascular dysfunction in metabolic and neurodegenerative disorders, including diabetes and Alzheimer's disease. Intranasal insulin (INI) enhances central insulin signaling in rodents and humans without causing systemic hypoglycemia, but the cellular mechanisms linking brain insulin signaling to cerebrovascular regulation remain unclear. Astrocytes are positioned at the neurovascular unit, where they coordinate metabolic communication between neurons and blood vessels, suggesting that astrocytic insulin signaling may regulate coupling. Further, prior evidence from our lab shows INI alters CBF and increases neuronal network synchronicity.

Here, we test the hypothesis that astrocytic insulin receptors also contribute to local neurovascular control and astrocytic networks by overexpressing a constitutively active truncated human insulin receptor β subunit (IRβ) in mouse cortical astrocytes. Two-photon calcium imaging in awake, freely ambulating mice was used to quantify astrocytic activity and vasoreactivity. In parallel, the effects of INI on vascular smooth muscle cell adrenergic signaling (i.e. alpha 1A) were assessed by correlating norepinephrine dynamics measured with nLightG (SMHC promoter), to vessel diameter changes (retro-orbital rhodamine dextran) during periods of rest and ambulation.

Astrocytic IRβ overexpression reduced the fraction of responsive astrocytes during ambulation and increased their intercellular distance. Despite reduced astrocyte network activity, vascular responses were enhanced, including larger baseline vessel diameters, a greater proportion of vessels dilating, and increased dilation amplitudes during ambulation. Consistently, INI strengthened the temporal correlation between nLightG signals and vessel diameter, indicating improved coupling between norepinephrine signaling and vascular responses, potentially mediated by astrocytic insulin pathways.

Together, these findings define clear central actions of insulin on astrocytes and vasoreactivity in the cortex of ambulating mice through enhanced brain insulin signaling. Targeting central insulin pathways may therefore represent a therapeutic strategy to preserve neurovascular function in metabolic and neurodegenerative disease.

Disclosures: T. Lu: None. **R. Lin:** None. **S. Sims:** None. **O. Thibault:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

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Program #/Poster #: PSTR123.22/O5

Topic: B.07. Network Interactions

Support: 1T32DK138894 (SS)
P01 AG078116 (OT)

Title: Single-Cell Assessment of Brain Metabolic and Adrenergic Signaling using 2P Imaging Techniques in the Awake Animal

Authors: *S. L. SIMS[1], R.-L. LIN[2], T.-H. LU[3], O. THIBAULT[4];
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Abstract: The dissociation of neuronal and astrocytic activity from blood flow regulation, known as neurovascular uncoupling, and associated vascular dysfunction have been detected with metabolic syndrome, diabetes, and Alzheimer's disease in preclinical and clinical studies, which may contribute to the risk of cognitive decline. Despite the decades of literature describing the neurovascular unit (NVU), the functional associations between the primary cells involved in vasoreactivity are contentious in healthy subjects and even more ambiguous under disease conditions. Therefore, it is necessary to investigate fundamental mechanisms by which neurovascular dysfunction develops in T2DM, including analyses of the networks between neurons, astrocytes and the vasculature. As a critical neurotransmitter and hormone engaged in blood glucose regulation, sympathetic response, arousal, and vasoconstriction, norepinephrine (NE) emerges as a potential mechanistic component of neurovascular uncoupling in the CNS. Craniotomies were performed on C57BL/J6 mice. Animals were injected with 1 uL nLightG (syn or SMHC promoter) or received no injection. A circular window was installed above the center of the S1 region (AP: -0.5 mm, ML: ± 1.62 mm). 3-4 weeks post-surgery, animals were first acclimated to the 2-photon environment, and then imaged across 10-minute intervals. Animals expressing nLightG AAV received a retro-orbital injection of rhodamine dextran and head-fixed under the objective, while animals that did not receive an intracranial injection were administered a 200 uL rhodamine dextran and 2 mM 2-NBDG mix to assess glucose diffusion kinetics across animals. Measures of nLightG fluorescence intensity changes or 2-NBDG diffusion kinetics were obtained at rest and during ambulation.
An initial cohort of animals injected with nLightG indicated the viability of the sensor for the measurement of NE dynamics in neurons and vascular smooth muscle cells. NE levels are anti-correlated with movement and are sensitive to changes in animal state (i.e. anaesthetized vs. awake). A cohort of animals injected with astrocytic nLightG (gfa104 promoter) report on network characteristics during the onset of metabolic dysregulation. In agreement with clinical findings, the 5xFAD animals administered 2-NBDG showed reduced loss of glucose across time compared to age matched controls.

Disclosures: S.L. Sims: None. **R. Lin:** None. **T. Lu:** None. **O. Thibault:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

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Program #/Poster #: PSTR123.23/O6

Topic: B.07. Network Interactions

Support: 1T32DK138894
P01 AG078116

Title: Loss of Astrocytic Insulin Receptors Alters Astrovascular Coupling in Awake Animals

Authors: *R.-L. LIN[1], S. SIMS[2], T.-H. LU[2], O. THIBAULT[3];
[1]Pharmacol. & Nutritional Sci., [3]Dept. of Pharmacol. and Nutritional Sci., [2]Univ. of Kentucky, Lexington, KY

Abstract: Previous studies from our group have indicated significant reductions in measures of functional connectivity, pairwise correlations, and network synchronicity in the 5xFAD mouse model of amyloidosis. Consistently, manipulations of insulin receptors (IR) using either intranasal insulin, or overexpression of a constitutively active form of the receptor alter neuronal network synchrony, reduce astrocyte communication but also enhance vasoreactivity. In the present study, we tested the hypothesis that reduced astrocytic insulin receptors would alter astrovascular coupling and astrocyte network communications. Young (8-12 weeks old; male and female) homozygous IR double-floxed C57Bl6 mice received the unilateral astrocytic calcium indicator GCaMP8f (AAV5-Gfa104-GCaMP8f) and either Cre recombinase (Gfa104-Cre-6x4T) or luciferase (as control) during a craniotomy over the S1. Four weeks later, astrocytic Ca^{2+} networks were imaged concomitantly with vasoreactivity (visualized by rhodamine dextran) using a two-photon microscope in ambulating animals. Methods for data extraction included continuous wavelet transforms to infer on power across encoding frequencies as well as traditional measures of astrocyte calcium responses (amplitude, decay and rise times). Pairwise cellular connectivity (CCs) were also examined as well as astrovascular communications. With reduced IRs in S1 astrocytes, we detected no significant changes in astrocytic networks (time-based synchronicity, CC, connectivity, and distance between cells) although trends for reductions in functional activity were noted. We did, however see a significant increase in some of the parameters measured including in the astrovascular coupling, in the CCs between astrocyte reactivity and ambulation, as well as in the vasoreactivity with movement. We also report that more pronounced effects were seen in female control animals. Overall, these results suggest that vasoreactivity appears to be significantly impacted by IR on astrocytes in S1 although it is not clear whether the results are dependent on changes in astrocyte communication. The approach appears to mimic previously published finding in the 5xFAD.

Disclosures: R. Lin: None. **S. Sims:** None. **T. Lu:** None. **O. Thibault:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

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Program #/Poster #: PSTR123.24/O7

Topic: B.07. Network Interactions

Support: NIH Grant R01MH124387
NIH Grant R34DA059511

Title: Hyperscanning the frontoparietal network in ferret naturalistic social behavior

Authors: *G. SAHYOUN[1,2,3,4], G. ROSS[2,3,4], M. REAMES[2,3,4], S. RADTKE-SCHULLER[2,3], J. REILING[7], M. ZHANG[7], F. FROHLICH[2,3,4,5,6];
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Abstract: Social interaction is continuous, dynamic, and integral to mental health. During interaction, individuals unconsciously adjust posture, position, and movement relative to one another, forming patterns of dyadic coordination. Hyperscanning, the simultaneous recording of neural activity from two individuals, has shown that human brains synchronize in the theta (4-8Hz) and alpha (8-12 Hz) bands across the frontoparietal network (FPN) during cooperative behavior and joint attention (Czeszumski et al., 2022). However, the real-time neuronal-level dynamics underlying this synchronization remain poorly understood. Invasive, multi-site recordings help bridge this gap by enabling the measurement of LFP and single-unit activity. Domestic ferrets (*Mustela putorius furo*) are an ideal model for investigating the circuit-level mechanisms of interbrain synchrony. Ferrets exhibit rich social-cognitive abilities and during cognitive tasks exhibit FPN theta and alpha oscillations homologous to the human rhythms implicated in interbrain synchrony. Our preliminary findings demonstrate that alpha oscillations in the posterior parietal cortex (PPC) mediate interbrain synchrony during bidirectional social interaction, while theta oscillations in the premotor cortex (PMC) do so during unidirectional interaction. These results identify frequency- and region-specific roles for each rhythm. However, whether these rhythms interact across FPN nodes within the same interaction and the role of single-unit in interbrain synchrony remain unclear. In an ongoing study, we build upon these preliminary findings and wirelessly record LFP and single-unit activity from PMC and PPC simultaneously in pairs of freely behaving ferrets. Behavior is manually coded to identify discrete coordination states. We characterize interbrain synchrony using phase-locking value and Granger causality analyses in the 200-500 ms window preceding each transition to a new coordination state. This enables the first direct comparison of interbrain synchrony across two FPN nodes in the same interaction. These findings will advance our understanding of the circuit and neuronal-level mechanisms underlying social behavior, with direct implications for neuropsychiatric conditions with disrupted social function.

Disclosures: G. Sahyoun: None. **G. Ross:** None. **M. Reames:** None. **S. Radtke-Schuller:** None. **J. Reiling:** None. **M. Zhang:** None. **F. Frohlich:** A. Employment/Salary (full or part-time):; University of Bern, Switzerland. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Electromedical Products International, Qortical Clinical Partners Inc., University of North Carolina at Chapel Hill, Academic Press. F. Consulting Fees (e.g., advisory boards); Electromedical Products International, University of Bern, Switzerland.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.25/O8

Topic: B.07. Network Interactions

Support: This study was funded by Electromedical Products International, Inc. (EPI).

Title: Frontal-Midline Theta Power and DMN Connectivity as Neural Signatures of Cranial Electrotherapy Stimulation Response in Generalized Anxiety Disorder

Authors: *G. ROSS[1], Z. STEWART[2], V. GUIRGUIS[4], S. NAPOLITANO[1], T. SCHWIPPEL[3], L. B. TOWNSEND[5], S. KORSAPATHY[1], C. CARLTON[6], F. FROHLICH[7];
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Abstract: Background: Cranial electrotherapy stimulation (CES; Alpha-Stim) has demonstrated anxiolytic efficacy in adults with Generalized Anxiety Disorder (GAD; Barclay & Barclay, 2014), yet its neurophysiological mechanisms remain poorly understood. **Methods:** We conducted a double-blind, sham-controlled randomized clinical trial of 6-week at-home CES (Alpha-Stim AID ®) in young adults diagnosed with GAD (NCT06124014). Participants were randomized to the Active (n = 65, 60-min daily, 200-500μA) or active Control group (n = 65, 5-min daily, 200μA). High-density resting-state EEG was recorded pre- and post-treatment. Clinical outcomes included the HAM-A (primary outcome), BAI, and GAD-7 (secondary outcome).**Results**: Blinding was successful, and treatment was well tolerated. Both groups improved significantly on HAM-A over time (main effect of time: $p < 0.001$) with no between-group difference (Active: 8.34±5.26, Control: 8.23±5.74). In an exploratory subgroup excluding participants whose HAM-A improved from screen to baseline, potentially from expectation of treatment (Active = 28, Control = 29), we identified significant improvement in self-reported anxiety symptoms in the Active group (BAI: 73% vs 39% response, $p = 0.016$; GAD-7: 80% vs 50%, $p = 0.047$). In the complete EEG subsample (n = 44), we identified a significant reduction in frontal-midline theta power (4-8 Hz) in Active relative to Control group via cluster-based permutation testing (13 channels, cluster mass = −34.14, cluster $p = 0.037$). This reduction correlated with improvement in somatic anxiety symptoms (BAI; 12 channels, mean $\rho = 0.48$, cluster mass = 32.71, $p = 0.03$). Network-level analysis further revealed a significant reduction in DMN alpha-connectivity in the Active group ($t(42) = -2.32$, $p = 0.025$), with an exploratory correlation with BAI somatic anxiety improvement.**Conclusion:** These findings provide the first neurophysiological evidence of a mechanistic basis for CES (Alpha-Stim) anxiolytic action in GAD. We further demonstrate a significant improvement in self-reported anxiety symptoms in participants with stable pre-randomization symptoms. Together with a favorable safety profile, these results support CES as an accessible and mechanistically grounded treatment option for GAD.

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Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.26/P1

Topic: B.07. Network Interactions

Support: Department of Defense Grant-W81XWH-22-2-0012

Title: Alpha reactivity reflects dietary adherence and predicts heterogeneous cognitive response to glutamate challenge

Authors: *N. AZARI JAFARI[1,2], S. L. MURRAY[4], K. F. HOLTON[3];
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[4]Maryland Psychiatric Res. Ctr., Univ. of Maryland Sch. of Med., Catonsville, MD

Abstract: Gulf War Illness (GWI) is characterized by cognitive impairment along with other neurologically related symptoms. Dysregulated alpha power response to eye opening (alpha reactivity) in electroencephalography (EEG), reflects cortical excitation-inhibition balance, and has been shown to predict cognitive function. Following our lab's prior finding that the low-glutamate diet (LGD) improves cognition in GWI, we investigated neurophysiological mechanisms underlying both dietary improvement, and monosodium glutamate (MSG) challenge response, in a more diverse group of veterans. Veterans with Gulf War Illness (N=100) completed baseline resting-state EEG (5-min eyes-closed/eyes-open), excitotoxin food frequency questionnaire, and CNS Vital Signs (CNSVS) cognitive testing. After online diet training,

participants followed the low-glutamate diet (LGD) for one month before a post-diet visit; then a subset (n=52) completed a double-blind MSG vs. placebo crossover challenge (3 days each, 1-week washout). EEG was processed with Electroencephalography Automated Processing platform (BEAPP) in MATLAB and analyzed in R; FDR correction was applied ($p<0.05$). Alpha reactivity was calculated as relative alpha power eyes-closed minus eyes-open. We examined whether post-diet alpha reactivity predicted cognitive improvement and differed across MSG challenge response groups defined by neurocognitive index (NCI) change (MSG-placebo; ±1 NCI threshold): C1: Improved (n=21), C2: No Response (n=6), C3: Worsened (n=22). The diet significantly improved cognition ($P < 0.0001$). Better dietary adherence correlated with higher alpha reactivity ($P < 0.05$). Post-diet global alpha reactivity was associated with cognitive response to MSG challenge ($r=0.345$, $p < 0.05$), with greater reactivity associated with better tolerance to glutamate exposure. Alpha reactivity differed by cognitive response category to MSG at baseline, post-diet, and MSG week (C1 > C2, C3; KW $p < 0.05$ all timepoints). MSG challenge differentially modulated alpha reactivity by category across frontal, central, and global regions ($Ps < 0.05$): C1 increased, C2 decreased, and C3 near-zero, with C1 differing from both C2 and C3 (post-hoc $p < 0.05$). Mediation analysis revealed alpha reactivity as the primary pathway linking dietary adherence to cognitive glutamate sensitivity (indirect effect $p=0.008$-0.010), with no significant direct effect. Alpha reactivity differentiated response categories and predicted cognitive outcomes during acute glutamate challenge, establishing it as a neurophysiological marker of glutamate vulnerability in GWI.

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Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

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Program #/Poster #: PSTR123.27/P2

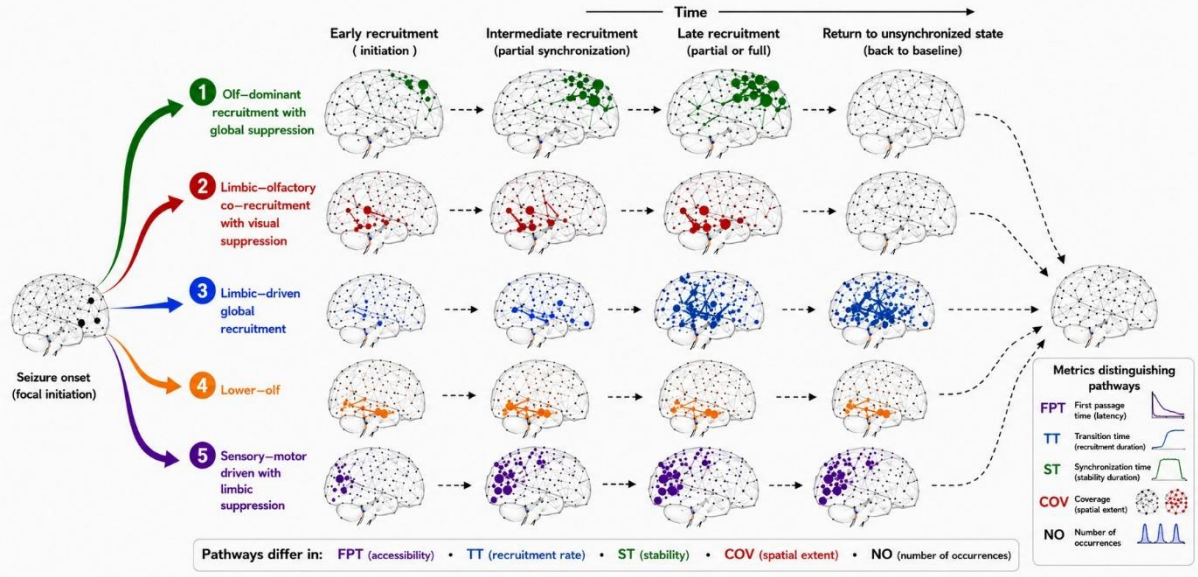
Topic: B.07. Network Interactions

Support: Science and Engineering Research Board (SERB) Grant SRG/2023/000595

Title: Multiple coexisting pathways to synchronization shape seizure dynamics in a mesoscale mouse brain model

Authors: N. KUMAR, ***S. R. GANDHI**;
Electrical and Electronics Engin., Birla Inst. of Technol. and Science, Pilani, Pilani, India

Abstract:



The computational study of epileptic seizure dynamics has primarily focused on the identification of seizure onset zones and propagation pathways. Here, we present a network dynamical model implemented on the empirically measured mesoscale mouse brain network that reveals previously unresolved organizational principles underlying seizure propagation. Rather than the conventional assumption of a single dominant pathway to synchronization, the model reveals multiple competing pathways to synchronization with distinct dynamical properties including transition propensity, recruitment speed, spatial coverage, synchronization stability and transition kinetics. Consequently, node ablation does not uniformly suppress synchronization across pathways, but instead selectively alters pathway occupancy, producing non-trivial alterations to seizure dynamics with potential implications for resection and network-targeted intervention strategies. Biologically, olfactory and limbic systems emerge as key mesoscale regulators of synchronization dynamics, with olfactory recruitment preferentially constraining global synchronization while limbic-driven pathways preferentially support seizure generalization. More broadly, these findings extend transient explosive synchronization theory by demonstrating that synchronization in biologically constrained networks may emerge through competing mesoscale recruitment programs rather than a single transition process. Together, these findings introduce a new conceptual framework for seizure propagation, suggesting that pathological synchronization emerges not through a single dominant route, but through competing mesoscale dynamical pathways whose accessibility depends on both network architecture and ongoing network state.

Disclosures: N. Kumar: None. **S.R. Gandhi:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.28/P3

Topic: B.07. Network Interactions

Support: National Science Centre (Poland) OPUS 2021/41/B/NZ4/03882

Title: Dissociable Network Mechanisms Underlie Ketamine-Enhanced High-Frequency Oscillations and Cortical Gamma in Freely Moving Rats

Authors: *M. J. HUNT[1], W. PODOLECKA[2];
[1]Nencki Inst., Warsaw, Poland; [2]Nencki Inst., Warszawa, Poland

Abstract: Ketamine induces robust high-frequency oscillations (HFOs; 130-180 Hz) in freely moving rats, observed across corticostriatal regions and particularly prominent in the olfactory bulb. To determine whether these oscillations depend on peripheral olfactory input, we disrupted the olfactory epithelium using intranasal gadolinium infusion; control animals received saline. Local field potentials were recorded from the olfactory bulb, ventral striatum, and prefrontal cortex. Ketamine (25 mg/kg, i.p.) was administered before and at multiple time points up to two weeks after intranasal treatment. Gadolinium infusion reduced respiration-coupled activity in the olfactory bulb, confirming disruption of peripheral olfactory signaling. Ketamine-enhanced HFO power was significantly attenuated in the olfactory bulb, ventral striatum, and PFC, with effects persisting for at least 7 days before gradually recovering. In contrast, ketamine-enhanced gamma oscillations in the cortex were unaffected. Likewise, ketamine-induced hyperlocomotion was unchanged despite marked reductions in HFO power. These findings reveal a dissociation between ketamine-enhanced HFO and gamma activity. Rather than reflecting a single coherent ketamine-induced brain state, HFOs and gamma oscillations appear to index distinct functional network dynamics.

Disclosures: M.J. Hunt: None. **W. Podolecka:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.29/P4

Topic: B.07. Network Interactions

Support: NIH Grant R01-GM056398
Center for Consciousness Science, Department of Anesthesiology, University of Michigan Medical School

Title: State- and frequency-dependent modulation of electrocortical traveling waves during desflurane anesthesia

Authors: *D. LI[1], A. G. HUDETZ[2];
[1]Univ. of Michigan, Ann Arbor, MI; [2]Dept. of Anesthesiol., Univ. of Michigan, Ann Arbor, Ann Arbor, MI

Abstract: Introduction: Emerging evidence suggests that cortical activity is often organized in traveling waves that may in turn coordinate underlying neural activity across space and time. Anesthesia suppresses overall neural activity but its effect on traveling waves is underexplored. We recently showed that cortical activity exhibits spontaneous transitions among discrete states despite constant anesthetic concentration indicating that brain state does not vary monotonically with anesthetic level. One of the states with reduced delta power and elevated complexity occurred unexpectedly in deep anesthesia, hence called paradoxical state, suggesting a structured neural organization shifting toward awake condition. Here, we aimed to determine whether cortical traveling wave patterns were different in discrete activity states at multiple steady-state anesthetic conditions. **Methods**: Electrocorticogram was recorded from the right hemisphere of rats equipped with chronically implanted 32-site flexible polymer arrays (4×8 grid) at four desflurane concentrations (6-0%) for 1 h each. Cortical states were identified using PCA of power spectrograms followed by density-based clustering across concentrations. Within each state, traveling wave episodes were detected as temporally stable and spatially coherent phase-gradient patterns in the delta, theta, and gamma bands. Wave occurrence rate and pattern richness (entropy of singular values from the episode similarity matrix) were quantified. Waves were categorized as planar, rotating, sinks and sources. Planar waves were classified as feedforward (posterior-to-anterior) or feedback (anterior-to-posterior). **Results**: Seven cortical states were identified. S1-S5 broadly tracked anesthetic concentration but were not tied to a specific level. S6 corresponded to burst suppression, and S7 indicated the paradoxical state. In S1, theta waves were mainly feedback-directed, whereas gamma were feedforward-directed. In states associated with deep anesthesia (4-6% desflurane), delta-band waves occurred more often while propagation patterns became more stereotyped and planar. Theta band feedback decreased, gamma feedforward persisted, and both showed reduced directional consistency. S7 showed partial reversals yet retained low delta complexity and disrupted theta feedback, indicating a dynamic regime distinct from normal awake state. **Conclusion**: Anesthetic modulation of traveling waves is state- and frequency-dependent, characterized by constrained delta-wave patterns and disrupted directional organization in theta and gamma bands during deep anesthesia, including the paradoxical state.

Disclosures: D. Li: None. **A.G. Hudetz:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.30/P5

Topic: B.07. Network Interactions

Support: CIHR
FRAXA
Fragile X Canada
ACHRI
Owerko Centre
HBI

Title: Tat-conjugated FMRP fragment changes transcriptome in Fragile X mice

Authors: *X. ZHAN, R. W. TURNER;
Univ. of Calgary, Calgary, AB, Canada

Abstract: Introduction: Fragile X syndrome (FXS) is caused by a loss of a critical protein-Fragile X Messenger Ribonucleoprotein (FMRP) due to a trinucleotide repeat expansion in the *Fmr1* gene. Currently, there is no cure for FXS. Previously, we reported that a tat-conjugated FMRP N-terminus peptide (N-tat) could rescue cell functions and behaviors in a Fragile X mouse model. **Objectives:** Understand the effect of N-tat on brain activity in the Fragile X mouse model and the molecular basis for its action. **Methods:** Resting EEG activity was recorded in the frontal cortex of male wildtype (WT) or Fragile X mice with surface electrodes and treatments delivered by single tail vein injection. Frontal cortical tissue was harvested and analyzed with RNA sequencing. **Results:** EEG recordings showed that Fragile X mice had decreased theta power (4 - 8 Hz) and increased gamma power (30 - 100 Hz) compared to WT mice. N-tat rescued gamma power mostly by decreasing high gamma (65 - 100 Hz) power. Rescue effects of N-tat were detected as early as 2 hr post-injection and lasted for at least 7 days with single dose injection. Transcriptomic analysis of Fragile X frontal cortical tissue found 131 up-regulated and 106 down-regulated genes, and N-tat ameliorated these trends for 69 genes. IPA pathway analysis further identified down-regulation of the glutaminergic receptor signaling pathway Fragile X that was reversed by N-tat. **Conclusion:** N-tat FMRP fragments exert effects on brain activity by rescuing the power of specific EEG frequency bands, and the extra longevity of this effect could be associated with transcriptional regulation by N-tat. **Acknowledgments**: Funded by grants/trainee salary awards from CIHR, ACHRI, Owerko Ctr, HBI/DCNS, FRAXA, and Fragile X Canada.

Disclosures: X. Zhan: None. **R.W. Turner:** None.

Poster

PSTR123: Oscillations and Synchrony

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR123.31/P6

Topic: B.08. Epilepsy

Support: Sophomore Research Fellowship

Title: Increased Functional Connectivity During Focal Impaired Awareness Seizures Suggests Altered Large-Scale Network Dynamics

Authors: *D. SANDHU[1], M. I. BANKS[2], U. GORSKA[3], M. BOLY[4];
[2]Anesthesiol., [3]Neurol., [1]Univ. of Wisconsin-Madison, Madison, WI; [4]Neurol. and Psychiatry, Univ. of Wisconsin, Madison, WI

Abstract: Impaired awareness during focal seizures is poorly understood but may arise from altered communication across large-scale brain networks. We investigated whether functional connectivity differs between focal aware seizures (FAS) and focal impaired awareness seizures (FIAS) using intracranial electroencephalography (iEEG) recordings from patients with medically refractory epilepsy undergoing clinical monitoring. Seizures from seven patients with both seizure types were analyzed, including 18 FAS and 24 FIAS. Electrodes were grouped into frontal, parietal, and limbic regions, and functional connectivity was quantified using imaginary coherence (iCOH), a measure of time-lagged neural synchronization. Connectivity was calculated within frontal networks (fronto-frontal and fronto-parietal) and between frontal and limbic regions during the ictal period. We hypothesized that FIAS would exhibit reduced connectivity relative to FAS, reflecting impaired large-scale communication associated with reduced awareness. Contrary to this hypothesis, iCOH values were consistently higher during FIAS across all network categories. Increased connectivity was observed in fronto-frontal, fronto-parietal, and fronto-limbic networks and was evident in both seizure-level and patient-averaged analyses, indicating that the effect was consistent across individuals rather than driven by a small subset of seizures. These findings suggest that impaired awareness during focal seizures may be associated with increased synchronization across cortical and limbic networks rather than a loss of interregional communication. Excessive synchronization may reflect a highly integrated network state that reduces the differentiation necessary for conscious processing. Future work will compare seizure-related network dynamics with sleep and anesthesia to further examine relationships between large-scale connectivity and consciousness.

Disclosures: D. Sandhu: None. **M.I. Banks:** None. **U. Gorska:** None. **M. Boly:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.01/Q1

Topic: B.09. Glial Mechanisms

Support: NIH

Title: Oligodendrocyte Progenitor Cell differentiation in the adult CNS is controlled by Notch

Authors: *J. ZHANG[1], Y. MIRONOVA[1], D. E. BERGLES[1,2];
[1]The Solomon H. Snyder Dept. of Neurosci., [2]Kavli Neurosci. Discovery Inst., Johns Hopkins Univ., Baltimore, MD

Abstract: Oligodendrocyte precursor cells (OPCs) emerge from several germinal zones during late prenatal and early postnatal life to populate the CNS, providing a pool of progenitors to generate oligodendrocytes and myelin. Unlike most CNS progenitors, OPCs are maintained throughout life, with each cell occupying a non-overlapping territory to tile the brain, allowing continued production of oligodendrocytes in gray and white matter. Our recent studies indicate that OPCs attempt to differentiate throughout the adult CNS, independent of myelin demand. However, the molecular mechanisms that maintain this highly ordered organization and regulate their lineage progression in the adult CNS have not been determined. Notch signaling is an evolutionarily conserved pathway that orchestrates the delicate balance of cell fates in developing CNS through lateral inhibition. Lateral inhibition is a process in which one cell inhibits its neighbor cells from adopting identical fates, which is a key regulator of neural progenitor cell homeostasis. Analysis of single cell RNA sequencing data obtained from OPCs isolated from the mouse cerebral cortex revealed that components of the canonical Notch pathway, such as the Notch receptor and downstream effectors such as Hes5, Ascl1, and Rbpj (recombination signal binding protein for immunoglobulin kappa J region) are still expressed by OPCs in the adult brain. Rbpj is a central hub of the Notch pathway, as it serves as a DNA binding element of the transcriptional activation complex formed with the Notch intracellular domain (NICD) that switches on expression of Notch targeted genes. To explore the role of Notch signaling in maintaining the adult OPC progenitor pool and the timing of lineage progression, we conditionally deleted Rbpj from OPCs in young adult mice. OPCs in these Rbpj conditional knockout (cKO) mice exhibited dramatically enhanced lineage progression, indicated by an increase in the density of oligodendroglia immunoreactive for Bcas1, a gene that is upregulated during differentiation. OPC proliferation was also markedly enhanced in Rbpj cKO mice, as expected if the remaining OPCs mounted a homeostatic response to replace cells lost through differentiation. These results suggest that Notch signaling between OPCs plays a crucial role in controlling the rate of OPC differentiation in the adult brain. A greater understanding of Notch pathway regulation within OPCs may reveal new directions for potential therapies to enhance the production of myelin following injury or disease.

Disclosures: J. Zhang: None. **Y. Mironova:** None. **D.E. Bergles:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.02/Q2

Topic: B.09. Glial Mechanisms

Support: Japan Agency for Medical Research and Development JP24gk0210041
Sumitomo Foundation 200490
Ministry of Education, Culture, Sports, Science and Technology, 20K07756, 20KK0188, 23721401, 24K10486
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Inamori Foundation

Title: Oligodendroglial differentiation with myelin membrane formation is promoted on laminin-411 and its derived peptide

Authors: ***B. SASAKI**[1], M. OOISHI[2], T. AOKI[1], M. YASHIMA[2], N. YAMADA[1], M. YAMADA[2], K. SEKIGUCHI[3], K. HAMADA[4], Y. YAMADA[4], Y. KIKKAWA[4], N. SUZUKI[1,2]; [1]Inst. of Sci. Tokyo, Tokyo, Japan; [2]Tokyo Med. and Dent. Univ., Tokyo, Japan; [3]Osaka Univ., Osaka, Japan; [4]Tokyo Univ. of Pharm. and Life Sci., Tokyo, Japan

Abstract: Oligodendrocytes (OLs) generate myelin sheaths that are essential for the rapid transmission of action potentials in the CNS and play key roles in maintaining motor and cognitive functions. OL development and maturation are regulated by multiple factors, including extracellular matrix (ECM) proteins. However, roles of ECM proteins in OL differentiation and myelination are not yet fully understood. In this study, we examined the expression and function of laminins (LMs), basement membrane ECM proteins with cell adhesion activity, during OL differentiation and myelin formation. An expression analysis of LM α chains (α1-5) in the white matter from 2-week-old mouse brains, a period of active myelination, demonstrated that LM α1, α2, and α4 chains were expressed in the vascular basement membrane. In addition, a certain percentage of OL populations adhered to the LMs. To investigate the function of these LMs, we performed in vitro analyses using recombinant LM isoforms containing α1, α2, or α4 chains (LM111, LM211, or LM411, respectively). While no substantial differences were observed in OL differentiation from OL precursor cells (OPCs) among the isoforms, LM411 significantly enhanced OL survival and promoted sheet-like myelin membrane formation compared with the other LM isoforms. We next examined the active region responsible for these effects using recombinant proteins of E8 and E3 fragments, which are binding regions of integrins and α-dystroglycan/heparan sulfate proteoglycans, respectively, from the LM isoforms. As a result, the E8 fragment of LM411 exhibited the promoting activity of the myelin membrane formation, whereas none of E3 fragments showed significant effects. Moreover, we screened cell-adhesive peptides derived from the LM411 E8 domain and identified A4G47 as a peptide capable of promoting the myelin membrane formation. Finally, we investigated the physiological relevance of LM411 with OL myelination. When we examined the expression of monocarboxylate transporter 1 (MCT1), which transports pyruvate and lactate from OL myelin to axons, MCT1 expression was upregulated in OLs on LM411. This result suggested that vascular LM411 may contribute to the maintenance of axonal homeostasis through the metabolic support by OLs. These our findings provide new insights into ECM-mediated regulation of OL biology and may facilitate to the development of novel OL culture methods and/or new therapeutic strategies for demyelinating diseases.

Disclosures: B. Sasaki: None. **M. Ooishi:** None. **T. Aoki:** None. **M. Yashima:** None. **N. Yamada:** None. **M. Yamada:** None. **K. Sekiguchi:** None. **K. Hamada:** None. **Y. Yamada:** None. **Y. Kikkawa:** None. **N. Suzuki:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.03/Q3

Topic: B.09. Glial Mechanisms

Support: NIH RF1AG086313

Title: Clasp2-Dependent Cytoskeletal Control of Oligodendrocyte Myelination and Hippocampal Circuit Function

Authors: *M. SHA[1], L. NGUYEN[2], U. BEFFERT[2], A. HO[2];
[2]Biol., [1]Boston Univ., Boston, MA

Abstract: Myelination of axons by oligodendrocytes is essential for rapid electrical conduction and neural circuit stability, and its disruption contributes to numerous disorders, including multiple sclerosis, leukodystrophies, and neurodegenerative diseases. Myelination requires morphological changes driven by cytoskeletal dynamics, yet the molecular mechanisms linking cytoskeletal regulation to oligodendrocyte differentiation and function remain poorly understood. Cytoplasmic linker-associated protein 2 (CLASP2), a microtubule plus-end tracking protein, regulates microtubule-actin interactions and has known roles in neuronal development. Recent single-cell RNA-sequencing (scRNA-seq) datasets reveal high CLASP2 expression in oligodendrocyte precursors and mature oligodendrocytes, suggesting an unexplored function in myelination.We hypothesize that CLASP2 stabilizes microtubules to support oligodendrocyte process extension and myelination, and its loss disrupts oligodendrocyte function and impairs synaptic and cognitive function. Our results in mice lacking Clasp2 in oligodendrocytes showed reduced process complexity, decreased myelin basic protein expression, and disrupted myelination in multiple brain regions including the stratum lacunosum moleculare (SLM) of the hippocampus. Notably, the SLM receives direct input from the entorhinal cortex, a circuit essential for learning and memory. In addition, we performed single-nucleus RNA sequencing (snRNA-seq) to identify transcriptional programs linking Clasp2-mediated cytoskeletal regulation to myelination. Future work will assess cognitive performance using contextual fear conditioning and measuring axonal conduction velocity and synaptic transmission through ex-vivo slice recordings. Together, these findings identify Clasp2 as a potential regulator of oligodendrocyte maturation and axonal ensheathment, providing insight into cytoskeletal control of myelin formation.

Disclosures: M. Sha: None. **L. Nguyen:** None. **U. Beffert:** None. **A. Ho:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.04/Q4

Topic: B.09. Glial Mechanisms

Title: Molecular composition of small- and large-caliber myelinated axons in the mammalian brain

Authors: *H. LEFAIVRE, T. WALTON;
Van Andel Inst., Grand Rapids, MI

Abstract: Myelinated axon caliber is a major determinant of conduction velocity and may contribute to the selective vulnerability of neuronal populations in aging and disease. Previous studies profile the unique protein, RNA and lipid composition of myelin- and axon-enriched fractions from across the brain, but cannot distinguish between small- and large-caliber myelinated axons, especially from the same anatomical region. We developed a novel approach to separate myelinated axon subclasses using bovine samples, and performed an in-depth study on the arbor vitae of the anterior vermis. Intact myelinated axons and myelin debris from the homogenate were floated through a step-wise gradient of Nycodenz that is adjusted for osmolarity using artificial cerebrospinal fluid. The three fractions containing myelinated axons displayed distinct morphologies and stable densities over multiple rounds of purification. Mass spectrometry revealed that myelinated axon fractions are enriched in classic myelin markers, such as MBP, CNP, and PLP1, relative to the starting homogenate. Comparison between fractions revealed that the large-caliber, low-density myelinated axons express high levels of PMP2, while OMG was enriched in small-caliber, high-density myelinated axons. Immunofluorescence confirmed the separation of PMP2 and OMG on different myelinated axon subpopulations within the cerebellum. RNA sequencing revealed that the myelinated axon fractions were enriched in mitochondrial and ribosomal transcripts relative to starting homogenate. A core set of genes, including *trak2*, *samd4a*, and *dor*, were upregulated across all three myelinated axon fractions. We are currently testing whether these markers of myelinated axon subclasses are conserved in human, and will adapt these methods to additional sample types.

Disclosures: H. LeFaivre: None. **T. Walton:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.06/Q6

Topic: B.09. Glial Mechanisms

Support: NSERC Discovery Grant (400555)

Title: Investigating the role of adaptor protein ShcD in oligodendrocyte development and myelination

Authors: *A. NIELISSEN, C. CLAUSEN, B. ALURAL, N. JONES;
Mol. and Cell. Biol., Univ. of Guelph, Guelph, ON, Canada

Abstract: Oligodendrocytes are the myelinating cells of the central nervous system, forming the myelin sheath required for rapid action potential propagation. Mature myelinating oligodendrocytes (OLs) arise from oligodendrocyte progenitor cells (OPCs) through tightly regulated mechanisms, including growth factor receptor tyrosine kinase (RTK) signalling pathways. The adaptor protein ShcD is involved in numerous RTK pathways with established roles in oligodendrocyte development and function, notably the tropomyosin receptor kinase B (TrkB) and epidermal growth factor receptor (EGFR) signalling cascades. ShcD is also uniquely enriched within the OL lineage, with expression highest in OPCs and progressively decreasing across differentiation. Although RTK signalling in the OL lineage has been well studied, the role of ShcD therein has yet to be fully elucidated. Given the high, specific expression of ShcD within the OL lineage, we hypothesize that ShcD is involved in regulating oligodendrocyte development and myelination through its activity in these pathways. To address this hypothesis, we generated primary OPC cultures capable of differentiation to mature OLs from ShcD wild-type (WT) and knockout (KO) C57BL/6NJ mice. Using scratch wound migration assays, we found the loss of ShcD significantly reduces OPC migration capacity compared to their WT counterparts. Additionally, Sholl analysis revealed a significant reduction in the morphological complexity of ShcD KO OLs during differentiation. Consistent with these findings, analysis of adult mouse brain tissue demonstrated that ShcD influences OL lineage marker expression in a region-specific manner. Ongoing work investigates the expression of OL lineage markers in young mice during a period of rapid developmental myelination. Together, these findings identify ShcD as a potential regulator of oligodendrocyte lineage and myelination, prompting further investigation into its mechanisms.

Disclosures: A. Nielissen: None. **C. Clausen:** None. **B. Alural:** None. **N. Jones:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.07/R1

Topic: B.09. Glial Mechanisms

Support: FBRI Seale Innovation Fund

Title: Human Milk-derived Exosomes Affect Murine Oligodendrocyte Precursor Cell Function In Vitro

Authors: M. SANCTUARY[1], M. NEJADIAN[1], R. CARPIO[1], P. D. MORTON[2], *B. HOWELL[3,4];
[1]Fralin Biomed. Res. Inst. at VTC, Virginia Tech., Roanoke, VA; [2]Biomed. Sci. and Pathobiology, Virginia Tech., Blacksburg, VA; [3]Virginia Tech., Roanoke, VA; [4]Dept. of Human Develop. and Family Sci., Virginia Tech., Blacksburg, VA

Abstract: Objectives:Substantial brain development occurs during the early postnatal period, particularly with regard to white matter (WM). Trajectories of this development differ significantly between human milk-fed and formula-fed infants, and is determined in part by activity and maturation of oligodendrocytes (OLs). Human milk exosomes (hmEXs) have been shown to survive digestion, circulate systemically, cross the blood brain barrier, and accumulate in the brain while carrying information-rich cargo. In this study, we sought to investigate the role of hmEXs on oligodendrocyte precursor cell (OPC) development in vitro, to provide a putative cellular mechanism for differences in WM development due to milk feeding.
Methods:OPCs were isolated from p6-8 mouse pups using the E3 method and cultured in vitro prior to exposure to hmEXs. Exosomes were isolated from previously frozen mature human milk samples from donors of term infants. OPCs were assessed for cellular uptake of labeled hmEXs, proliferation, and differentiation upon exposure to varying doses of hmEXs. Proliferation was assessed via immunofluorescence staining of EdU using confocal microscopy and flow cytometry. Differentiation was assessed via immunofluorescence staining for markers of OPCs (PDGFRα), immature OLs (O4), and mature OLs (CC1) at multiple time points using confocal microscopy.
Results:Murine OPCs internalized hmEXs after 6 hours of exposure with accumulation after 24 hours. Exposure to hmEXs affected the cell cycle, as indicated by a lower percentage of EdU+ cells compared to untreated controls. Exposure to hmEXs promoted progression of OPCs to mature OLs, as indicated by increased expression of CC1 compared to untreated controls at days 4 and 8 of differentiation. Interestingly, exposure to hmEXs also dramatically affected cellular adherence. All of these effects appear to be dose-dependent.
Conclusions:Human milk-derived exosomes affect the cellular function of OPCs in vitro and may contribute to differences in WM development observed between human milk-fed and formula-fed infants. We hypothesize that the effects are due to acceleration of lineage progression of OPCs into mature OLs. Further studies are required to elucidate a mechanistic understanding of the effects of hmEXs on OPC activity as well as translatability to human infants.

Disclosures: M. Sanctuary: None. **M. Nejadian:** None. **R. Carpio:** None. **P.D. Morton:** None. **B. Howell:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.08/R2

Topic: B.09. Glial Mechanisms

Title: Human iPSC-Derived Oligodendrocyte Progenitor Cells as a Translational New Approach Methodology for In Vitro Myelination

Authors: *C. FLIGOR, C. HIELSBERG, G. S. SAHIN, K.-D. CHOI;
BrainXell, Madison, WI

Abstract: In the central nervous system (CNS), oligodendrocytes produce myelin sheaths that insulate axons and enable efficient neural signaling. Loss of myelin or oligodendrocyte dysfunction contributes to a broad spectrum of neurological disorders, including leukodystrophies, neurodegenerative diseases, and traumatic injuries. Although oligodendrocyte progenitor cells (OPCs) persist in the adult CNS and can initiate remyelination following injury, repair remains incomplete in chronic demyelinating conditions, highlighting the need for improved therapeutic strategies. To date, no approved treatment directly promotes myelin regeneration, a gap driven in part by the lack of physiologically relevant human in vitro models. Conventional two-dimensional (2D) cultures rarely form compact myelin sheaths, and functional validation often relies on animal transplantation models that do not fully recapitulate human disease biology. To address these limitations, we developed a human induced pluripotent stem cell (hiPSC)-derived OPC platform for modeling oligodendrocyte maturation and myelination in both 2D and three-dimensional (3D) multicellular culture formats. Using an optimized differentiation protocol, we generated highly pure OPC populations, with greater than 95% $O4^+$ cells by flow cytometry. Within one week of maturation, these OPCs robustly upregulated oligodendrocyte-associated genes, including MBP, PLP1, MAG, MOG, and MYRF. In 2D co-culture with astrocytes and neurons, OPCs differentiated into MBP^+ oligodendrocytes that associated with and wrapped $TUJ1^+$ neurites, enabling compound screening using ELISA-based quantification of MBP expression. In 3D myelinoid tri-cultures, transmission electron microscopy revealed compact multilamellar myelin sheaths after eight weeks of maturation, consistent with mature CNS myelin ultrastructure and providing direct evidence of functional myelination in vitro. Together, these findings demonstrate that multicellular context and 3D organization are critical drivers of human oligodendrocyte maturation and myelin formation. This platform provides a human-relevant New Approach Methodology for studying myelination without reliance on in vivo transplantation and offers a scalable, translational foundation for modeling demyelinating disease biology, evaluating promyelinating compounds, and accelerating the discovery of remyelination therapeutics.

Disclosures: C. Fligor: None. **C. Hielsberg:** None. **G.S. Sahin:** None. **K. Choi:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.09/R3

Topic: B.09. Glial Mechanisms

Support: NIH Grant AG079320
NIH Grant AG083942

Title: The Essential Role of Very Long Chain Ceramide Synthase Cers2 in Myelin Function and Neuronal Health

Authors: E. U. OGAUGWU[1], *J. LI[1,2];
[1]Texas A&M Univ., College Station, TX; [2]Texas A&M Inst. for Neurosci., College Station, TX

Abstract: Myelin abnormalities are central to the pathophysiology of demyelinating diseases and leukodystrophies and are increasingly implicated in Alzheimer's disease. Although lipids comprise ~70% of myelin, their specific roles in regulating myelin formation, stability, and axon-glia interactions remain incompletely understood. Ceramide synthase 2 (*Cers2*), highly expressed in oligodendrocytes, generates very long-chain (C22-C24) ceramides that are required for the synthesis of very long-chain sphingolipids, including sphingomyelin, galactosylceramide, and sulfatide in the brain. While global *Cers2* loss has been linked to myelin instability, the cell type-specific mechanisms and its impact on neuronal integrity remain poorly defined. Here, we generated inducible oligodendrocyte lineage-specific *Cers2* conditional knockout mice (*Cers2* cKO-OL; PDGFRα-Cre^{ERT}) and employed immunohistochemistry, transmission electron microscopy, and sphingolipid-targeted lipidomics to assess myelin and axonal integrity throughout development and early adulthood. Early postnatal ablation of oligodendroglial *Cers2* had limited effects on myelination at postnatal day (P) 9 but progressively impaired myelin formation at P14 and P30 compared with wild-type littermate controls. By 4 months of age, *Cers2* cKO-OL mice exhibited severe myelin loss and marked neurodegeneration, accompanied by robust gliosis. Ultrastructural analysis revealed extensive demyelination, myelin decompaction, axonal degeneration, and microglial activation and accumulation of myelin debris. In addition, *Cers2* cKO-OL mice developed prominent axonopathy and paranodal disorganization, indicative of disrupted myelin-axon interactions and ongoing axonal injury. Lipidomic profiling demonstrated a profound loss of C24 ceramides and sphingomyelin in *Cers2* cKO-OL brains, suggesting that disruption of very long-chain sphingolipid homeostasis contributes to the observed myelin and axonal pathology. Collectively, these findings establish oligodendrocyte *Cers2* as a critical regulator of myelin formation, long-term myelin stability, and myelin-axon organization, and highlights its essential role in maintaining neuronal health.

Disclosures: E.U. Ogaugwu: None. **J. Li:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.10/R4

Topic: B.09. Glial Mechanisms

Support: NIH R01NS122800
NIH R01NS140248

Title: In Vivo Interrogation of Gap Junctions Across the Oligodendrocyte Lineage

Authors: *M. E. CIOLKOWSKI, R. A. HILL;
Dartmouth Col., Hanover, NH

Abstract: Gap junctions are a ubiquitous form of cellular communication found throughout the body. In the brain, gap junctions link the glial syncytium, an expansive network of glial cells made up of astrocytes and oligodendrocytes. Astrocyte to oligodendrocyte (A/O) gap junctions allow for the distribution of ions, metabolites, and signaling molecules amongst coupled cells. A/O gap junctions are critically important for proper myelination, neuronal function, and central nervous system health. Despite this, the precise timing of when oligodendrocyte lineage cells first couple to the glial syncytium is not clear. Here we use new in vivo and fixed tissue optical imaging tools to determine when A/O gap junctions form across the oligodendrocyte lineage in the mouse cortex. We find that functional and structural markers of A/O gap junction coupling are absent in oligodendrocyte precursor cells and become detectable in oligodendrocyte lineage cells during a distinct stage of oligodendrocyte maturation. Understanding when oligodendrocyte lineage cells integrate into the glial syncytium provides insights into whether establishing A/O gap junction coupling is critical for successful oligodendrocyte generation and/or myelin sheath maintenance throughout life.

Disclosures: M.E. Ciolkowski: None. **R.A. Hill:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.11/R5

Topic: B.09. Glial Mechanisms

Support: University of Maryland School of Medicine
NIH Grant 1F31NS134126-01A1
NIH Grant R37MH080046

Title: A Cellular Basis for Calcitonin Gene-Related Peptide Signaling to Oligodendrocyte Precursor Cells

Authors: *R. AITKEN[1], Y. JI[2], T. A. BLANPIED[3], A. KELLER[2], R. LORSUNG[2]; [1]Univ. of Maryland Baltimore, Baltimore, MD; [2]Dept. of Neurobio., [3]Dept. of Pharmacol. and Physiol., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Oligodendrocyte precursor cells (OPCs) are highly dynamic glial cells that communicate bidirectionally with neurons. Neuronal activity regulates diverse OPC functions, including proliferation, differentiation, immunomodulation, synapse engulfment, and axonal remodeling. Dysregulated OPC function has been implicated in chronic pain and stress conditions, where neuronal activity-dependent neurotransmitter and neuropeptide release likely shapes OPC responses. One neuropeptide strongly implicated in chronic pain and stress is calcitonin gene-related peptide (CGRP). Here, we tested the hypothesis that OPCs receive direct inputs from CGRP-containing neurons in the adult brain. Using RNAscope, immunofluorescence, Stimulated Emission Depletion (STED) microscopy and analysis of single-

cell transcriptomic datasets, we find that OPCs express CGRP receptor components and exhibit frequent close appositions with CGRP-positive puncta, many of which are localized within 1 μm of an OPC process. A subset of these contacts displays synaptic-like features, colocalizing with the presynaptic marker Bassoon and the postsynaptic protein PSD95. Together, these findings suggest that CGRP signaling to OPCs may occur through direct contact potentially via synapses and by diffusion from extrasynaptic release sites. Ongoing studies are investigating the mode of CGRP release onto OPCs and the functional consequences of these distinct forms of neuron-OPC communication.

Disclosures: R. Aitken: None. **Y. Ji:** None. **T.A. Blanpied:** None. **A. Keller:** None. **R. Lorsung:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.12/R6

Topic: B.09. Glial Mechanisms

Support: Esther A. and Joseph Klingenstein Fund
Simons Foundation
NIH NINDS: R01NS135206

Title: Mnk1-Dependent Protein Synthesis and Regulation of Myelin Sheath Growth

Authors: *A. DATTA[1], B. POLIS[1], J. REYNGOUDT[1], E. DAS[1], A. CANDIA FLORES[1], M. BECHLER[2];
[1]Cell and Developmental Biol., [2]Cell and Developmental Biology, Neurosci. and Physiol., SUNY Upstate Med. Univ., Syracuse, NY

Abstract: Myelin sheaths, generated by oligodendrocytes (OLs) in the central nervous system, support rapid and efficient neuronal communication. Differences in myelin sheath length can influence conduction properties and may contribute to the coordination of neural activity. Although sheath length scales with axon diameter in vivo, the mechanisms that allow OLs to adjust sheath growth in response to axonal properties remain unclear. Using a 3D synthetic axon culture system that allows us to change axon diameter while holding other factors constant, we previously found that OLs form longer sheaths on larger synthetic axons (fibers). To investigate molecular pathways associated with this response, we performed phospho-protein analysis and identified increased activation of the translational regulator Mnk1 in OLs cultured on larger diameter fibers. Mnk1 activates eIF4E, a key driver of protein synthesis that influences sheath length in vivo. We hypothesize that larger axons stimulate Mnk1-dependent translation to promote myelin sheath expansion. Using nascent protein labelling, we found that protein synthesis is significantly enriched within sheaths on larger fibers during active myelination. Unexpectedly, disrupting Mnk1 activity during early sheath growth caused complete

fragmentation of forming sheaths, revealing a critical early window in which Mnk1-dependent translation is required for sheath stability. Remarkably, inhibiting Mnk1 just 24 hours later produced a distinct phenotype: sheaths remained intact, but elongation was selectively reduced on larger-diameter fibers. We also found that Mnk1 activity is important for a subset of myelin protein synthesis. Together, these findings establish a model in which a critical early window of protein synthesis is essential for initial myelin sheath wrapping, after which increased Mnk1 activity promotes sheath elongation in proportion to axon diameter. These findings identify a mechanism that links axonal physical cues to the regulation of myelin sheath growth.

Disclosures: A. Datta: None. **B. Polis:** None. **J. Reyngoudt:** None. **A. Candia Flores:** None. **M. Bechler:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.13/S1

Topic: B.09. Glial Mechanisms

Title: Development of 3D -printed Artificial axons using Elastomeric Materials for Myelination studies

Authors: *F. SHIRALIPOUR[1], M. OSO[2], R. CLEMENTS[2], E. HEGMANN[2];
[1]Biol. Sci., Kent state university, Kent, OH; [2]Kent State Univ., Kent, OH

Abstract: Multiple sclerosis (MS) affects over 2.8 million people worldwide, yet no current therapy promotes remyelination. A critical problem is the absence of physiologically relevant in vitro models that recreate the three-dimensional (3D) geometry, mechanical compliance, and axon-scale architecture that oligodendrocytes encounter in vivo. Existing two-dimensional (2D) cultures and animal models fail to capture these features, limiting our ability to study myelination mechanisms or screen remyelination-promoting drugs effectively. To address this gap, we developed a 3D-printed artificial axon platform using a photocrosslinkable six-arm star-shaped polycaprolactone acrylated elastomer (SBC-Acry) fabricated via digital light processing stereolithography (DLP). Three scaffold geometries were designed: micropillar, ladder-shaped, and mesh-shaped, with fiber diameters matching native axon dimensions (~20 μm). Material characterization confirmed successful synthesis, shear-thinning printability, moderate hydrophilicity (contact angle 55.1 ± 1.5°), and structural stability over 15 weeks. MO3.13 oligodendrocyte-lineage cells showed geometry-dependent viability, with mesh scaffolds supporting significantly greater cell survival and metabolic activity. Following differentiation, cells on mesh scaffolds demonstrated MBP expression, process elongation, and circumferential coiling around axon-like fibers, hallmarks of early myelination. These results establish the SBC-Acry mesh scaffold as a biomimetic, cytocompatible platform for studying oligodendrocyte behavior in vitro and as a foundation for high-throughput remyelination drug screening in demyelinating disease research.

Disclosures: F. Shiralipour: None. **M. Oso:** None. **R. Clements:** None. **E. Hegmann:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.14/S2

Topic: B.09. Glial Mechanisms

Support: NIH/HEAL DP2NS140734
NIH/NINDS R21NS138850
National Science Foundation Graduate Research Fellowship

Title: Rapid differentiation of spinal cord region-specific oligodendrocytes from human pluripotent stem cells

Authors: *N. TEANEY[1,2], E. PALLACK[2], L. A. STOLLER[2], M. MAZUREK[2], M. IQBAL[2], N. IYER[2];
[1]Dept. of Neurosci., Tufts Univ. Sch. of Med., Boston, MA; [2]Biomed. Engin., Tufts Univ., Medford, MA

Abstract: Oligodendrocytes (OLs), the myelinating cells of the central nervous system, are integral to neuronal integrity and contribute to spinal neurodegenerative disorders including spinal cord injury, amyotrophic lateral sclerosis, and multiple sclerosis (MS). Existing human pluripotent stem cell (hPSC)-derived OL protocols predominantly generate cortical-lineage populations, bypass developmental programming via transcription factor overexpression, and require differentiation timelines exceeding 80 days, limiting investigation of region-specific mechanisms in spinal cord disease. To address these gaps, we developed the Teaney Timeline, a modular framework generating regionally specified spinal cord OLs from hPSCs within 40 days. To our knowledge, this is the first hPSC-derived OL differentiation strategy to establish region-specific spinal identity by recapitulating developmental progression through neuromesodermal progenitors and ventral spinal cord patterning before OL induction. Using defined caudalization conditions, we reproducibly generated bulbar, brachial, and thoracolumbar progenitor populations expressing region-appropriate homeobox (HOX) genes. OL progenitor cell (OPC) induction produced cells co-expressing the canonical markers neuron-glial antigen 2 (NG2), platelet-derived growth factor receptor alpha (PDGFRα), and O4 (pre-myelinating marker), quantified by image-based analysis. Over 99% of cells expressed myelin basic protein (MBP) across all regional subtypes and developed arborized morphologies after two weeks of maturation (n=3 independent differentiations per region). Bulk RNA- and ATAC-seq will validate regional cell identity against primary datasets and define transcriptomic and chromatin landscapes across spinal levels. Multi-electrode array recordings confirmed co-culture with Teaney Timeline OLs increased neuronal firing rates and network synchrony, establishing functional capacity. Long-term 3D co-culture with region-matched motor neurons (MNs) produced multilamellar myelin sheaths and healthy g-ratios, confirming myelination

competence. To evaluate disease-modeling capability, MN-OL co-cultures exposed to MS patient serum exhibited myelin decompaction and disorganization, including collapsed and fragmented loops and myelin debris accumulation, consistent with MS lesion ultrastructure. Collectively, the Teaney Timeline provides a rapid, efficient, and developmentally informed platform for generating human spinal OLs, enabling investigation of region-specific myelination, neurodegeneration, and therapeutic vulnerability across spinal cord disorders.

Disclosures: N. Teaney: None. **E. Pallack:** None. **L.A. Stoller:** None. **M. Mazurek:** None. **M. Iqbal:** None. **N. Iyer:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.15/S3

Topic: B.09. Glial Mechanisms

Support: 5R01NS129632-04
5R01NS105691-07

Title: 10 Hz Uniform and Burst-Patterned Intracortical Microstimulation Divergently Modulate Oligodendrocyte Calcium Event Occurrence and Per-Event Dynamics

Authors: *C. GARCIA PADILLA, A. M. FORREST, G. ZHANG, V. SINGH, T. D. Y. KOZAI;
Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Oligodendrocyte (OL) intracellular calcium (Ca^{2+}) signaling is coupled to activity-dependent myelination. Prior electrical stimulation studies have identified 10 Hz as an effective paradigm for driving myelination, yet how distinct intracortical microstimulation (ICMS) temporal patterns (TP) modulate OL Ca^{2+} signaling in vivo remains poorly characterized. We hypothesized that 10 Hz ICMS would modulate OL Ca^{2+} event occurrence and dynamics in a TP-dependent manner, and that responses would vary with cortical depth and electrode distance. Two-photon Ca^{2+} imaging was performed in layer 1 (L1) of V1 in PLP-Cre^{ERT};TdTomato/GCaMP6f mice (N=6) during ICMS delivered to L1 or L2. We tested four ICMS paradigms: 10 Hz, 100 Hz, 10 Hz Burst, and theta burst stimulation (TBS). Ca^{2+} events within ROIs (n=120) were compared across pre-, during-, and post-stimulation epochs, layers, and electrode distance (0-275 μm) using linear mixed models. 10 Hz and 10 Hz Burst suppressed active OL proportion (10 Hz: 0.64 ± 0.17, $p = 0.047$, N=6; 10 Hz Burst: 0.76 ± 0.08, $p = 0.011$, N=6) and event counts (10 Hz: 2.29 ± 0.43, $p = 0.0002$, n=45; 10 Hz Burst: 3.09 ± 0.63, $p = 0.042$, n=46) compared to baseline, yet 10 Hz Burst and TBS increased event AUC (both ~36% increase, all $p < 0.05$) indicating fewer but larger events. During ICMS, 10 Hz evoked the highest somatic event counts and amplitudes across paradigms (all pairwise $p < 0.05$). In processes, 10 Hz Burst produced ~23% longer event durations than the next-highest paradigm

(10 Hz, $p < 0.01$). Under 10 Hz in L1, somatic activation time increased with electrode distance ($\beta = 0.45$ s/μm, 95% CI [0.07, 0.84], $p = 0.022$), while TBS showed the opposite trend ($\beta = -0.26$ s/μm, 95% CI [−0.57, 0.04], individually NS), with significantly different slopes between paradigms (Bonferroni-corrected $p = 0.022$), indicating opposing paradigm-dependent spatial gradients. Under 10 Hz, L1 delivery drove higher somatic event counts (7.64 ± 0.78 vs. 5.44 ± 0.62, $p = 0.004$, n=50 L1, 45 L2) and activation time (95.29 ± 12.42 s vs. 60.49 ± 7.51 s, $p = 0.007$, n=50 L1, 45 L2) than L2, while 10 Hz Burst in L1 recruited a higher proportion of active process ROIs than in L2 (0.90 ± 0.06 vs. 0.81 ± 0.07, $p = 0.041$, N=6). Post-ICMS, 10 Hz effects persisted with elevated somatic event count (pre: 5.28 ± 0.22 vs. post: 8.52 ± 0.74, $p<0.0001$, n=50) and activation time (pre: 60.92 ± 1.89 s vs. post: 99.15 ± 13.36 s, $p = 0.003$, n=45). The divergence between uniform and burst-patterned 10 Hz ICMS demonstrates that TP, beyond frequency, shapes OL Ca^{2+} responses in compartment- and distance-specific ways that persist beyond stimulation, which can be used to refine cellular targets for pro-myelinating stimulation protocols.

Disclosures: C. Garcia Padilla: None. **A.M. Forrest:** None. **G. Zhang:** None. **V. Singh:** None. **T.D.Y. Kozai:** None.

Poster

PSTR124: Oligodendrocytes Development

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR124.16/S4

Topic: B.09. Glial Mechanisms

Support: NIMH Intramural Research Program
1ZIAMH002985-03

Title: Activity-dependent myelin plasticity in the mPFC links early social experience to adult behavior

Authors: T. MEDIAVILLA, J. TAI, D. RAI-GERSAPPE, *T. D. MERSON;
Oligodendroglial Interactions Group, NIMH, NIH, Bethesda, MD

Abstract: Research in mice has linked juvenile social isolation to hypomyelination of the medial prefrontal cortex (mPFC), accompanied by changes in oligodendrocyte gene expression and morphology. These observations parallel the reductions in cortical volume reported in children exposed to institutional rearing, a population that also shows cognitive delays and elevated risk for psychiatric disorders. In the mature neocortex, sensory experience drives adaptive myelin remodeling by oligodendrocytes, reshaping myelination across neuronal populations and thereby diversifying circuit tuning. Two questions, however, remain unresolved: first, whether activity-dependent myelination operates through comparable mechanisms during neurodevelopment; and second, whether social isolation reduces oligodendrocyte density in the mPFC. We hypothesize that early social isolation selectively impairs myelination of specific neuron classes, disrupting

excitatory/inhibitory balance and ultimately producing adult behavioral dysfunction. To test whether isolation impairs myelination in a neuron subtype-specific manner, we combine the TRAP2 mouse line with viral labeling to permanently mark neurons activated during social interaction and to resolve their excitatory and inhibitory subpopulations and axonal projections. Notably, mice isolated for one week after weaning exhibited more social interaction-activated neurons in the mPFC than group-housed controls. We interpret this apparent hyperactivity as a possible loss of inhibitory tone, a hypothesis we are actively testing. Applied together with correlative light-electron microscopy, this genetic (TRAP2) and neuron subtype-specific viral labeling strategy will allow us to assess how isolation affects myelination of socialization-activated neuronal ensembles. Immunohistochemical detection of myelin proteins revealed myelin deficits in the mPFC of socially isolated mice. Behaviorally, mice single-housed from weaning into adulthood displayed social aversion, anhedonia, and anxiety-like behaviors relative to group-housed controls. Strikingly, the composition of the social environment during re-socialization shaped these outcomes: previously isolated juveniles re-socialized with group-housed mice showed greater social interaction than those re-socialized with other formerly isolated mice. Together, these findings challenge the view that mPFC myelin plasticity is confined to an early critical period, instead pointing to continued responsiveness to the quality of social experience beyond initial developmental windows.

Disclosures: T. Mediavilla: None. **J. Tai:** None. **D. Rai-Gersappe:** None. **T.D. Merson:** None.

Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.01/S5

Topic: B.10. Neuro-Oncology

Support: Croatian Science Foundation Grant No. IP-2022-10-8493 (Uniqueness in development of interneurons in human prefrontal cortex during fetal life and first postnatal year—implications in pathogenesis of schizophrenia and autism, PI: Zdravko Petanjek)
National Recovery and Resilience Plan (NRRP) institutional project No. 10106-25-3005 (Neural phenotype and disrupted neuronal migration in glioblastoma: molecular and transcriptomic analysis - NEUROGLIM, PI: Zdravko Petanjek)

Title: High-grade gliomas exhibit a strong neuronal phenotype

Authors: *J. BILANDZIC[1,4], T. PETANJEK[1,2], M. ČAVKA[1,3], M. ZANZE BEADER[1,3], A. HLADNIK[1,3], Z. PETANJEK[1,3];
[1]Croatian Inst. for Brain Res., [2]Dept. of Physiol., [3]Dept. of Anat. and Clin. Anat., Univ. of Zagreb, Sch. of Med., Zagreb, Croatia; [4]Dept. of Neurosurg., Univ. Hosp. Ctr. Sisters of Charity, Zagreb, Croatia

Abstract: Glioblastoma multiforme (GBM) is the most common and most lethal primary malignant brain tumor. Although it is traditionally considered a tumor of glial lineage, the exact cells of origin responsible for tumor initiation remain a subject of debate. Recent transcriptomic studies have implicated outer radial-glia-like cells and tripotential-intermediate-progenitor-like cells in the genesis of gliomas, yet the presence of neuronal lineages within GBM has not been fully characterized. We therefore investigated whether cells expressing markers of immature and mature neurons could be identified within GBM tissue using immunohistochemistry and RNAscope in situ hybridization. We conducted a descriptive study on surgically resected GBM samples from ten patients with histologically confirmed IDH-wildtype, CNS-WHO grade 4 located deep within the white matter. We identified a substantial population of cells expressing neuronal markers within GBM tissue. NeuN-positive cells were abundant, occasionally outnumbering GFAP-positive glial cells, with no observed GFAP/NeuN colocalization. Additional evidence of neuronal differentiation was provided by MAP-2 expression, alongside detection of markers of migratory neurons including doublecortin and βIII-tubulin. Notably, some cells atypically co-expressed doublecortin and NeuN, while a subset of NeuN-positive cells expressed Ki-67, indicating proliferative activity that warrants further investigation. Calretinin, regularly expressed in cortical interneuron subpopulation, was co-expressed with NeuN in a proportion of cells. Furthermore, mRNA transcripts for the vesicular glutamate and GABA transporters (VGLUT1 and VGAT) were detected within the GBM tissue. This distinctive pattern of neuronal marker expression and neurotransmitter transporter transcripts was absent in control metastatic brain tumor samples Our findings indicate that cells exhibiting features of neuronal progenitors, as well as immature and mature neurons, constitute a significant fraction of the cellular population within glioblastoma. These observations support the hypothesis that tripotential-intermediate-progenitor-like cells serve as the cells of origin in the genesis of gliomas, or that GBM cells maintain significant multi-lineage plasticity during oncogenesis.

Disclosures: J. Bilandzic: None. **T. Petanjek:** None. **M. Čavka:** None. **M. Zanze Beader:** None. **A. Hladnik:** None. **Z. Petanjek:** None.

Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.02/S6

Topic: B.10. Neuro-Oncology

Support: NIH grant 1R35 CA253119-01A1 (E.C.H)
K22 CA258953 (S.S.P).

Title: Transcriptomic Analysis Uncovers Differential Synaptic Component Regulation Across Pediatric and Adult Brain Tumors

Authors: *J. LOW[1], S. ARORA[2], A. RAJENDRAN[3], E. HOLLAND[4], S. S. PATTWELL[5];
[1]Ben Towne Ctr. for Childhood Cancer and Blood Disorders Res., Seattle Children's Res. Inst.,

Seattle, WA; [2]Fred Hutchinson Cancer Ctr., Seattle, WA; [3]Univ. of Washington Sch. of Med., Seattle, WA; [4]Div. of Human Biol., Fred Hutchinson Cancer Res. Ctr., Seattle, WA; [5]Human Biol., Seattle Children's/University of WA Sch. of Medicine/Fred Hutchinson Cancer Ctr., Seattle, WA

Abstract: Neuronal signaling is increasingly recognized as a key component of brain tumor biology, yet the organizational principles governing neuron-tumor interactions remain incompletely defined. We construct a transcriptomic reference map of ~4,300 adult and pediatric brain tumors—including gliomas, medulloblastomas, ependymomas, and meningiomas—and ~1,400 normal brain samples to systematically characterize neuronal-associated signaling across brain cancers. We interrogate synaptic pathways, receptor-level expression, and non-synaptic communication programs, and define their tumor-specific transcriptional implementation across major brain tumor entities. This multi-layered framework reveals substantial heterogeneity in synapse-associated signaling programs, reflecting lineage- and context-dependent modes of tumor-microenvironment interaction. Across tumors, we identify recurrent upregulation of HNRNPH2 in gliomas and medulloblastomas in silico and in human tissue microarrays (TMA), linking altered RNA processing programs to neuronal regulatory programs. We further observe enrichment of cholinergic signaling-associated transcriptional programs, including CHRNA9, across multiple tumor types, although protein-level engagement was not confirmed, as we did not see conclusive CHRNA9 staining in human TMA. Together, these findings define a hierarchical landscape of synapse-associated signaling in brain tumors, providing a framework and resource for understanding neuron-tumor crosstalk and potential therapeutic targets in neuro-oncology.

Disclosures: J. Low: None. **S. Arora:** None. **A. Rajendran:** None. **E. Holland:** None. **S.S. Pattwell:** None.

Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.03/S7

Topic: B.10. Neuro-Oncology

Support: K22CA258953 (to S.S.P.)

Title: Alternatively spliced NTRK2 variant, TrkB.T1, links PLCy mediated calcium signaling to cytoskeletal control.

Authors: *M. M. SHABAR[1], H. L. JAGANA[2], J. LOW[1], A. RAJENDRAN[3,1], L. MERINO GALAN[1], D. CONNER[4,1], M. HATHAWAY[1], J. M. HEMENWAY[1], D. E. JOHNSON[1], T. JACKSON[1], A. LUKASIK[1], V. MUKKAMALA[1], S. S. PATTWELL[1,5,4];
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Seattle, WA; [2]Vollum Inst., Oregon Hlth. and Sci. Univ., Portland, OR; [4]Sch. of Med., [3]Univ. of Washington, Seattle, WA; [5]Human Biol. Div., Fred Hutchinson Cancer Res. Ctr., Seattle, WA

Abstract: The neurotrophin receptor TrkB, along with its ligand brain derived neurotrophic factor (BDNF) are critical for proper neural development. The truncated splice variant, TrkB.T1, is involved in glial development. It contains altered expression in many neurological diseases and is overexpressed across several cancers including low grade glioma and glioblastoma. TrkB.T1 stimulation by BDNF initiates a signaling cascade that increases intracellular Ca2+ in astrocytes. In addition, TrkB.T1 associates with Rho-GDI1 leading to morphological changes in astrocytes and glioma cells. Both Ca2+ transients and Rho GTPases regulate neural developmental pathways including cytoskeletal changes. Although links between TrkB.T1 and Ca2+ signaling and TrkB.T1 with Rho GTPase activity have been individually identified, a gap in how they interact to maintain TrkB.T1 specific signaling and the implications of such signaling throughout the lifespan remains. Using affinity-purification mass-spectrometry (AP-MS) in transduced 3T3 cells and phospho-proteomics in patient-derived glioblastoma stem cells (GSCs), we deconstructed the TrkB.T1 interactome. This proteomic profiling revealed novel signaling axes which we functionally tested. Live-cell imaging was deployed to capture these signaling dynamics in real time, quantifying their direct phenotypic impacts on GSC morphology and cytoskeletal dynamics. Finally, to probe the precise molecular interactions within this mechanism, we pharmacologically targeted the TrkB.T1 pathway at multiple distinct nodes. Disrupting this axis attenuated the motile, aggressive phenotype characteristic of cells expressing high levels of TrkB.T1. F-actin was stained with phalloidin and visualized using immunofluorescence microscopy. Western blot and co-immunoprecipitation were used for further analyses of downstream signaling and binding partners to clarify the mediators of the observed morphological changes. Our results contribute to the growing body of evidence that TrkB.T1 possesses signaling capabilities beyond what we previously knew. This work helps to unveil TrkB.T1's specific role in neurodevelopment and the impact of its dysregulation.

Disclosures: M.M. Shabar: None. **H.L. Jagana:** None. **J. Low:** None. **A. Rajendran:** None. **L. Merino Galan:** None. **D. Conner:** None. **M. Hathaway:** None. **J.M. Hemenway:** None. **D.E. Johnson:** None. **T. Jackson:** None. **A. Lukasik:** None. **V. Mukkamala:** None. **S.S. Pattwell:** None.

Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.04/S8

Topic: B.10. Neuro-Oncology

Support: Gilbert Family Foundation

Title: Structural and Functional Pathology Associated with Retinal Ganglion Cell Dysfunction and Death in a Neurofibromatosis type 1 Mouse Optic GliomaModel

Authors: *S. DE LIMA[1], B. K. YOUNG[2], S. YU[7], C. SUN[10], K. BEHERA[3], P. CASEY-CAPLAN[8], G. DUQUE SALAZAR[9], X. XIA[4], A. M. BLUEBELL[5], Z. HE[11], J. L. GOLDBERG[6];
[1]Univ. of Pittsburgh Sch. of Med., Pittsburgh, PA; [2]Ophthalmology and Visual Sci., [4]Byers Eye Inst. - Ophthalmology, [5]Ophthalmology, [6]Byers Eye Institute--Ophthalmology, [3]Stanford Univ., Palo Alto, CA; [7]Boston Children's Hosp., Boston, MA; [8]Neurobio., Boston Children's Hosp., Westborough, MA; [9]Neurol., Boston Children's Hosp., Jamaica Plain, MA; [10]Stanford, Palo Alto, CA; [11]Children's Hosp Boston, Boston, MA

Abstract: Structural and Functional Pathology Associated with Retinal Ganglion Cell Dysfunction and Death in a Neurofibromatosis type 1 Mouse Optic Glioma Model
Silmara de Lima[1-5], Brent K. Young[6], Shuguang Yu[2,4], Aboozar Monavarfeshani[2,4,7], Catalina Sun[6], Krish Behera[6], Christina Tsien[6], Peter Casey-Caplan[2,4], Geraldine Duque Salazar[2,4], Fei Zhao[5], Xin Xia[6], Julianna Maya[6], Ayame Bluebell[6], Tianuye Zhang[2,4], Kristina Russano[6], Yuan Zhu[7], David. H. Gutmann[8], Zhigang He[2,4,9,10,b], Larry I. Benowitz[1,3,5,9,10,b], and Jeffrey L. Goldberg[6,b]**Affiliations:**Departments of [1,3]Neurosurgery, [2,4]Neurology, and [10]Ophthalmology, Boston Children's Hospital, Boston, MA; Harvard Medical School[3,4], Boston MA; [5]Dept. Ophthalmology, University of Pittsburgh, Pittsburgh PA; [6]Spencer Center for Vision Research, Byers Eye Institute, Stanford University, Stanford, CA. [7]UT Southwestern Medical Center, Dallas, TX; [8]Department of Neurology, Washington University, St. Louis, MO; [9]F.M. Kirby Neurobiology Center.Children with neurofibromatosis type 1 (NF1) are prone to the development of low-grade tumors involving the optic pathway, 30% of which lead to reduced visual acuity. Current management of these patients includes cytotoxic and molecularly-targeted therapies, which are limited by issues with drug tolerability and inconsistent improvements in tumor-induced vision loss. Therefore, there is a pressing need to identify and evaluate therapies in preclinical models of *Nf1*-OPG. One of the barriers to clinical translation is the lack of harmonization across laboratories and variations in disease-related phenotypes. To characterize phenotypes related to visual pathway structure and function across institutions, we performed a longitudinal investigation of pathophysiology using a well-characterized mouse model of *Nf1* optic pathway glioma (*Nf1*-OPG mice) maintained in separate colonies. Our findings reveal variable reductions in retinal ganglion cell (RGC) density (5-18%) of *Nf1*-OPG mice across institutions. Studies revealed a range of tumor-associated alterations in the optic nerve, including axon degeneration, myelin defects, and oligodendrocyte precursor cell (OPC) proliferation, with enlargement of the prechiasmatic area beginning at different ages depending on the colony. Importantly, *Nf1*-OPG pathology was accompanied by defects in visually evoked potentials (VEPs) in one colony, but not the optokinetic motor response 2 colonies. Our results reveal variation in optic glioma phenotypes and visual pathway alterations that need to be considered when using preclinical murine avatars to identify and evaluate new therapeutic strategies.

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Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.05/T1

Topic: B.10. Neuro-Oncology

Support: CMSRU- BMS

Title: Transcriptomic Characterization of Cannabinoid and Opioid Receptor Agonism in Glioblastoma: Effects of CP-55940, Morphine, and Their Combination on Gene Expression

Authors: *C. KAPETANAKIS[1], S. CHUNN[3], Y. CHEN[3], G. A. CARRASCO[2], A. K. FAKIRA[2], R. J. BUONO[2], T. N. FERRARO[2];
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Abstract: Glioblastoma (GBM) is the most prevalent primary malignant brain tumor in adults, with a median survival of approximately 15 months despite multimodal therapy. Cannabinoid receptor agonists demonstrate preclinical anti-tumor activity in GBM. Additionally, cancer patients are routinely prescribed opioids, which have been demonstrated to increase sensitivity to chemotherapeutic agents. There is documented interaction between CB1 and opioid receptors, the downstream transcriptomic effects of which are incompletely characterized. Human T98G GBM cells were treated with 100 nM CP-55940 (a CB1/CB2 receptor agonist), 10 μM morphine, or both compounds for 1 hour, 1, 2, or 3 days (n=3 biological replicates per group). Data from RNA sequencing were analyzed using gene ontology differential expression analysis to compare each treatment to time-matched controls and within-group baselines, and to assess pairwise adjacent timepoints (false discovery rate [FDR] < 0.05). CP-55940 significantly enriched cellular processes related to the cell cycle, apoptosis, TGF-β receptor signaling, chromatin organization, and cytoplasmic translation over 2 days of exposure, with ATP-dependent chromatin remodeling complexes among the most significant cellular component findings. After 3 days of CP-55940 exposure, we found no significant enrichment relative to control despite continued internal transcriptional activity, indicating convergence with the control trajectory rather than drug-induced silencing. Morphine exposure resulted in transcriptional divergence from control at all timepoints and, at 3 days, produced striking enrichment of TGF-β receptor signaling (fold enrichment [FE] 39.5×), ERK1/2 cascade regulation (FE 15.3×), integrin-mediated signaling (FE 37.9×), and positive regulation of apoptosis (FE 8.6×). Combined treatment uniquely enriched FGF stimulus response (FE 48.4×) and sprouting angiogenesis at 3 days and produced the highest ERK1/2 enrichment in the dataset (FE 21.4×). Pairwise temporal analyses revealed that all drug conditions, but not the untreated control, significantly enriched DNA replication between days 1 and 2. These findings demonstrate that cannabinoid and opioid receptor activation drive temporally distinct and partially non-overlapping transcriptional programs in GBM cells, highlighting opioid co-exposure as a clinically relevant variable that may modify cannabinoid-associated anti-tumor responses.

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Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.06/T2

Topic: B.10. Neuro-Oncology

Support: AACR-NovocureTumor Treating Fields Research Grant (21-60-62-PICC; PI: Piccirillo)
ACS Post-Baccalaureate Fellows Grant (DICR POST-BACC-22-1041994-01DPBACC)
UNM Cancer-PREP
NIH Grant P30CA118100
NIH Grant P20GM121176

Title: The impact of Tumor Treating Fields (TTFields) on the transcriptome and the secretome of cancer stem-like cells isolated from the sub-ventricular zone of glioblastoma patients

Authors: *A. E. SAJCHE SAPON[1,2], R. B. SIDEBOTTOM[1], Y. LICON MUNOZ[1,2], G. BACCHIN[1], C. A. BOWERS[3], S. G. M. PICCIRILLO[1,2];
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Abstract: Glioblastoma (GBM) is the most aggressive brain tumor in adults that almost inevitably recurs despite radical treatments. Recurrence is driven by residual disease, which is extremely difficult to identify and target. We were the first to identify and characterize specific anatomic/functional areas of residual disease in GBM patients, including the sub-ventricular zone (SVZ), the most well-characterized neurogenic area in the mammalian brain. Specifically, we showed that the SVZ is a reservoir of cancer stem-like cells (CSCs) seeding recurrence. Thus, the SVZ holds the key to identifying novel therapeutic targets for GBM patients. We previously evaluated the impact of Tumor Treating Fields (TTFields) - electric fields exerting physical forces on tumor cells - on the morphology and proliferation of CSCs isolated from the SVZ of GBM patients. We observed that the proliferation of CSCs treated with Temozolomide and ionizing radiation is significantly inhibited by TTFields (200 kHz for 48 hours). Moreover, we observed that this antiproliferative effect of TTFields is maintained among patients. Recently, we examined the impact of TTFields on the transcriptome and the secretome of CSCs using single-cell transcriptomics and functional phenotyping. Our results indicate that TTFields alter the expression of genes related to cell cycle and GBM cell states. Moreover, secretome analysis revealed that CSCs treated with TTFields secrete less VEGF and more soluble CD137 (sCD137) than untreated cells. CD137 is a member of the TNF family contributing to the activation of cytotoxic responses in T cells, while sCD137 exhibits immunoinhibitory functions. Clinical trials involving agonistic anti-CD137 antibodies that also counteract sCD137-mediated immunoinhibition are currently underway in patients with advanced tumors. Combined with TTFields, these antibodies offer a novel therapeutic opportunity for the treatment of GBM.

Collectively, our results point to the effectiveness of TTFields in GBM and identify a novel therapeutic target in GBM residual disease.

Disclosures: A.E. Sajche Sapon: None. **R.B. sidebottom:** None. **Y. Licon Munoz:** None. **G. Bacchin:** None. **C.A. Bowers:** None. **S.G.M. Piccirillo:** None.

Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

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Program #/Poster #: PSTR125.07/T3

Topic: B.10. Neuro-Oncology

Support: Grant ANR-17-CE16-0025-02
ANR-21-CE16-0034-01
ANR-21-CE13-0003

Title: Combining 3D imaging and light sheet guided 2D spatial multiplexing for deep characterization of a glioblastoma mouse model

Authors: *K. BIGOTT[1], V. SCHOPPEL[1], M.-C. TIVERON[5], D. BARLEBEN[1], S. BORNEMANN[2], M. JUNGBLUT[3], H. CREMER[6], A. BOSIO[4];
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Abstract: Spatial biology is an emerging field that studies the spatial organization of cells and molecules within tissues to better understand complex biological processes. Currently available methods may only provide information from thin tissue sections, limiting analysis to rather roughly selected areas, while sectioning is time consuming and often prone to artifacts, especially if slicing entire samples. Our workflow combines 3D imaging with light sheet guided multiplex spatial analysis to get an overview of complex organs, identify target structures within and to further analyze a carefully selected region in depth with multiparameter 2D microscopy - all on the same valuable specimen. While clearing methods in combination with light sheet fluorescence microscopy have emerged as powerful tools for 3D reconstruction of tissues, most clearing techniques involve toxic reagents which require special safety provisions and generate extra effort for sample preparation as well as imaging. To address these shortcomings, we developed an optimized clearing workflow based on non-toxic reagents that allows for efficient 3D imaging (MACS® Deep Clearing Kit) of even whole organs. We performed staining, clearing and 3D light sheet imaging of mouse brain hemispheres derived from a glioblastoma mouse model using the MACS® Deep Clearing Kit and the UltraMicroscope Blaze™. With the full specimen's 3D view, we were able to identify GFP positive glioblastoma cells using an anti-GFP antibody in order to prepare tissue sections that precisely cover these regions of interest, a

process termed light sheet guided sectioning for 2D immunofluorescence analysis. The tissue sections were further analyzed by MACSima™ Imaging Cyclic Staining (MICS) technology, providing deep spatial protein phenotyping of individual cells on a single sample. Remarkably, the fluorochrome conjugate used for 3D-IF staining remained detectable after sectioning, enabling us to verify the location of the target region. Furthermore, most epitopes remained stable throughout the entire process of sample preparation for 3D imaging, 3D imaging itself, and sample preparation for 2D microscopy, allowing for deep phenotyping via MICS using relevant glioblastoma, neural cell and immune cell markers. Thus, we have demonstrated that it is possible to apply the MICS technology to a previously cleared tissue, providing a workflow that combines two cutting edge imaging technologies. The ability to obtain both, a comprehensive 3D context, and detailed information about cellular diversity in a spatial context by multiparameter 2D microscopy from a single sample opens up new possibilities in spatial biology.

Disclosures: K. Bigott: A. Employment/Salary (full or part-time):; Miltenyi Biotec B.V. & Co. KG. **V. Schoppel:** A. Employment/Salary (full or part-time):; Miltenyi Biotec B.V. & Co. KG. **M. Tiveron:** A. Employment/Salary (full or part-time):; Developmental Biology Institute of Marseille. **D. Barleben:** A. Employment/Salary (full or part-time):; Miltenyi Biotec B.V. & Co. KG. **S. Bornemann:** A. Employment/Salary (full or part-time):; Miltenyi Biotec B.V. & Co. KG. **M. Jungblut:** A. Employment/Salary (full or part-time):; Miltenyi Biotec B.V. & Co. KG. **H. Cremer:** A. Employment/Salary (full or part-time):; Developmental Biology Institute of Marseille. **A. Bosio:** A. Employment/Salary (full or part-time):; Miltenyi Biotec B.V. & Co. KG.

Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.08/T4

Topic: A.01. Neurogenesis and Gliogenesis

Support: NPRP14S-0404-210140

Title: Role of DIAPH3 in Neurogenesis and Gliomagenesis

Authors: *F. TISSIR;
Hamad Bin Khalifa Univ., Education City, Qatar

Abstract: DIAPH3 is a master regulator of the cytoskeleton with key roles in cell division. In the mouse brain, DIAPH3-deficient neural stem cells exhibit abnormalities in karyokinesis and cytokinesis, leading to cell cycle arrest, aneuploidy, and mitotic catastrophe. We investigated the role of DIAPH3 in glioma genesis in mouse models. We selectively deleted the Diaph3 and Trp53 genes in the mouse cerebral cortex and thoroughly analyzed single (Diaph3 cKO and Trp53 cKO) and double (dcKO) conditional knockout mice. The tumors appeared earlier in dcKO than in Trp53 cKO mice, and this was associated with increased whole chromosome copy

number alterations, endogenous DNA damage, and shorter survival of dcKO mice. We performed a comparative transcriptomic analysis prior to the onset of tumors and identified changes in cancer gene signatures specifically in dcKO, suggesting that the loss of DIAPH3 hastens the tumorigenic process. We isolated cancer stem-like cells and assessed their sensitivity to ionizing radiation and found that DIAPH3 regulates the resistance of glioma stem-like cells to irradiation. Our data suggest that DIAPH3 has a tumor-suppressor function and that its deficiency promotes aneuploidy and genome instability, accelerating tumorigenesis and leading to early onset of high-grade diffuse glioma with DNA damage, and resistance to ionizing radiation.

Disclosures: F. Tissir: None.

Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.09/T5

Topic: B.10. Neuro-Oncology

Support: National Institutes of Health grant R01 CA276174
National Institutes of Health grant R01 CA203861

Title: Functional clustering within glioblastoma identifies a network-integrated subtype with improved survival

Authors: *D. ZENG[1], A. SNYDER[2], K. PARK[3], B. T. ACLAND[1], J. SHIMONY[4], E. C. LEUTHARDT[5,1];
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Abstract: Glioblastomas (GBM) conventionally are viewed as disrupting brain function. However, emerging evidence shows that glioma cells can form activity-dependent synaptic connections with neurons. We hypothesized that resting-state functional magnetic resonance imaging (rs-fMRI) can identify functionally distinct tumor subregions which interact with canonical resting-state networks (RSNs). We analyzed preoperative rs-fMRI from 190 patients with IDH-wildtype GBM and 347 healthy controls. Voxelwise blood oxygen level-dependent (BOLD) time series were extracted from contrast-enhancing tumor regions, reduced using principal component analysis, and clustered using fuzzy c-means clustering. Cluster-average time series were correlated with seven canonical RSNs and compared with anatomically matched regions in healthy subjects. Fifty-two of 190 tumors (27.4%) exhibited multiple spatially coherent functional clusters. In many cases (29/52 (55.8%) multi-cluster tumors; 14/138 (10.1%) single-cluster tumors), these functional connections were stronger than those in a reference cohort. Elevated RSN coupling was strongly associated with multi-cluster status after adjustment

for age, sex, and tumor size (OR=14.11, 95% CI 6.05-32.93, $p=9.1\times10^{-10}$). Multi-cluster tumors demonstrated increased seizure prevalence (adjusted OR=3.33, 95% CI 1.53-7.23, p=0.00245) and longer survival than single-cluster tumors (median survival 506 vs. 367 days; adjusted RMST difference +95.7 days, p=0.018). These findings identify a subset of GBMs characterized by functional subregions and selective coupling to distributed brain networks, suggesting a potential prognostic biomarker based on rs-fMRI.

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Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.10/T6

Topic: D.04. Brain Injury and Trauma

Support: CMU Neuroscience program
Covenant HealthCare College of Medicine at CMU
Office of Research and Sponsored Program
E. Malcolm Field , Gary Leo Dunbar endowed chair
John G. Kulhavi Professorship in Neuroscience at CMU
Field Neuroscience institute

Title: Targeting Mitotic Drivers in Glioblastoma Through Dual siRNA Delivery with PAMAM Dendrimers

Authors: *N. SIMON[1], O. DUBEY[1], R. B. PETERSEN[3], G. L. DUNBAR, Sr.[4], J. ROSSIGNOL[2];
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Abstract: Aberrant expression of kinesin motor proteins, particularly Kif23 and Kif18a, is frequently observed in glioblastoma and plays a critical role in tumor cell division, survival, and invasive behavior. Small interfering RNAs (siRNAs) represents a specific strategy to silence these oncogenic drivers; however, its there are challenges related to siRNA instability, limited cellular uptake, and off-target toxicity. G4 70/30 poly(amidoamine) (PAMAM) dendrimers have emerged as a promising nanocarrier platform, offering efficient siRNA protection, enhanced cellular internalization, and improved brain-targeted delivery. This study evaluates the therapeutic potential of co-delivering Kif23 and Kif18a siRNAs using G4 70/30 PAMAM dendrimers for glioblastoma treatment. Physicochemical characterization demonstrated that dendrimer-siRNA complexes formed stable nanosized structures at an optimal N/P ratio of 1.5:1, while maintaining low cytotoxicity in normal astrocytes, supporting their biocompatibility and suitability as an RNA delivery platform. In GL261 cells, dual siRNA delivery efficiently suppressed Kif23 and Kif18a expression, as confirmed by WB analysis. Gene silencing induced significant apoptotic activity, demonstrated by decreased BCL2 expression and increased levels of BAX and cleaved Cas3. Cell proliferation was evaluated using an EDU incorporation assay, which revealed a substantial reduction in proliferative capacity following treatment. wound healing assays showed markedly impaired migratory behavior in treated cells, accompanied by significant downregulation of migration-associated markers MMP2, MMP7, and MMP9. For *in vivo* evaluation, an orthotopic glioblastoma mouse model was established through intrastriatal implantation of GL261/luc2-tdTomato cells. Tumor formation and progression were monitored using IVIS bioluminescence imaging. Kif23/Kif18a siRNA loaded G4 70/30 PAMAM dendrimers were administered intracranially at the tumor site, and therapeutic efficacy was assessed through survival analysis and molecular characterization of tumor tissues. Immunohistochemical analysis further included Nestin staining to evaluate glioma stem-like cell populations and IBA1 staining to assess microglial/macrophage responses within the tumor microenvironment. These findings demonstrate that G4 70/30 PAMAM dendrimers provide a safe and effective nanocarrier system for the co-delivery of therapeutic siRNAs targeting Kif23 and Kif18a. The treatment strategy effectively inhibited glioblastoma proliferation and migration, promoted apoptotic signaling, and modulated tumor-associated molecular pathways

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Poster

PSTR125: Neuro-Oncology: Molecular Mechanisms and Signaling Pathways

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR125.11/T7

Topic: I.06. Social Cognition

Title: Utilization of Multiomic Factor Analysis and Single-Cell RNA-seq Confirmation to Investigate Meningioma Aggression

Authors: *D. J. POWELL[1], R. P. SIROLE[1], J. VERGIS[1], J. F. WOOD[1], R. E. MCCULLUMSMITH[2];
[1]The Univ. of Toledo, Toledo, OH; [2]Neurosciences, Univ. of Toledo, Toledo, OH

Abstract: While efforts have been made to improve precision medicine in meningioma treatment, the biological modules that drive meningioma aggression or grade are not well understood. Thus, in this study, we aimed to deconvolve which biological signatures in meningioma correlate with WHO grade by performing exploratory data analysis following multiomic integration with bulk transcriptomics, bulk epigenetics, and single-cell RNA-seq. First, biological signatures correlating with grade were determined via separate multiomic factor analysis (MOFA) for male (n=201) and female (n=101) profiles in the bulk transcriptomic and epigenetic datasets. Pathways enriched in the same datasets for the most grade-correlated factors were determined via GSEA using the Hallmark gene sets from MSigDB. Next, three single-cell RNA-seq datasets were integrated to form a large single-cell RNA-seq atlas (male N = 14, female N = 23) of meningioma samples including tumor parenchyma and stroma using Harmony. Dimensionality reduction was performed via Uniform Manifold Approximation and Projection (UMAP), with clustering performed via the Louvain algorithm, with broad cell lineages overlaid onto the clusters. The MOFA biological factors for males and females were separately mapped over the single-cell atlas UMAPs. MOFA factor 1 and factor 3 were most correlated with grade in the female and male populations, respectively. Female factor 1 is associated with grade (correlation=4.8) but not age (correlation=0), while male factor 3 was associated with age (correlation=1.8) and grade (correlation=5.6). The pathways represented in factor 1 are TNF-α signaling via NF-κB (NES=1.703) and heme metabolism (NES=-1.526). Within factor 3, the top upregulated pathway is MYC targets V1 (NES=1.790) and the top downregulated pathway is Interferon alpha response (NES=-1.983). From the single-cell atlas UMAP 38 clusters were identified. Mapping MOFA factor scores to patient-wise pseudobulked clusters and grades indicated that, in males, there were no significant differences in factor 3 module score across grade. In females, there was a significant difference in factor 1 module score between grade I and II ($p < 0.03$), but from grade I-III, or II-III, there was no significance when it came to factor 1. Further study is needed to examine other factor scores and use the single-cell atlas to deconvolve the bulk signal to more accurately correlate grade with factor score vs cell type.

Disclosures: D.J. Powell: None. **R.P. Sirole:** None. **J. Vergis:** None. **J.F. Wood:** None. **R.E. McCullumsmith:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.02/T9

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

Support: NIH Grant R01AG066831
Barnard SRI Grant

Title: Sex Differences in Microglial Gene Expression Predict Amyloid and Tau Pathology Burden in Alzheimer's Disease

Authors: *R. KARUMANCHI[1,2], L. STARR[2], V. MENON[2];
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Abstract: Alzheimer's disease (AD) is the leading cause of dementia, and prevalence of AD continues to rise with an aging population. The hallmarks of AD pathology are amyloid-beta (Aβ) plaques and tau neurofibrillary tangles (NFTs). There is a growing body of literature that recognizes the importance of the role sex plays in AD risk and progression, yet the extent to which sex-specific transcriptomic signatures drive pathology burden across distinct cell types remains unclear. To date, there are few studies that have analyzed the association between these differences at the level of individual cell types. The specific objective of this study was to build sex-stratified transcriptomic models of AD pathology across six cell types and identify cell-type-specific gene signatures associated with Aβ plaques and tau NFTs pathology. Here, we applied Elastic net regression (ELN), a regularized machine learning model to pseudobulked, cell type-specific RNA-sequencing data from 695 male and female donors 65+ years old at death across three studies (Green et al., 2024; Mathys et al., 2023; Gabitto et al., 2024) and across six cell types: astrocytes, microglia, oligodendrocytes, oligodendrocyte precursor cells, excitatory neurons, and inhibitory neurons. Combined and sex-stratified models were trained and validated across cohorts. One of the more significant findings is that microglial gene expression showed the strongest model performance across all cell types for both AD pathologies. Sex-stratified models identified that while microglial gene expression was most strongly associated with pathology for both females and males, the most strongly weighted genes differed considerably between sexes. One interesting finding is that, in the male models, OPC gene expression was correlated with both Aβ plaques and tau NFTs to a degree comparable to that of microglia, whereas in the female models the OPC association was weaker and microglial gene expression remained the strongest predictor. Taken together, these findings suggest that sex-associated transcriptomic mechanisms of AD pathology are cell-type specific and that microglial gene expression may serve as a particularly informative lens through which these differences can be elucidated. The present study adds to the growing body of research on sex differences in neurodegeneration, and the current data highlight the importance of sex as a biological stratifier. The findings of this study have a number of important implications for the development of sex-stratified microglial biomarkers for AD.

Disclosures: R. Karumanchi: None. **L. Starr:** None. **V. Menon:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.03/T10

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

Support: Edson Seed Grant ASU

Title: Biomarker study of longitudinal blood RNA prior to cognitive decline

Authors: E. DELVAUX[1], D. HECKER[1], F. PROMETI[1], P. D. COLEMAN[2], ***C. HUSEBY**[1]; [1]Arizona State Univ., Tempe, AZ; [2]ASU-Banner Neurodegenerative Res. Ctr., Tempe, AZ.

Abstract: Blood-based biomarkers have the potential to reduce the cost and complexity of diagnosing and monitoring Alzheimer's disease (AD) and other neurodegenerative disorders. An ideal biomarker study design includes serial blood sample collection over time, allowing comparison of individuals who subsequently develop cognitive impairment with those who remain cognitively healthy. The Alzheimer's Disease Anti-inflammatory Prevention Trial (ADAPT) provided such a framework. ADAPT was a multicenter clinical trial designed to evaluate whether nonsteroidal anti-inflammatory drugs (NSAIDs) could delay the onset of Alzheimer's disease (ADAPT Research Group et al., 2009). Participants were randomized to receive naproxen, celecoxib, or placebo. Eligibility criteria included age ≥70 years, absence of dementia according to DSM-IV criteria, and at least one first-degree relative diagnosed with AD. Participants underwent annual neurological evaluations, semiannual psychometric assessments, and serial blood collection throughout the study. The Rochester, New York cohort consisted of 153 individuals who were cognitively intact at enrollment. Serial blood samples were collected at each cognitive assessment, and RNA was extracted from these samples for molecular analysis. Here we sequenced the RNA from 321 de-identified longitudinal blood samples from this cohort. Using established gene expression analysis and machine learning approaches (Huseby et.al., 2022), we identified transcriptomic differences both within individuals over time and between participants who experienced cognitive decline and those who remained cognitively stable. These analyses revealed molecular pathways associated with early cognitive decline and may provide insights into blood-based biomarkers for preclinical neurodegenerative disease detection and monitoring.

Disclosures: E. Delvaux: None. **D. Hecker:** None. **F. Prometi:** None. **P.D. Coleman:** None. **C. Huseby:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.04/T11

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

Support: NIH/NIA AG072510

Title: Single-nucleus transcriptomics identifies rolipram-associated reduction of immediate-early/AP-1 stress-response gene expression in inhibitory and immature cortical neurons of P301S tau mice

Authors: *A. A. DWAMENA, A. POTOKIRI, H. WANG;
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Abstract: The Ubiquitin-proteasome system (UPS) declines with age, and impaired UPS activity is linked to Alzheimer's disease (AD) and tauopathy. Rolipram, a selective phosphodiesterase-4 (PDE4) inhibitor, increases cyclic AMP and activates protein kinase A (PKA), which can phosphorylate the 26S proteasome, thereby enhancing UPS function and reducing toxic tau burden. Despite these promising effects on toxic tau accumulation, little is known about cell-type-specific responses to PDE4 inhibition in tauopathy. To address this gap, we conducted a pilot single-nucleus RNA sequencing study of cortical tissue from 8-10-month-old P301S tau-transgenic and wild-type (WT) mice treated with rolipram or vehicle for 1 month. This 2 x 2 design included four groups: rolipram-treated tau, rolipram-treated WT, vehicle-treated tau, and vehicle-treated WT, and yielded 21,362 nuclei across 21 clusters spanning major cortical cell types, allowing us to separate tau-driven transcriptional changes from treatment-associated effects. Cell composition analysis revealed tau-associated changes in inhibitory and immature neuronal populations. Compared with vehicle-treated WT mice, vehicle-treated tau mice had a lower proportion of GABAergic neurons (17.7% vs. 20.6%) and a higher proportion of neuroblast-like cells (8.1% vs. 5.7%). Rolipram treatment in tau mice shifted these populations toward the WT vehicle profile, increasing GABAergic neurons to 20.1% and reducing neuroblast-like cells to 5.9%. In contrast, rolipram produced little compositional change in WT mice. Differential expression (DE) analysis identified a tau-specific rolipram-associated reduction in immediate-early genes and AP-1 stress-response signals, including *Arc, Fos, Egr1, Nr4a3, Npas4*, and *Junb* (logFC: -2.3 to -5.2; Bonferroni-adjusted $p<0.05$), most pronounced in neuroblast-like cells and GABAergic neurons. In neuroblast-like cells, the percentage of *Arc*-expressing nuclei decreased from 18.7% to 0.34% after rolipram treatment, a 55-fold decrease, suggesting that rolipram quiets an abnormal tau-linked stress state in immature neurons. Gene Ontology analysis highlighted processes including synaptic vesicle trafficking, postsynaptic organization, protein catabolic processes, and neurotransmitter secretion, indicating coordinated regulation of synaptic and proteostatic stress pathways. These findings reveal a tau-specific, rolipram-sensitive transcriptional program centered on the AP-1/immediate-early gene pathway in inhibitory and immature cortical neurons and support future testing of the NGF/NTRK-MAPK-AP-1 pathway for PDE4 inhibition in tauopathy.

Disclosures: A.A. Dwamena: None. **A. Potokiri:** None. **H. Wang:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.05/T12

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

Support: The International Foundation for Ethical Research Graduate Student Fellowships for Alternatives to the Use of Animals in Science

Title: Developing a Human Locus Coeruleus Organoid Model to Investigate Selective Regional Vulnerability in Alzheimer's Disease Pathogenesis

Authors: *Y. GAO[1], M. TISH[1], Z. OU[2], C. EISENBERG[1], N. KEBEDE[1], D. WEINSHENKER[1], F. BIREY[1];
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Abstract: The locus coeruleus (LC) is among the earliest brain regions to develop hyperphosphorylated tau and degenerate in Alzheimer's disease (AD). As the brain's primary norepinephrine (NE) source, the LC regulates arousal, attention, stress, and memory, and its degeneration is predicted to lead to early cognitive decline in AD. Existing animal models fail to capture human-specific features of LC such as LC-first pathogenesis in AD, neuromelanin accumulation, and disease-relevant gene expression. To address this bottleneck, we have developed the human LC organoid (hLCO) as a platform to study LC biology and AD pathophysiology. hLCOs capture defining neurochemical features of the human LC, including NE and dopamine production, expression of noradrenergic markers (*PHOX2A/2B, TH, DBH, SLC6A2*), and neuromelanin granules. Transcriptomic analysis confirmed strong similarity to postmortem human LC tissue. Calcium imaging revealed tonic, pacemaker-like firing in LC neurons, along with CO_2 chemosensitivity, with increased firing frequency under elevated CO_2. In hCO-hLCO assembloids, NET-immunolabeled LC axons projected extensively into the cortical compartment, and MEA recordings suggested that LC innervation modulates cortical network dynamics, with assembloids showing reduced synchrony relative to hCOs alone.
To better understand hLCO-specific signatures of disease in AD, hLCOs and cortical organoids (hCOs) were derived from induced pluripotent stem cells of healthy individuals and familial AD (fAD) patients carrying *PSEN1*, *PSEN2*, or *APP* mutations. Organoids were characterized via HPLC, RNAscope, bulk RNA-seq, immunohistochemistry, and Fontana-Masson staining. Functional properties were assessed using calcium imaging and multielectrode array (MEA) recordings. hCO-hLCO assembloids were generated to evaluate LC projection and network-level interactions. AD-related pathology was examined by western blot and semi-quantitative PCR of 3R/4R *MAPT* isoforms. Bulk RNA-seq of three fAD hLCO lines revealed line-specific transcriptional changes and shared downregulation of synaptic genes. Semi-quantitative PCR showed enrichment of 4R tau isoforms in fAD hLCOs relative to controls, and western blot demonstrated increased p-tau and total tau in both fAD hCOs and hLCOs.
We established and validated a human LC organoid model that recapitulates the molecular, neurochemical, and neuromodulatory properties of the human LC, providing a tractable platform to investigate LC function and dysfunction in development and disease.

Disclosures: Y. Gao: None. **M. Tish:** None. **Z. Ou:** None. **C. Eisenberg:** None. **N. Kebede:** None. **D. Weinshenker:** None. **F. Birey:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.06/T13

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

Support: NIH/NIA AG072510

Title: Cell-type-resolved transcriptional signatures of Alzheimer's disease and rolipram treatment in 5xFAD mouse brain: a single-cell RNA-seq pilot atlas

Authors: *A. POTOKIRI[1], A. A. DWAMENA[2], H. WANG[2];
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Abstract: Current therapies for Alzheimer's disease (AD) address symptoms rather than the underlying circuit-level dysfunction. A major barrier to therapeutic progress is the lack of cell-type-resolved maps of transcriptional disruption, knowledge essential for identifying which populations to target. Rolipram, a phosphodiesterase inhibitor that elevates intracellular cAMP to enhance proteasome activity via activating protein kinase A and subsequently phosphorylating proteasomal subunit Rpn6, has shown cognitive benefit in rodent AD models, but its cell-type-specific transcriptional effects remain uncharacterized. We performed single-cell RNA sequencing of cortical tissue from 5xFAD and wild-type mice treated with rolipram or vehicle using the Parse Biosciences Evercode WT v2 100K kit (29,664 cells retained after quality control). Unsupervised clustering identified 17 transcriptionally distinct populations spanning all major cortical cell types. Comparative analysis revealed the most pronounced transcriptional divergence in a calcium-computation neuron cluster, showing coordinated downregulation of calcium homeostasis genes including Itpr1, Calb1, Prkg1, and Cacna1g (GO: intracellular calcium ion homeostasis, $p=2.6\times10^{-7}$), consistent with excitotoxic calcium dysregulation implicated in AD neurodegeneration. VIP/Reln disinhibitory interneurons showed extensive downregulation of synaptic organization and learning-associated gene programs (GO: learning or memory, $p=2.4\times10^{-12}$), implicating E/I imbalance as a transcriptionally encoded feature of 5xFAD cortex. Microglia exhibited a homeostatic-to-disease-associated transition marked by elevated AD GWAS risk genes Inpp5d, Mertk, and Hexb. Rolipram treatment was associated with 72 candidate rescue genes in VIP interneurons, including restoration of the cAMP phosphodiesterase Pde7b, and broad suppression of reactive gene programs in astrocytes. These findings identify calcium-computation neurons and VIP interneurons as priority cell populations for AD therapeutic investigation and suggest cell-type-specific cAMP signaling as a tractable mechanism for circuit rescue.

Disclosures: A. Potokiri: None. **A.A. Dwamena:** None. **H. Wang:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.07/T14

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

Title: Alirocumab-Induced Transcriptomic Remodeling Across the Liver-Brain Axis

Authors: *V. AGARWAL[1], J. WAGNER[2], C. VELA[1], J. JUNG[3], D. ROSOFF[3,4], D. KROPP[3], T. PERLSTEIN[3], E. HUI[3], J. REITZ[3], L. F. VENDRUSCOLO[5], F. W. LOHOFF[3];
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Abstract: Alirocumab, a monoclonal antibody targeting PCSK9, enhances LDLR recycling and reduces circulating low-density lipoprotein cholesterol (LDL-C). While its lipid-lowering efficacy is well established, the broader transcriptomic consequences of PCSK9 inhibition across the liver-brain axis remain incompletely understood.Bulk RNA sequencing was performed on liver, hippocampal, and prefrontal cortex (PFC) tissues collected from alirocumab-treated and untreated rats. Differential gene expression analysis was conducted using DESeq2 with significance thresholds of false discovery rate (FDR) < 0.05 and log2 fold change$| \geq 0.58$. Functional enrichment was assessed using Gene Set Enrichment Analysis (GSEA) and Over-Representation Analysis (ORA) across Gene Ontology (GO), KEGG, Reactome and STRING. Alirocumab induced extensive transcriptomic remodeling across hepatic and brain-associated tissues. In liver, the dominant molecular signature was characterized by negative enrichment of oxidative phosphorylation, respiratory electron transport, mitochondrial ATP synthesis, and ribosomal pathways, driven primarily by mitochondrial respiratory chain genes including *Nduf*, *Cox*, *Uqcr*, and *Atp5* family members. Concurrently, receptor-mediated signaling and lipid regulatory pathways demonstrated positive enrichment, involving genes linked to LDLR-associated signaling and cholesterol homeostasis, including *Ldlr*, *Lrp1*, *Lrp5*, *Lrp6*, *Sort1*, *Apoe*, *Insr*, *Rxra*, *Ppard*, *Tgfbr1*, and *Tgfbr2*. Hippocampal and PFC analyses similarly revealed enrichment of mitochondrial respiration, oxidative phosphorylation, synaptic signaling, neuronal projection organization, translational regulation, and neurodegeneration-associated pathways, including Parkinson’s disease, Huntington’s disease, and Alzheimer’s disease. Additional enrichment of neuronal signaling and remodeling genes, including *Ngfr* and *Fgf22*, suggested indirect modulation of synaptic and neuroplasticity-related pathways. STRING PPI analysis identified highly interconnected modules linking mitochondrial respiratory function, LDLR-associated lipid metabolism, receptor-mediated signaling, and neuronal remodeling pathways. Because alirocumab does not efficiently cross the blood-brain barrier, the observed hippocampal and prefrontal cortex transcriptomic alterations likely reflect indirect downstream effects of peripheral metabolic regulation. These findings suggest that PCSK9 inhibition exerts broader biological effects beyond LDL-C lowering and may influence mitochondrial and cellular stress-response networks across multiple tissues.

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Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.08/Web Only

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

Support: NIH NeuroBioBank Repositories Provided Brain Tissue

Title: Novel perspective on Alzheimer's disease: Linking MEN1 to cholinergic and synaptic changes in human postmortem brain tissue

Authors: *D.-A. CHOUDHARY[1], Z. KHAN[1,2], B. ABBAS[3], N. I. SYED[4,2];
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Abstract: Dementia affects over 55 million people worldwide and Alzheimer's disease (AD) is the leading cause. Despite significant progress in understanding amyloid-β and tau pathology, AD's fundamental mechanisms remain elusive. The Cholinergic Hypothesis proposes that degeneration of cholinergic synaptic pathways underlies deficits in learning, memory and cognition. MEN1, a tumor suppressor gene, encodes menin, a highly conserved scaffold protein involved in transcriptional regulation, DNA repair, and cell signaling. Prior studies show that MEN1 loss disrupts synapse formation, nicotinic acetylcholine receptor (nAChR) expression and clustering, learning, and memory, while MEN1 reintroduction rescues these deficits. Our laboratory previously demonstrated, for the first time, menin in the cortex and the hippocampus of human AD brains. However, transcriptional-level evidence of MEN1 expression in the human brain remains lacking and warrants further investigation. Human entorhinal cortex tissue from late-onset AD groups and non-AD controls was analyzed for transcriptional perturbations in MEN1, alongside genes implicated in amyloid (APP), tau (MAPT), and cholinergic (nAChR5, nAChR7) pathology, and synaptic function (DLG4, SYP). Total RNA was isolated, reverse-transcribed, and gene expression was quantified using qPCR. Relative expression was calculated using the ΔΔCt method, normalised to a housekeeping gene (ACTB), and compared using the Mann-Whitney test. In this exploratory dataset, MEN1 expression was elevated by an average of 8.9-fold in late-onset AD tissue (n=3) relative to controls (n=3). Similar upward trend was observed in genes encoding α7 nAChR and α5 nAChR subunits previously shown to be regulated by menin. DLG4, encoding a synaptic scaffolding protein PSD-95 involved in receptor clustering, stability, and recruitment, also showed increased expression. In contrast, MAPT and APP770 trended toward lower expression in AD samples. These data extend prior protein-level observations of menin in the human AD brain by providing evidence of MEN1 upregulation in the AD entorhinal cortex. Together with coordinated changes in synaptic genes and prior evidence linking menin to cholinergic synapse formation, suggests that MEN1 may be involved in compensatory or neuroprotective mechanisms aimed at preserving synaptic integrity. Its upregulation may also reflect broader cellular stress responses in AD. These findings highlight

the novel role of menin as a potential regulator of cholinergic synapse vulnerability, providing valuable insights into the mechanisms underlying AD and identifying MEN1 as a compelling candidate in AD research.

Disclosures: D. Choudhary: None. **Z. Khan:** None. **B. Abbas:** None. **N.I. Syed:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.09/T15

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

Support: 5R01 AG072643-04

Title: NPTX2-Centered Cognitive Resilience Mechanisms in the Context of AD Pathology

Authors: *Y. LAO[1], M. XIAO[3], S. JI[2], I. S. PIRAS[4], K. KIM[6], A. BONFITTO[7], S. SONG[5], A. ALDABERGENOVA[8], M.-M. MESULAM[9], T. GEFEN[10], A. TREJO[11], C.-H. NA[12], J. SLOAN[13], C. GEULA[14], E. J. ROGALSKI[15], C. H. KAWAS[16], M. CORRADA[16], G. E. SERRANO[17], T. G. BEACH[18], J. C. TRONCOSO[19], M. HUENTELMAN[4], C. A. BARNES[20], P. F. WORLEY[21], C. COLANTUONI[22];
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Abstract: Cognitive resilience to Alzheimer's disease neuropathologic change (ADNC) is associated with preserved NPTX2, an activity-regulated synaptic protein involved in circuit plasticity, excitation-inhibition balance, and complement-linked synapse regulation. The broader molecular programs coordinated with NPTX2 in resilient individuals remain unclear. We analyzed postmortem middle temporal gyrus using targeted PRM-MS (135 individuals) and bulk RNA-seq (575 samples). NPTX2-associated coordination was assessed across cognitively

normal low-pathology controls (CN-LoPath), cognitively normal high-pathology controls representing preservation despite ADNC (CN-HiPath/resilient), and impaired MCI and AD phenotypes with ADNC. Correlation-based trajectory frameworks used NPTX2 protein and mRNA as anchors; resilient candidates were transcripts preserved or recruited between CN-LoPath and CN-HiPath but reciprocally altered in MCI and AD. NPTX2 protein was preserved across all controls regardless of age and pathology, but reduced in MCI and AD versus CN-HiPath. Proteomics identified preserved NPTX2 relationships with synaptic and inhibitory-circuit proteins, plus CN-HiPath-specific recruitment of trafficking, lysosomal, metabolic, and proteostasis proteins. Transcriptome-wide analyses revealed a CN-HiPath-preserved activity-dependent program (BDNF, VGF, SCG2, SST, SERTM1, DUSP4, EGR4), while CN-HiPath-recruited genes implicated immune, neuroprotective, translation, and proteostasis pathways. Resilient analysis identified eight candidates—SST, NRN1, SLC17A6, PCP4, MAL2, CMAS, RFK, SERTM1—preserved in CN-HiPath but altered in MCI and AD. Findings suggest resilience engages a coordinated molecular state distinct from normative aging and AD, organized around preserved and selectively remodeled NPTX2-associated relationships. Rather than broad transcript abundance changes, resilience was characterized by maintained synaptic and inhibitory programs and adaptive proteostasis and trafficking pathways, distinguishing cognitively preserved high-pathology individuals from impaired AD, while identifying programs shared with low-pathology cognitively normal aging.

Disclosures: Y. Lao: A. Employment/Salary (full or part-time):; Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine. **M. Xiao:** A. Employment/Salary (full or part-time):; Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine. **S. Ji:** A. Employment/Salary (full or part-time):; Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine. **I.S. Piras:** A. Employment/Salary (full or part-time):; Translational Genomics Research Institute. **K. Kim:** A. Employment/Salary (full or part-time):; Department of Neurology, Institute for Cell Engineering, Johns Hopkins University School of Medicine. **A. Bonfitto:** A. Employment/Salary (full or part-time):; Translational Genomics Research Institute. **S. Song:** A. Employment/Salary (full or part-time):; Translational Genomics Research Institute. **A. Aldabergenova:** A. Employment/Salary (full or part-time):; Translational Genomics Research Institute. **M. Mesulam:** A. Employment/Salary (full or part-time):; Mesulam Institute for Cognitive Neurology & Alzheimer's Disease, Northwestern University School of Medicine. **T. Gefen:** A. Employment/Salary (full or part-time):; Mesulam Institute for Cognitive Neurology & Alzheimer's Disease, Northwestern University School of Medicine. **A. Trejo:** A. Employment/Salary (full or part-time):; Translational Genomics Research Institute. **C. Na:** A. Employment/Salary (full or part-time):; Department of Neurology, Institute for Cell Engineering, Johns Hopkins University School of Medicine. **J. Sloan:** A. Employment/Salary (full or part-time):; Translational Genomics Research Institute. **C. Geula:** A. Employment/Salary (full or part-time):; Mesulam Institute for Cognitive Neurology & Alzheimer's Disease, Northwestern University School of Medicine. **E.J. Rogalski:** A. Employment/Salary (full or part-time):; Healthy Aging & Alzheimer's Research Care (HAARC) Center, University of Chicago. **C.H. Kawas:** A. Employment/Salary (full or part-time):; University of California, Irvine. **M. Corrada:** A. Employment/Salary (full or part-time):; University of California, Irvine. **G.E. Serrano:** A. Employment/Salary (full or part-time):; Banner Sun Health Research Institute. **T.G. Beach:** A. Employment/Salary (full or part-time):; Banner Sun Health Research Institute. **J.C. Troncoso:** A. Employment/Salary (full or part-time):; Department of Pathology, Johns Hopkins

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Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.10/T16

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

Title: Investigating the Role of the Psychiatric Risk Gene ZNF804A in Alzheimer’s Disease

Authors: *T. PURI[1], J. MOTT[3], Y. MAO[2];
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[3]Pennsylvania State Univ., University Park, PA

Abstract: Emerging evidence suggests a profound, yet poorly understood, molecular overlap between psychiatric vulnerability and neurodegenerative disease processes. Genetic risk factors historically associated with psychiatric disorders are increasingly recognized as active modulators of homeostatic maintenance in the aging brain, though their mechanisms remain elusive. ZNF804A represents a prominent psychiatric risk gene that may act as a novel link to Alzheimer’s disease (AD) pathology through post-transcriptional regulation, yet its specific role in modulating the transcript-specific binding landscape in AD has not yet been defined. We used RNA Immunoprecipitation Sequencing (RIP-seq) on whole mouse brains from wild-type (n = 3 females) and 5xFAD (n = 3 males, 3 females) mice to characterize the target RNA binding features of ZNF804A. In addition to standard input controls, we utilized this high-throughput sequencing approach to follow the shifting landscape of ZNF804A-mRNA interactions. Bioinformatic pipelines were then applied to map differential enrichment and cluster targets across functional biological pathways, establishing a framework for downstream mechanistic validation. We find that the ZNF804A-bound RNA landscape undergoes a robust, coordinated reorganization in the diseased brain, showing distinct directional shifts related to specific cellular pathways that differ from expressions in the healthy control state. For example, there is evidence for clear alterations in pathways connected to cellular homeostatic maintenance. Transcripts showing a significant gain in ZNF804A binding in the disease context are heavily concentrated in synapse assembly and cell-signaling pathways, in contrast to a significant loss of binding to transcripts responsible for intracellular vesicle organization and endosomal trafficking. These molecular maps reveal more about the hierarchical role of psychiatric risk factors operating as post-transcriptional regulators in mature neurodegenerative states. Our results suggest that

ZNF804A selectively redirects translational control away from protective traffic machinery toward synaptic assembly pathways. These maps provide a precise biochemical foundation for future directions, which will focus on using nascent proteomics and targeted cell-type assays to isolate the direct functional consequences of these vesicular and synaptic binding shifts.

Disclosures: T. Puri: None. **J. Mott:** None. **Y. Mao:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.11/T17

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

Support: NIH R01 AG071859-01A1
NIH R01AG073826-01A1

Title: A Dopaminoceptive Hippocampal Interneuron Associated with Cognitive Severity Links Retinoic Acid, Circadian Signaling, and Synaptic Scaffolding Failure in the J20 Alzheimer's Mouse Model

Authors: *P. LIE[1,6,2,3,7], A. BAKER[4,6,2,3], D. SELF[4,6,2], N. KHANNA[4,6,8], C. ZHANG[5,4], S. SALINAS[4,6], S. SMITH[4,6,7], S. SKAWRATANANOND[5], B. R. KISBY[4,2,6], S. SHANMUGAM[4,9], I. PONOMAREV[4,6,2,10,9], M. TELIAS[11,12], J. J. LAWRENCE[4,6,2,10,13]; [2]Grad. Sch. of Biomed. Sci., [3]M.D./Ph.D. Program, [4]Pharmacol. and Neurosci., [5]Sch. of Med., [1]Texas Tech. Hlth. Sci. Ctr., Lubbock, TX; [6]Garrison Inst. on Aging, Lubbock, TX; [7]Julia Jones Sch. of Population and Publ. Hlth., Abilene, TX; [8]TTU Ctr. for Biotech. and Genomics, Lubbock, TX; [9]South Plains Alcohol and Addiction Res. Ctr., Lubbock, TX; [10]Ctr. of Excellence for Translational Neurosci. and Therapeut., Lubbock, TX; [11]Mol. and Cell Biol., Univ. of Pittsburgh, Pittsburgh, PA; [12]Flaum Eye Inst., Rochester, NY; [13]Ctr. of Excellence for Integrative Hlth., & Ctr. for Membrane Protein Res., Lubbock, TX

Abstract: Dysfunction of the dentate gyrus (DG) is an early prognostic feature of Alzheimer's disease (AD), but the circuits and molecular pathways linking amyloid pathology to learning impairment remain poorly understood. Using hybrid J20 AD/RARE-LacZ transgenic mice under vitamin A normal (VAN), deficient (VAD), and supplemented (VAS) conditions, we integrated computational ethology-based water T-maze (WTM) analyses (DeepLabCut/MoSeq, n=192, two independent cohorts), snRNA-seq (274k nuclei, 96 mice, four conditions), pseudobulk DE, entropy/KLD linear mixed models, retinoic acid (RA) signaling, and CellChat. J20 mice showed a robust acquisition deficit across both cohorts (OLS β=+0.679, p=0.0005); reversal rigidity was strongest in the VAD cohort (KLD p=0.0004). VAS did not rescue path length or KLD. MoSeq identified a conserved looping syllable in J20 (LME p=0.001), loss of a navigation motif in reversal (p=0.008), and a positive KLD/entropy relationship (β=+0.069, p<0.001), indicating rigid animals search chaotically rather than adopting a stable strategy. snRNA-seq identified a

total molecular layer cell (TMLC)-like GABAergic population in the hippocampus with an MSN-like dopaminergic signature (Gpr88/Meis2/Rgs9/Adora2a, hemisegregated Drd1/Drd2), high Rarb expression, and Rora-dominant clock gene burden. RA-active (LacZ+) TMLC-like fraction tracked reversal rigidity across all animals (rho=+0.440, p=0.005). RARE-LacZ data reveal these cells are receptor-maximal but potentially ligand-limited (1-7% LacZ+), while DGGC LacZ surged 8-fold in J20 (3.4%→27.1%); LacZ+ cells expressed more Rara, Bdnf, Ext1, St8sia2, and Nrxn3 (p<0.0001). Rarb predicted Nrxn3 within TMLC-like cells (rho=+0.913, p<0.0001) and Rora predicted Nrxn3 independently (rho=+0.979, p<0.0001). CellChat and pseudobulk DE identified hilar mossy cells (HMC) as a disease-activated node: HMC→TMLC Nrxn3-Nlgn1 signaling falls 5.6-fold WT/VAN→J20/VAD; HMC Rara and Nrxn3 are nominally higher in J20/VAN vs J20/VAD (p=0.021, p=0.074), consistent with RA-dependent maintenance lost in the two-hit condition. VAD also reduced Nrxn3 across cell types (LME p=0.037), suppressed Npy in DGGC under J20/VAD (padj=0.005), and drove Cyp26b1 upregulation in canonical interneurons under J20/VAD (padj=0.017), establishing a competing RA catabolism sink at the circuit level. These data support two RA-dependent convergent arms, RARβ/RORα→clock→Nrxn3 and Ext2→heparan sulfate→GPC4/Lrrtm4, to stabilize DGGC synaptic gating; failure of this axis, compounded by interneuron-mediated RA catabolism, links amyloid stress, RA depletion, and behavioral rigidity.

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Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.12/T18

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

Support: RS-2023-00302751
RS-2026-25508103

Title: The role of miR-126 in the pathological network of Alzheimer's disease

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Abstract: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, neuronal degeneration, and impaired metabolism, particularly within the hippocampus and entorhinal cortex. MicroRNAs (miRNAs) are small non-coding RNAs

involved in diverse cellular functions—including signaling, cellular homeostasis, and stress responses—by regulating gene expression at the post-transcriptional level. Recently, miR-126, a known regulator of angiogenesis and vascular integrity in endothelial cells, has emerged as a novel modulator in multiple neurodegenerative diseases, including AD and Parkinson's disease. While previous studies have shown that miR-126 expression increases in Aβ1-42 treated cortical and hippocampal neurons, thereby influencing PI3K/AKT/GSK-3β and ERK signaling, its precise downstream molecular mechanisms in neuronal cells remain poorly understood. In this study, we aimed to reveal the specific molecular pathways driven by miR-126 in an AD model. To profile these changes under an Aβ1-42-induced pathological environment, we transduced Neuro-2a (N2a) cells with a lentivirus overexpressing miR-126 or a control vector, followed by bulk RNA and small RNA sequencing. Notably, the differentially expressed gene (DEG) profiles of miR-126-transduced cells included PFKFB1 (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 1), a bifunctional enzyme that regulates the steady-state concentration of fructose-2,6-bisphosphate (F-2,6-BP). Because F-2,6-BP is the most potent allosteric activator of PFK-1, the major rate-limiting enzyme of glycolysis, these findings suggest a direct link to glucose metabolism. To confirm these roles in AD pathology, selected DEGs were functionally evaluated in vitro using siRNA and miRNA mimics. Together, these findings elucidate a novel, miR-126-driven molecular pathway that may represent a potential target for future AD therapeutics.

Disclosures: H. Choi: None. **H. Noh:** None. **Y. Park:** None. **K.C. Sonntag:** None. **H. Seo:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.13/T19

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

Support: 5R01AG077692-05

Title: Altered Transcriptomic Signatures in Alzheimer's Disease Patients with Seizures

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Abstract: Rationale. Seizures are highly comorbid with Alzheimer's disease (AD) and have been linked to worsening pathology and cognitive decline. A key hallmark of AD progression is the spread of pathological tau along neuronal connections. Prior studies have shown that seizure history exacerbates cognitive deficits, tau, and amyloid beta pathology. Given the long-term changes induced by seizures we thus assessed transcriptomic alterations. How seizures impact

the transcriptional signatures of patients with AD remains unknown. We hypothesize that AD patients with seizures will have transcriptomic changes in pathways that mediate neurodegeneration, synaptic transmission, and plasticity and that these changes will be highly expressed in excitatory neurons.**Methods.** To determine whether genes mediating synaptic transmission and plasticity are differentially regulated in excitatory neurons, we processed cortical tissue from post-mortem brain tissue. We compared sequencing data from 4 control participants, 4 AD patients without seizures (AD-SZ), and 4 AD patients with seizures (AD+SZ) (total of n=12). We used the BD Rhapsody system for single-nucleus RNA-seq (snRNAseq). The nuclei were isolated from flash frozen post-mortem brain tissue. Isolated nuclei were loaded onto BD Rhapsody HT Xpress. Bioinformatic analyses using Seurat and enrichR enabled the identification of cell types, differential gene expression, and comparisons against established online gene datasets relevant to synaptic function (SynGO Synaptic Gene Ontologies Consortium) and neurological disorders (DisGeNET Gene-Disease Associations Database).**Results.** After comparing AD+SZ and AD-SZ we found that genes implicated in vesicle-mediated transport at the synapse, regulation of neuron projection development, and postsynaptic density in excitatory neurons were upregulated. When we compared the excitatory neurons of AD+SZ to the control participants, we found that genes implicated in the regulation of trans-synaptic signaling and the modulation of chemical synaptic transmission were downregulated while postsynaptic specialization and ion channel activity was upregulated. Our single snRNA-seq dataset provides a powerful resource by which we can investigate why patient decline is worsened in the presence of seizures.

Disclosures: A. Chavez: None. **D.M. Talos:** None. **F.E. Jensen:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.14/T20

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

Support: NIH grant 5U24AG061340-08

Title: The AD Knowledge Portal Cohort Discovery Tool: Cross-Study Data Discovery in Alzheimer's Disease Research

Authors: *E. K. COSTA, T. ZINTEL, T. ADAMS, S. AHMED, P. ATRI, R. AYYALA, J. BECK, J. S. BRITTON, A. CAMPTON, J. DRISCOLL, J. GRAY, A. KALLAHER, M. KLEIN, K. LEAL, J. LUNDIN, J. MALENFANT, E. D. NELSON, A. PENA, W. POEHLMAN, B. SALDANA, J. SCANLAN, Z. L. SPACE, M. VU, C. SUVER, S. VARMA, L. HEATH; Sage Bionetworks, Seattle, WA

Abstract: The Sage Bionetworks Alzheimer's Disease Knowledge Portal (ADKP) is an NIH-designated data repository for multi-omic data from both human and model systems, enabling

broad access to raw and processed omics data, analytical methodology, and research tools generated by the AD research community. Many ADKP studies draw from shared patient biobanks, meaning the same individuals have been profiled across several omic modalities by different research groups and deposited as separate studies. Despite this wealth of data, interoperability has remained a challenge: a single participant may carry different IDs across studies, their data may be distributed across dozens of files, and the ADKP was built to query files rather than people, leaving researchers with no simple way to identify all data corresponding to a given patient. The ADKP Cohort Discovery (CD) tool was developed to enable users to explore participant data availability in a study-agnostic-manner, based on any combination of available phenotypic attributes. CD supports two primary use cases: identifying all individuals meeting a defined set of criteria (e.g. female participants over age 80 with both RNA-seq and proteomics data), and retrieving all files across the portal for a given set of individual identifiers. This tool is available to all ADKP visitors, enabling researchers to assess data sufficiency before committing to a data request, and without compromising data privacy. CD is powered by a data pipeline that addresses the core technical challenge of linking individuals to files across a file-oriented repository. File-level annotations, standardized to a community-maintained data model, are integrated with harmonized phenotypic metadata consistent with field standards (e.g. ADSP-PHC). A relational database structure joins these using database objects that enable real-time querying across the individual-to-file mappings. This architecture supports cross-study queries on attributes including diagnosis, tissue, and assay without requiring users to navigate the underlying file structure. CD currently integrates data across some of the Portal's most often accessed cohorts, including AMP-AD Diverse Cohorts, SEA-AD, and MSBB, and is being continually expanded. By making participant metadata modeling a first-class feature of the ADKP and positioning the portal as an interoperable node within the broader AD data ecosystem, the CD tool enables the kind of multi-modal, cross-study analyses essential for understanding disease heterogeneity and progression in human populations, while upholding sound data governance and transparent, FAIR-aligned research practices.

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Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.15/T21

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

Support: CIHR Grant PJT-178123
Tier-1 Canada Research Chair 2023-00155
Queen's Research Initiation Grant
Bruce Mitchell Research Program - Doctoral Trainees fund

Title: Skeletal Muscle Transcriptomic Remodeling Associated with Exercise-Induced Cognitive Rescue in APP/PS1 Mice

Authors: *R. C. GEISLER[1], N. L. SILVA[1,2], F. G. DE FELICE[1,2,3,4];
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Abstract: Physical exercise attenuates cognitive decline in Alzheimer's disease (AD) models, likely exerting effects through the skeletal muscle-brain axis. While extensive literature demonstrates the systemic benefits of exercise in neurodegeneration, the specific alterations in the skeletal muscle molecular transcriptome associated with cognitive improvement remain largely enigmatic. To address this knowledge gap, 11-13-month-old male and female APP/PS1 transgenic mice and wild-type (WT) controls were assigned to either a 5-week forced swimming protocol or to sedentary housing, yielding four experimental groups. Following the intervention, behavioural outcomes were assessed using the novel object recognition task and the open field test. Sedentary APP/PS1 mice showed significant impairments in object recognition memory compared with sedentary WT controls, as evidenced by reduced discrimination index scores. The 5-week swimming intervention reversed these behavioural deficits in APP/PS1 mice, restoring performance to WT levels. No significant baseline differences in locomotor activity or exploration were observed among the four groups, indicating that the recognition memory deficit was not attributable to motor impairment or anxiety. Characterization of the peripheral transcriptomic landscape across all groups were carried out by Bulk RNA-sequencing on isolated right gastrocnemius tissue. This study seeks to map changes in the muscle transcriptome to specific behavioural outcomes in an APP/PS1 transgenic model, thereby identifying novel peripheral targets for AD intervention.

Disclosures: R.C. Geisler: None. **N.L. Silva:** None. **F.G. De Felice:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.16/T22

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

Support: NIH/NINDS RF1-NS113548-01A1
NIH/NIA R01 AG057522
NIH/NIA RF1 AG077695

Title: Long-Read Transcriptomic Gene Expression Reveals Alzheimer's Disease Associated Isoform Diversity in an African American Ancestry Cohort

Authors: *S. VENKATESAN[1], E. SHWAB[2], D. HODGSON[2], O. CHIBA-FALEK[2];
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Abstract: An estimated 7.4 million Americans currently live with late-onset Alzheimer's disease (LOAD), with the approximate economic value of care at $446.3 billion (Alzheimer's Association, 2026). LOAD outcomes also vary across demographic populations. In the United States, African Americans (AA) experience a dementia risk 40% higher than European Americans (EA) (Mayeda et al., 2016). While socioeconomic factors may contribute to these outcomes, there is also strong evidence for a genetic component, with LOAD-relevant polymorphisms being shared among those of AA ancestry (Rosenthal et al., 2014, Barnes & Bennett, 2014). This study examines the genetic underpinnings of LOAD in AA ancestry by utilizing a high-resolution long-read single-cell sequencing approach to analyze changes in gene expression across cell types between LOAD and control temporal cortex samples from AA donors. This long-read sequencing approach enabled transcriptome-wide profiling of full-length transcript expression within specific cell types, providing regulatory insight into alternative splicing, isoform diversity, and transcript structural variation. These factors currently remain poorly characterized in LOAD, particularly in AA populations. We first performed a gene-level differential expression analysis and identified broad LOAD-associated changes in gene expression within specific cell types, particularly in excitatory neurons. Differentially-expressed gene sets were enriched for genes relating to biological pathways relevant to LOAD, such as synaptic function, myelination, intracellular signaling, and protein processing. Next, we examined transcript isoform-level expression patterns in a mixed AA and EA dataset, and catalogued 585,097 unique isoforms representing splicing variants of 6,294 genes, with 35% of identified transcript isoforms representing novel splice variants. Finally, based on single-cell annotations, specific transcript isoforms were mapped to specific cell types, and we performed differential expression analysis at the isoform level to identify splicing variants with altered abundance in LOAD across ancestries. This work provides valuable new insight into the transcriptional mechanisms underpinning LOAD in different ancestral demographics and paves the way for future translational research to develop precision medicine strategies for combatting this disease within specific patient populations.

Disclosures: S. Venkatesan: None. **E. Shwab:** None. **D. Hodgson:** None. **O. Chiba-Falek:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.17/T23

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

Title: Systemic Aging Factors and Impaired Microglial Mitochondrial Function Promote Alzheimer's Disease-Related Molecular Alterations

Authors: F. CHU[1], ***Q. WANG**[2];
[1]iLar Res. Inst., San Jose, CA; [2]iLab research Inst., Mountain View, CA

Abstract: Background: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by memory loss, cognitive decline, behavioral changes, neuroinflammation, and widespread disruption of cellular metabolism. Despite extensive research, there is currently no curative treatment.**Methods:** To investigate molecular mechanisms linking aging, mitochondrial function, and neurodegeneration, two publicly available transcriptomic datasets were analyzed: GSE270289 and GSE269239. GSE270289 examined the effects of circulating factors from young and older individuals on circadian gene expression in human fibroblasts, whereas GSE269239 investigated the role of mitochondrial respiration in microglial responses to demyelinating injury. Bulk RNA-seq data were reanalyzed by R. Lowly expressed genes were filtered, library sizes were normalized, and differential gene expression analysis was performed using edgeR. Principal component analysis, hierarchical clustering, heatmap visualization, and pathway enrichment analyses were used to characterize transcriptomic differences and identify biological processes associated with aging and neurodegeneration.**Results:** Analysis of GSE270289 revealed age-dependent remodeling of circadian transcriptional programs. Fibroblasts exposed to blood-borne factors from older individuals showed reduced rhythmicity in genes associated with oxidative phosphorylation, mitochondrial energy production, and neurodegenerative disease pathways, including pathways linked to AD. These findings suggest that systemic aging factors may disrupt normal circadian regulation of cellular metabolism and weaken mitochondrial homeostasis. Analysis of GSE269239 demonstrated that impaired mitochondrial respiration substantially altered the microglial transcriptional profile. Mitochondrial dysfunction reduced the expression of genes involved in phagocytosis, lysosomal activity, immune regulation, and cellular energy metabolism, while increasing inflammatory and stress-related signaling. These alterations were associated with reduced microglial capacity to respond to tissue injury and may impair amyloid-β uptake and plaque clearance during the early stages of AD.**Conclusion:** These integrative analysis findings highlight potential interactions among circadian dysregulation, mitochondrial failure, oxidative stress, and neuroinflammation in AD pathogenesis. These pathways may provide mechanistic insight into how systemic aging contributes to neurodegeneration and may identify potential biomarkers or therapeutic targets to slow AD progression.

Disclosures: F. Chu: None. **Q. Wang:** None.

Poster

PSTR126: Alzheimer's Disease: Transcriptomics and Genomics

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR126.18/T24

Topic: J.01. Molecular, Biochemical, and Genetic Techniques

Support: Ministry of Trade, Industry & Energy (MOTIE) Grant 20024391
Ministry of Trade, Industry & Energy (MOTIE) Grant RS-2024-00451981
Ministry of Trade, Industry & Energy (MOTIE) Grant RS-2024-00508420
National Research Foundation of Korea (NRF) Grant RS-2024-00454407

Title: SLACS-enabled spatial transcriptomic profiling reveals APOE-dependent GLP-1R signaling states in plaque-associated microglia of human brain assembloids

Authors: *Y. LEE, S. LEE, A. C. LEE;
Meteor Biotech Co., Ltd, Seoul, Korea, Republic of

Abstract: Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as promising therapeutic candidates for Alzheimer's disease (AD), yet the influence of APOE genotype on GLP-1R-associated microglial programs within plaque-associated microenvironments remains poorly understood. Resolving such spatially defined cellular states requires approaches capable of selectively isolating cells while preserving disease-relevant spatial context. To address this challenge, we applied Spatially-resolved Laser Activated Cell Sorting (SLACS), a spatially resolved cell isolation technology that enables selective recovery of cells from defined pathological microenvironments for downstream molecular profiling. To investigate APOE-dependent microglial states, we established a panel of isogenic induced pluripotent stem cell (iPSC) lines representing four APOE genotypes (APOE2/2, APOE3/3, APOE3/4, and APOE4/4). Microglia and brain organoids were independently differentiated from each genotype and subsequently co-assembled to generate APOE-defined human brain assembloids recapitulating key features of the amyloid-β (Aβ) plaque microenvironment. Using SLACS, plaque-associated and plaque-free microglia were selectively isolated from assembloid sections and subjected to transcriptomic profiling, enabling systematic characterization of microglial states according to both plaque proximity and APOE background. Our analyses revealed APOE genotype-dependent differences in GLP-1R-associated molecular programs within plaque-associated microglia. While shared molecular alterations associated with plaque proximity were observed across genotypes, distinct genotype-dependent transcriptional states were identified within disease-relevant microenvironments. These findings suggest that APOE background influences microglial responsiveness to GLP-1R-associated signaling. Together, these results demonstrate the utility of SLACS-enabled spatial transcriptomics for resolving genotype-dependent cellular states within neurodegenerative microenvironments and highlight its potential for investigating therapeutic response mechanisms that may not be readily captured using conventional bulk or dissociated-cell approaches.

Disclosures: Y. Lee: None. **S. Lee:** None. **A.C. Lee:** None.

Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.01/T25

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

Support: NIH Grant 5R01AG063975

Title: Baseline plasma brain-derived tau predicts cognitive response to virtual mind-body exercise in subjective cognitive decline

Authors: *N. YANG[1], V. SACCA[1], Q. QUAN[2], B. SIEGEL[1], J. KONG[1];
[1]Dept. of Psychiatry, Massachusetts Gen. Hosp., Boston, MA; [2]NanoMosaic Inc, Waltham, MA

Abstract: Subjective cognitive decline (SCD) is an early risk stage for Alzheimer's disease (AD), yet biomarkers that identify individuals most likely to benefit from behavioral interventions remain poorly defined. We examined whether baseline plasma brain-derived tau (BD-tau) or pTau217 predicts cognitive improvement during a remotely delivered mind-body exercise intervention. Community-dwelling adults aged 50-80 years with SCD were randomized to tele-coached Baduanjin (BDJ) or matched-duration cognitive fitness training. Cognitive performance was assessed using the Preclinical Alzheimer Cognitive Composite (PACC) at baseline and 6 months. Baseline plasma BD-tau and pTau217 were quantified. Multivariable regression models examined associations between baseline biomarkers and 6-month change in PACC (ΔPACC), adjusting for baseline cognition and demographic and study variables. Forty-three participants were included (BDJ, n=23; cognitive fitness, n=20). PACC improved from baseline to 6 months in both groups, with no significant between-group difference (p=0.789). In adjusted analyses, log-transformed, but not raw BD-tau predicted ΔPACC (95% CI: 0.011-1.101, p=0.046). Stratified analyses showed that both raw and log-transformed BD-tau predicted ΔPACC in the BDJ group (p=0.008 and p=0.004, respectively), whereas no significant associations were observed in the cognitive fitness group. Neither pTau217 nor log-transformed pTau217 predicted ΔPACC. These findings suggest that plasma BD-tau may identify older adults with SCD who are most likely to benefit from BDJ. BD-tau warrants further investigation as a biomarker for stratifying responsiveness to behavioral interventions and informing precision prevention approaches in preclinical AD.

Disclosures: N. Yang: None. **V. Sacca:** None. **Q. Quan:** None. **B. Siegel:** None. **J. Kong:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Equity in MNT and BTT startup; inventor on granted patent US 2018/0339148 plus pending applications.

Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.02/T26

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

Support: R01AG068330
R01AG093847

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CART Fund
Cure Alzehimer's Fund
P30GM127211
R25AG092311

Title: Glyburide Mitigates Tau Pathology and Restores Neuroimmune and Metabolic Homeostasis in P301S Tauopathy Mice

Authors: *S. M. TURNER[1], J. GRIZZANTI[5], A. SNIPES[2], R. IRMEN[3], M. PAIT[5], S. L. MACAULEY[4];
[1]Mol. and Cell. Biochem., [3]Neurosci., [4]Physiol., [2]Univ. of Kentucky, Lexington, KY; [5]Wake Forest Sch. of Med., Winston Salem, NC

Abstract: Neuroinflammation, metabolic dysfunction, and neurodegeneration are central features of Alzheimer's Disease (AD) and related tauopathies. Since ATP sensitive potassium (KATP) channels regulate cellular metabolism, neurovascular coupling, inflammatory signaling, and pathology, pharmacological inhibition of these channels may provide therapeutic benefit. Here we investigated whether chronic KATP channel inhibition with glyburide modulates tau pathology, neuroimmune responses, neuronal health, and neurodegeneration in the P301S PS19 mouse model of tauopathy. Slow release glyburide or placebo pellets were implanted subcutaneously in 5 month old P301S PS19 and wildtype mice for three months. Interstitial fluid (ISF) tau and lactate were measured by *in vivo* microdialysis. Following treatment, tau pathology (AT8), neuronal abundance (NeuN), lysosomal autophagic markers (LAMP1, p62), neuroinflammatory markers (Iba1, GFAP), and transcriptomic changes were assessed in the hippocampus and cortex. Glyburide treatment reduced ISF tau and caused a trending decrease in ISF lactate levels, consistent with altered tau dynamics and metabolic activity. Transcriptomic analysis demonstrated normalization of neuroimmune and inflammatory pathways including reduced signatures associated with reactive microglia, astrocytes, and neuroinflammation. Concurrently, glyburide enhanced pathways involved in mitochondrial ATP production, protein synthesis, autophagy, and lysosomal function, suggesting metabolic and proteostatic homeostasis. These molecular changes were accompanied by increased neuronal number, modulation of lysosomal-autophagic markers, reduced glial reactivity, and perserved cortical structure. Glyburide also altered tau pathology, decreasing somatic AT8 positive tau accumulation and changing neuronal AT8 localization, suggesting redistribution of tau. Collectively, these findings indicate that glyburide attenuates tau-associated pathology while supporting neuronal maintenance and resilience. These results demonstrate that KATP channel inhibition with glyburide mitigates tau pathology, normalizes neuroimmune and metabolic dysfunction, and prevents neurodegenerative changes. Thus, targeting KATP channels represents a promising therapeutic strategy in tauopathies.

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Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.03/Web Only

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

Support: ARC-NL Graduate Fellowship 2025
CIHR Project Grant PJT-197770

Title: Modulation of the Gut-Brain Axis Protects Against Cognitive Dysfunction in a Locus Coeruleus Pretangle Tau Model

Authors: *H. M. STAPLETON[1], T. OMOLUABI[2], O. BELOLISE[1], J. SETIAWAN[3], S. HASAN[2], Q. YUAN[4];
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Abstract: Alzheimer's disease (AD) is the leading cause of dementia worldwide and remains incurable. The gut-brain axis has emerged as a promising target for modifiable risk factors. Gut dysbiosis can accelerate neuroinflammation and early AD tau pathology, while preclinical studies suggest probiotics may restore gut health and improve cognition. However, little is known about sex-specific effects, despite women accounting for nearly two-thirds of AD cases. This study investigates whether maintaining gut health protects against early AD-like changes and whether these mechanisms differ by sex.

To model early tau pathology, human pre-tangle tau (hTauE14) was selectively expressed in the locus coeruleus (LC) of male and female tyrosine hydroxylase (TH)-Cre rats of both sexes via AAV infusion at 3 months of age, mimicking pretangle tau origin in humans. At 6 months, rats were randomly assigned to one of four groups: hTauE14 or GFP (control) infusion combined with either a probiotic or control diet. Dietary supplementation with Probiotic-4 and the prebiotic fructooligosaccharide (FOS) lasted for 3 months. Between 10-12 months of age, blinded behavioral testing assessed locomotion, exploration, anxiety, odor and spatial discrimination. Statistical significance across diet, AAV, and sex groups was determined using 3-way ANOVA with post-hoc testing.

hTauE14-infused rats exhibited reduced exploration in the open field and elevated plus maze, increased anxiety-like behavior as indicated by greater marble burying, and deficits in odor discrimination and spatial memory. Probiotic supplementation reversed spatial learning impairments in Y-maze and spontaneous location recognition tests. No significant sex × diet or sex × AAV interactions were detected. Ongoing studies are investigating potential sex-dependent gut-to-brain biomarkers that may underlie tau pathology and probiotic treatment.

These findings suggest that probiotic supplementation may mitigate cognitive deficits associated with early tau pathology, supporting the gut-brain axis as a promising target for AD prevention. Ongoing molecular and microbiome analyses will determine whether sex-specific gut-to-brain mechanisms contribute to resilience or vulnerability during the earliest stages of disease progression.

Disclosures: H.M. Stapleton: None. **T. Omoluabi:** None. **O. Belolise:** None. **J. Setiawan:** None. **S. Hasan:** None. **Q. Yuan:** None.

Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.04/T27

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

Support: Alzheimer's Association Research Grant 25AARG-1375299

Title: Acidic nanoparticles as a lysosome restoration strategy to attenuate tau-mediated neurotoxicity in cellular and mouse models of tauopathy

Authors: *Y. ZHONG[1,2], D. MURPHY[1,2], K. ABD-ELRAOUF[1,2], Y. LIU[3,2], J. ZENG[3,2], C. LO[1,2];
[1]Biol., [2]Interdisciplinary Neurosci. Program, [3]Biomed. and Chem. Engin., Syracuse Univ., Syracuse, NY

Abstract: Lysosomal acidification is essential for maintaining proteostasis, and its disruption is increasingly implicated as an early event in Alzheimer's disease (AD) and related tauopathies. Reduced lysosomal acidity impairs proteolytic degradation, compromises autophagic flux, and is associated with progressive tau accumulation. While acidic nanoparticles (AcNPs) have the potential to restore lysosomal pH, their application in the brain is limited by the blood-brain barrier (BBB). To address this, we developed BBB-penetrating acidic nanoparticles (BBB-AcNPs) designed to enable brain delivery and promote lysosomal re-acidification. In a BBB transwell system, BBB-AcNPs were able to cross the barrier and were detected in neuronal compartments, supporting their transport capability. In tau-overexpressing mouse neuronal cultures, BBB-AcNP treatment improved tau clearance, increased cell viability, and reduced markers of tau-associated cellular stress, suggesting partial restoration of proteostatic function. We are currently extending this approach to the PS19 tauopathy mouse model expressing P301S mutant tau. Early in vivo observations suggest potential improvements in cognitive performance following systemic administration of BBB-AcNPs, and ongoing studies are assessing tau burden, neuroinflammatory responses, and broader neuropathological outcomes. Together, these findings provide initial support for BBB-penetrating acidic nanoparticles as a strategy to restore lysosomal function in tau-related neurodegeneration and motivate further investigation in in vivo disease models.

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Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.05/T28

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

Support: NRF Grant RS-2025-00560220

Title: Lysosomal Activation Protects Against Zinc-Induced Tau Hyperphosphorylation in Primary Cortical Neurons

Authors: *H. LEE[1,2], Y.-H. KIM[1,2];
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Abstract: Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by amyloid-β plaques and neurofibrillary tangles composed of hyperphosphorylated tau. Increasing evidence suggests that dysregulated zinc homeostasis contributes to AD progression by promoting protein aggregation, tau pathology, and neuronal dysfunction. Zinc enhances tau hyperphosphorylation through activation of kinase signaling pathways and inhibition of protein phosphatase 2A (PP2A). In the present study, we investigated the mechanisms underlying zinc-induced tau hyperphosphorylation and evaluated whether lysosomal activation could attenuate this pathological process in primary cortical neurons. Zinc induced tau phosphorylation in a concentration-dependent manner, whereas EDTA, an extracellular zinc chelator, significantly reduced it. Zinc-induced tau phosphorylation was accompanied by activation of Src family kinases and inhibition of PP2A. Both GM6001, a broad-spectrum MMP inhibitor, and ZCC1, a selective MMP-9 inhibitor developed in our laboratory, attenuated tau hyperphosphorylation, supporting a role for MMP-9 in zinc-mediated tau pathology. Notably, sublethal zinc concentrations failed to induce tau hyperphosphorylation, suggesting that robust tau phosphorylation requires both zinc-triggered kinase activation and a sufficient increase in intracellular free zinc. To determine whether lysosomal modulation could mitigate zinc-induced tau pathology, we examined trehalose and EGF, which increase lysosomal abundance, and ZCS1, a compound that enhances both lysosomal biogenesis and acidification. Trehalose and EGF increased lysosomal abundance but failed to suppress tau hyperphosphorylation, suggesting that lysosomal expansion alone may be insufficient to counteract zinc-induced signaling. In contrast, ZCS1 markedly suppressed tau phosphorylation, consistent with its ability to enhance both lysosomal biogenesis and acidification, thereby facilitating intracellular zinc sequestration. Collectively, these findings identify lysosomal activation as a key protective mechanism against zinc-induced tau pathology and support therapeutic strategies that enhance both lysosomal biogenesis and acidification in AD.

Disclosures: H. Lee: A. Employment/Salary (full or part-time):; Zincure Corp. **Y. Kim:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Zincure Corp..

Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.06/T29

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

Support: NIH Grant AG052350
NIH Grant AG076921

Title: APOE4 and P301S tauopathy synergistically contribute to the severity of neurodegeneration and vascular pathology in mice

Authors: *M. ZHANG[1], A. P. SAGARE[2], R. RUST[3], K. KISLER[4], C. TORRES SEPULVEDA[1], V. CLEMENTEL[1], G. SPILLARD[2], D. M. HOLTZMAN[5], H. N. YASSINE[1], M. P. COBA[1];
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Abstract: The E4 allele of the *APOE* gene, *APOE4*, is the major genetic risk factor for Alzheimer's disease (AD), compared to *APOE3* that carries lower risk. Early blood-brain barrier (BBB) breakdown occurs in AD and is thought to contribute to cognitive impairment. *APOE4* exerts substantial cerebrovascular toxicity including BBB breakdown both in humans and in *APOE* transgenic models, which we previously showed precedes cognitive impairment and synaptic deficits.Here, we investigated neurodegenerative and BBB changes in 9.5-month-old *APOE3* and *APOE4* knock-in floxed (F) mice, i.e., *E3F* and *E4F,* alone and crossed with a mouse model of tauopathy (Tau *P301S*). We observed neurodegenerative changes at 9.5-months, with reduced hippocampal neuronal density in *E4F* compared to *E3F* mice and further degeneration in mice with tauopathy, with *E4F; P301S* mice exhibiting the greatest loss of neuronal density. Liquid chromatography-mass spectrometry proteomic and phosphoproteomic analysis of post-synaptic density (PSD) fractions isolated from these mice indicated substantial synaptic protein loss and dysregulation of synaptic signaling networks. The synaptic phenotypes followed a similar pattern with a synergic increase in the severity with *E4F; P301S* mice most affected. Immunostaining for blood-derived fibrinogen revealed increasing BBB leakage in *E4F* compared to *E3F* mice, which was further exacerbated by tauopathy, with the most severe BBB leakage observed in the *E4F; P301S* mice.Together this data suggests that neurodegenerative changes and BBB breakdown are more severe in *APOE4* compared to *APOE3* mice, and *APOE4* expression combined with tau pathology co-act to increase the severity of neurodegenerative and BBB pathology.

Disclosures: M. Zhang: None. **A.P. Sagare:** None. **R. Rust:** None. **K. Kisler:** None. **C. Torres Sepulveda:** None. **V. Clementel:** None. **G. Spillard:** None. **D.M. Holtzman:** None. **H.N. Yassine:** None. **M.P. Coba:** None.

Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.07/T30

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

Support: NIH NIA R25AG076396
AARGD-22-972117

Title: Longitudinal Assessment of Sleep, Associative Memory, and Locomotor Decline in Aging and Tauopathy

Authors: *C. M. RODRIGUEZ[1], A. CALAVIA[2], A. MARTIN-PEÑA[2];
[2]Neurosci., [1]Univ. of Florida, Gainesville, FL

Abstract: Aging is associated with progressive changes in locomotor activity, sleep, and cognition, and is a primary risk factor for neurodegenerative diseases such as Alzheimer's disease (AD). Cognitive decline varies across domains, with some forms of memory more vulnerable than others. An important hallmark of AD and other tauopathies is the abnormal accumulation of tau, a microtubule-associated protein. The disease-associated P301L mutation in tau, linked to Frontotemporal Dementia (FTD), accelerates tau aggregation and is a good model for studying early-stage neurodegeneration. We have established a behavioral timeline of tau-induced neurodegeneration in Drosophila melanogaster, showing that sleep disturbances precede locomotor deficits and cognitive impairment. Spontaneous alternation behavior, a measure of spatial working memory, remains resilient during aging, suggesting that other cognitive domains may be better indicators of early decline. However, it remained unclear in our model how associative learning changes across the lifespan and whether this domain is more sensitive to aging and tau-induced neurodegeneration. We employed Drosophila melanogaster as a genetically tractable model to characterize age-dependent changes in locomotor activity, sleep, and associative memory. Wild-type Canton-S flies and tauopathy models expressing either wild-type Tau or the P301L Tau were assessed longitudinally from 1 to 60 days of age. Sleep architecture and locomotor activity were continuously monitored using Drosophila Activity Monitors (DAM2). To test associative learning, we developed a Y-maze that enables testing of individual flies for further classification into resilient and vulnerable individuals. Flies are recorded in three different phases of 1 minute each: (1) a baseline recording to establish arm preference (flies evenly visit the three arms), (2) conditioning in which one arm is paired with an electric shock of 90V, and (3) postconditioning testing to assess memory retention and avoidance behavior. Arm visits (entries) and the proportion of time spent in each arm are calculated, with flies spending less time in the shocked arm upon conditioning. By utilizing longitudinal measures of locomotion, sleep, and associative learning, this study aims to define the molecular underpinnings of the stratification between vulnerable and resilient individuals. Defining the relationship among these behavioral changes will allow for identification of mechanisms underlying cognitive resilience and vulnerability during aging and help future interventions to delay neurodegenerative progression.

Disclosures: C.M. Rodriguez: None. **A. Calavia:** None. **A. Martin-Peña:** None.

Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.08/T31

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

Support: NIH Grant AG077991

Title: Clinically relevant blood biomarkers for tau and inflammation are reduced by treatment with OLX-07010 in P301L Tau x APPSwe mice

Authors: *E. J. DAVIDOWITZ, D. R. PATEL, P. LOPEZ, J. G. MOE;
Oligomerix, Inc., Bronx, NY

Abstract: OLX-07010 is a clinical stage, small molecule investigational drug in development for Alzheimer's disease (AD) and progressive supranuclear palsy (PSP). The phase 1a study in healthy adults and in an elderly cohort has successfully completed with preliminary results showing a favorable safety profile at and above equivalent levels shown to be effective in animal models. OLX-07010 was selected in vitro for inhibiting tau-self association into dimers and into progressively larger aggregates. In vivo studies have been performed in htau mice, expressing human WT tau isoforms, modeling tau aggregation in AD (PMID: 31771053), and in P301L tau mice modeling tau aggregation in 4R tauopathies using preventive and therapeutic treatment study designs (PMID:37556474; PMID: 40052227). OLX-07010 was administered in diet for 4-5 months of chronic treatment or by daily oral gavage in an acute, 4-week treatment study in aged mice. A daily dose of 40 mg/kg was generally effective in preventing the formation of tau aggregates 4-7 months of age and in blocking accumulation of tau aggregates in aged mice and in ameliorating motor impairment. The present treatment study in mice expressing both human constructs of P301L Tau (4R0N isoform) and APP Swe (TAPP mice) showed that treatment with 40 mg/kg/day from 4 to 10 months prevented the accumulation of tau aggregates and gait impairment.

This study also included characterization of clinically relevant blood biomarkers for CNS and inflammation targets to evaluate biomarkers showing a treatment effect in an animal model for AD that may be useful to gauge success in a phase 1b study in AD patients. Serum samples from terminal blood draws were sent to Alamar Biosciences to perform the high multiplex analysis using their NULISA (NUcleic acid Linked Immuno-Sandwich Assay) 120-plex Mouse Neuroinflammation Panel of 120 murine Neuro and inflammation proteins. The strongest effect was on tau biomarkers for total tau and phosphorylated tau (181, 217 and 231) indicating the specificity of OLX-07010 treatment on tau. Treatment also reduced markers of inflammation that were induced by expression of tau and amyloid including S100A4, interleukin pro-16, PDGFβ, GMCSF, chemokine 20 and galectin 1.

These results suggest that OLX-07010 is engaging the tau target, and that tau in the periphery may serve as a mechanistic biomarker for tau aggregation in the brain. Reduction of markers of inflammation also suggest show further benefit of treatment. This data supports evaluation of

these blood biomarkers in clinical studies of AD patients to enable clinical development and to establish the translation of results from an animal model for AD to the clinic.

Disclosures: E.J. Davidowitz: A. Employment/Salary (full or part-time):; Oligomerix, Inc.. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIA/NIH. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **D.R. Patel:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **P. Lopez:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc. **J.G. Moe:** A. Employment/Salary (full or part-time):; Oligomerix, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Oligomerix, Inc..

Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.09/Web Only

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

Support: CIHR Project Grant - PJT 197770

Title: Vagus Nerve Stimulation Rescues Cognitive Deficits and Enhances Extinction Memory in a Pretangle Tau Model

Authors: *T. OMOLUABI[1], T. SEPAHVAND[1], B. HANNAM[1], H. STAPLETON[1], N. NAZARI[1], H. IGARASHI[2], T. SASAKI[2], Q. YUAN[1];
[1]Biomed. Sciences, Fac. of Med., Mem. Univ. of Newfoundland, St. John's, NL, Canada; [2]Dept. of Pharmacol., Tohoku Univ., Sendai, Japan

Abstract: The locus coeruleus (LC), the brain’s primary source of norepinephrine, plays a critical role in cognition and is among the earliest sites of pathology in Alzheimer’s disease (AD). Soluble pretangle tau appears in the LC decades before clinical symptoms and is associated with LC dysfunction, neuroinflammation, and cognitive decline. We previously developed a pretangle tau rat model by expressing a human pretangle tau mimic (htauE14) in LC noradrenergic neurons and demonstrated that LC activity bidirectionally regulates disease progression: phasic optogenetic stimulation rescues cognitive deficits and LC fiber degeneration, whereas tonic activation exacerbates neuronal dysfunction. Because optogenetics has limited translational potential, we investigated whether vagus nerve stimulation (VNS), a clinically approved neuromodulatory therapy that engages the LC, could provide similar therapeutic

benefits. Two- to three-month-old male and female TH-Cre rats received bilateral LC infusion of AAV-DIO-htauE14. Five months later, stimulating cuff electrodes were implanted on the left cervical vagus nerve. After a 2-week recovery period, rats received VNS (0.8 mA, 20Hz, 600 pulses, 0.1 ms pulse width, 3 h/day) for 3 weeks before behavioural assessment. Preliminary findings indicate that VNS ameliorates multiple behavioural deficits induced by pretangle tau pathology. VNS increased exploratory rearing and reduced marble-burying behaviour, consistent with reduced anxiety-like phenotypes, while phasic LC stimulation similarly increased center exploration in the open field. In the object location recognition task, both VNS and phasic LC stimulation rescued spatial memory deficits in htauE14 rats. In olfactory threat conditioning, VNS did not alter acquisition, memory recall, or extinction but significantly reduced spontaneous recovery, indicating enhanced extinction memory retention. These findings support the hypothesis that VNS beneficially modulates LC function and partially mimics the effects of phasic LC activation in a pretangle tau model of early AD. By improving anxiety-like behavior, spatial memory, and extinction memory retention, VNS shows promise as a clinically translatable neuromodulatory strategy to enhance resilience during the earliest stages of AD pathogenesis.

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Poster

PSTR127: Alzheimer's Disease Therapeutic Strategies: Tau

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR127.10/T32

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

Title: Evaluating Patient Screening for LY3954068, an Anti-Tau siRNA Protein Therapy, in Symptomatic Early Onset Alzheimer’s Disease

Authors: *V. S. INDUGULA;
Duke Early Phase Res. Unit, Duke Univ. Sch. of Med., Durham, NC

Abstract: Introduction: Alzheimer’s disease (AD) is a chronic neurodegenerative disorder accompanied by progressive decline in cognitive function. Global AD prevalence is ~22% in people ≥50 years of age, helping direct recruitment for AD-related trials.1 Advances in AD-dementia research have identified therapeutic approaches, including amyloid-targeting agents (ATTs), yet tau pathology correlates closer with neurodegeneration and clinical progression2. This trial evaluates a novel Dicer-substrate small interfering RNA (siRNA) antisense oligonucleotide (ASO) designed to reduce intracellular microtubule-associated protein tau (MAPT) mRNA levels and, consequently, tau protein levels.
Methods: The IP is being tested in a phase 1 randomized, placebo-controlled study administered intrathecally in patients with early symptomatic AD. The overall trial will enroll four sequential single-ascending dose (SAD) cohorts (n=32) followed by two multiple-ascending dose (MAD)

cohorts (n=16). Data presented will include descriptive statistics of the rare-disease recruitment process, as safety and PK/PD data are not yet available.
Results: Preclinical studies support ASO tau suppression, with ≥50% reduction in PS19 transgenic mice3. Recent Phase 1b studies of MAPT ASOs indicate a 30-50% reduction in p-tau is acceptable for progression to a phase 2 study.4 332 total patients underwent chart review. Of these, 249 were excluded (75.0%) for exclusionary criteria/diagnoses (n=108, 43.4%), ATTs (n=38, 15.3%), Medication contraindications (n=30, 12.0%), lack of pathology (n=30, 12.0%), clinical exam failure (n=21, 8.4%), trial involvement (n=17, 6.8%), and/or imaging contraindications (n=9, 3.6%). Of the 39 identified participants (11.8%), 2 patients (0.6%) are undergoing pre-screening visits.
Conclusions: The correlation of tau and cognitive decline links tau accumulation to neurodegeneration. The IP is expected to reduce measurable tau levels and improve patient impressions on F18 tau PETs and in other secondary endpoints. The most common exclusion reason involved medications, ATTs, and exclusionary criteria like dementias, neuropsychiatric diseases, and more. These considerations help improve screening processes and better characterize patient populations in AD-related clinical trials.

Disclosures: V.S. Indugula: None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.01/U1

Topic: C.03. Parkinson’s Disease

Support: Intramural Research Programs of the National Human Genome Research Institute (ZIA HG200336-19)
Aligning Science Across Parkinson’s initiative (ASAP-000458) through the Michael J. Fox Foundation for Parkinson’s Research (MJFF)

Title: From Gaucher Disease to Parkinson's Disease: An Age-Preserved Neuronal Model of Disease Progression

Authors: *H. ESMAEILI[1], M. KAPPLER[2], M. BHATTIPROLU[3], Y. CHEN[4], E. SIDRANSKY[4];
[1]The Natl. Inst. of Hlth. (NIH), Rockville, MD; [2]The Natl. Inst. of Hlth. (NIH), Arlington, VA; [3]The Natl. Inst. of Hlth. (NIH), Potomac, MD; [4]NHGRI, NIH, Bethesda, MD

Abstract: Objective: The deficiency of acid β-glucocerebrosidase (GCase), the lysosomal hydrolase encoded by *GBA1*, leads to the accumulation of glucosylceramide and other sphingolipids and results in the lysosomal storage disorder Gaucher disease (GD). *GBA1* is the most common genetic risk factor for Parkinson’s disease (PD), however, most GBA1 variant carriers never develop PD, indicating incomplete penetrance and highlighting the importance of

identifying modifying factors that influence disease onset and progression. Although patient-derived iPSC models are widely used to study PD (**Figure 1a, top**), cellular reprogramming may not retain aging-associated features that contribute to neurodegeneration. To address this limitation, we implemented a direct transdifferentiation protocol (**Figure 1a, bottom)** to generate age-preserved neurons from two unique patients with GD followed longitudinally over multiple decades with divergent PD outcomes to investigate modifiers of PD development.**Results:** Fibroblasts from the older GD and GD/PD donors exhibited increased DNA damage, as indicated by elevated γ-H2AX puncta (**Figure 1b**). Optimization of transdifferentiation conditions revealed that a multiplicity of infection (MOI) of 5 for each transcription factor, delivered at a 1:1 ratio, yielding up to ~60% NCAM-positive ($NCAM^+$) cells by day 5 (**Figure 1d.i**). Continued culture for an additional 30 days under optimized media conditions promoted further maturation of the transdifferentiated cells toward a cortical neuronal phenotype (**Figure 1d.ii**).**Conclusions:** This optimized transdifferentiation approach using fibroblasts from a GD patient before and after the development of PD provides a novel model to identify factors that influence GD-associated PD. Multiomics evaluations performed on the four samples will be compared to identify features contributing to PD pathogenesis and penetrance

Methods: Fibroblasts from the two patients were collected at two different time points over 30 years apart. One, diagnosed with GD (**N370S/L444P**) at age 27, had no signs of PD at age 67, whereas the second was diagnosed with GD (**N370S/c.203delC + R257X**) at age 22 and subsequently developed PD at age 56. Patient-derived fibroblasts were stained for S100A4 (a fibroblast marker) and the DNA damage marker γ-H2AX, while nuclei were counterstained with DAPI (**Figure 1b)**. Confocal images were analyzed using Fiji software. We implemented a transdifferentiation protocol (**Figure 1c**) based on the transcription factors Brn2, Ascl1, Myt1l, and Ngn2, in combination with small molecules, to directly convert fibroblasts into neurons. Transdifferentiation efficiency was assessed by flow cytometry, with the conversion rate determined by the percentage of NCAM-positive ($NCAM^+$, neuronal progenitor marker) cells.

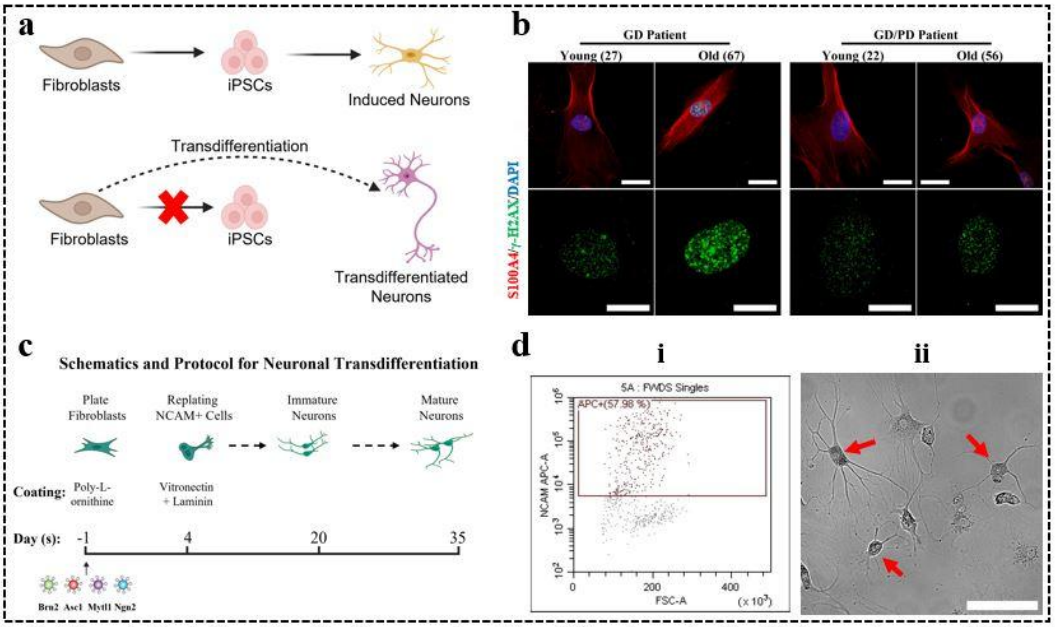


Figure 1. (**a**) Schematic illustration of fibroblast-to-neuron transdifferentiation, bypassing the iPSC generation step. (**b**) DNA damage levels, assessed by γ-H2AX immunofluorescence (green), in human fibroblasts (red). Scale bars: 30 µm (top panel) and 15 µm (bottom panel). (**c**) Schematic illustration of the transdifferentiation protocol used to generate cortical neurons from fibroblasts (PMID: 40140603). (**d**) Flow cytometric analysis of NCAM-positive ($NCAM^+$) cells demonstrating that a 1:1 lentiviral cocktail ratio yields up to ~60% neuronal progenitors at day 5 post-transdifferentiation (**i**). The brightfield image shows mature transdifferentiated neurons (red arrows) at day 35 post-transdifferentiation. Scale bar: 100 µm (**ii**).

Disclosures: H. Esmaeili: None. **M. Kappler:** None. **M. Bhattiprolu:** None. **Y. Chen:** None. **E. Sidransky:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.02/U2

Topic: B.09. Glial Mechanisms

Title: Familial Parkinson's Disease Mutations Alter Microglial Transcriptomic Programs and Function in an Isogenic Human Stem Cell Model

Authors: *M. HAERLE, O. BUSQUETS FIGUERAS, D. ZHENG, F. SOLDNER;
Albert Einstein Col. of Med., Bronx, NY

Abstract: Neuroinflammation and reactive gliosis are key pathological hallmarks of neurodegenerative diseases, including Parkinson’s disease (PD). Microglia, the brain’s resident immune cells and phagocytes, play a central role in mediating neuroinflammatory responses and can adopt disease-associated transcriptional states. Although over 20 genes have been linked to familial forms of PD, how mutations in these genes alter microglial transcriptional programs and function, and whether these changes contribute to PD pathogenesis, remains poorly understood. To address this gap, we established an isogenic collection of genome-edited human pluripotent stem cell (hPSC) lines harboring 13 high-risk familial PD mutations across 11 PD-associated genes (iSCORE-PD) and differentiated them into microglia-like cells (iMicroglia) *in vitro*. By controlling for genetic background, this platform enables direct comparison of mutation-specific effects on microglial biology. Bulk RNA sequencing of PD-mutant iMicroglia revealed widespread transcriptomic dysregulation, including alterations in gene modules involved in vesicle trafficking, inflammatory signaling, and ATP synthesis. Notably, PD-associated mutations also altered the expression of other PD-linked genes, suggesting convergent transcriptional pathways and shared functional networks underlying PD pathogenesis. Distinct mutation-specific signatures were observed for VPS13C W395C and A444P variants, with VPS13C W395C iMicroglia showing greater dysregulation of pathways related to cytoskeletal remodeling and mitochondrial-lysosomal dysfunction. To determine the functional consequences of PD-associated mutations, we assessed phagocytosis and reactive oxygen species (ROS) production. PD-mutant iMicroglia showed impaired phagocytic activity and altered ROS generation, consistent with disruptions in metabolic and inflammatory states. Together, these findings define both convergent and mutation-specific microglial signatures in familial PD and provide insight into microglial contributions to PD pathogenesis.

Disclosures: M. Haerle: None. **O. Busquets Figueras:** None. **D. Zheng:** None. **F. Soldner:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.03/U3

Topic: C.03. Parkinson's Disease

Support: NIH IRP Project 1ZIAHG200336-18

Title: Comparative Transcriptomic Analysis of GBA1-KO Zebrafish and Mouse Brains Reveals Shared Pathways of Neuronopathic Gaucher Disease

Authors: *M. KAPPLER[1], T. CHEN[1], N. NARISU[1], T. YAN[1], B. BERHE[1], B. CARRINGTON[2], T.-U. HAN[1], E. SIDRANSKY[1];
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Abstract: Mutations in *GBA1*, which encodes the lysosomal enzyme glucocerebrosidase (GCase), cause Gaucher disease (GD), a lysosomal storage disorder characterized by lipid accumulation and progressive pathology. While type 1 GD is non-neuronopathic, type 2 GD (GD2) is associated with severe neurodegeneration, neuroinflammation, and microglial activation. Importantly, variants in *GBA1* also represent the most common genetic risk factor for Parkinson's disease (PD), suggesting shared mechanisms involving lysosomal dysfunction and neuroinflammatory pathways. To investigate conserved molecular signatures underlying acute neuronopathic GD2, we performed comparative transcriptomic analyses in *GBA1* knockout (KO) mouse and zebrafish models. *GBA1*-KO zebrafish were generated using CRISPR-Cas9, while a previously published model was used for KO mouse. Bulk RNA sequencing of whole-brain lysates was conducted to characterize species-specific and shared transcriptional responses to *GBA1* deficiency.Phenotyping of the models revealed that both *GBA1*-KO mice and zebrafish recapitulate key features of GD2, including severe neurologic defects resulting in early lethality. Transcriptomic profiling identified a number of shared differentially expressed genes such as regulators of lysosomal homeostasis, neuroinflammation, and α-synuclein processing (*GPNMB*, *GRN*, *HSP70)*, and members of the *CTSH/D/C/B/A* family. Cross-species gene set enrichment analysis highlighted conserved pathways associated with neuroinflammation, particularly microglial phagocytosis and reactive oxygen species (ROS) production, along with dysregulation of lipid metabolism and neuronal processing pathways. These findings demonstrate robust conservation of disease-associated molecular pathways across the vertebrate models and highlight candidate biomarkers and therapeutic targets relevant to both GD2 and *GBA1*-associated PD. Future studies will validate identified differential gene targets by RT-qPCR and compare these findings with patient-derived single-cell and bulk transcriptomic datasets to further define conserved disease mechanisms.

Disclosures: M. Kappler: None. **T. Chen:** None. **N. Narisu:** None. **T. Yan:** None. **B. Berhe:** None. **B. Carrington:** None. **T. Han:** None. **E. Sidransky:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.04/U4

Topic: C.03. Parkinson's Disease

Support: NIH R01NS148118

Title: Essential function of microglial LRRK2 in dopaminergic neuronal survival in the aging mouse brain

Authors: *A. SHAHAPAL[1], S. YIM[2], J. SHEN[3];
[1]Neurol., [2]Brigham and Women's Hosp., Boston, MA; [3]Neurol., MGB Harvard Med. Sch., Boston, MA

Abstract: Mutations in leucine-rich repeat kinase 2 (LRRK2) are the most common genetic cause of Parkinson's disease (PD), and microglia have been implicated in PD pathogenesis. However, the pathogenic mechanism underlying LRRK2-mediated dopaminergic (DA) neurodegeneration remains unresolved. LRRK2 is an evolutionarily conserved large protein containing multiple functional domains and is highly expressed in neurons and microglia. Our previous generation and analysis of germline and dopaminergic (DA) neuron-specific conditional knockout (KO) mice of *Lrrk2* and its functional homologue *Lrrk1* revealed an essential, cell-autonomous role of LRRK in DA neuronal survival. The less severe DA neurodegeneration phenotypes in DA neuron-specific conditional KO compared to germline KO mice suggest a possible contribution of non-DA neurons or glia to the PD-relevant phenotypes. To address this question, we generated and validated microglia-specific *Lrrk* conditional double KO (cDKO) mice using *Tmem119-CreERT2*, in which Cre recombinase is inducibly expressed by tamoxifen under control of the microglia-specific *Tmem119* promoter. Interestingly, microglia-specific *Lrrk* cDKO mice develop age-dependent loss of DA neurons, as evidenced by a significant reduction of DA neurons in the substantia nigra pars compacta (SNpc) at the age of 25 months but not at 20 months of age. DA neurodegeneration is preceded by increases of apoptotic DA neurons at 20 months of age and is accompanied with elevated microgliosis in the SNpc. Lastly, quantitative EM analysis revealed that selective inactivation of *Lrrk* in microglia results in increases of large autophagic and lysosomal vacuoles in SNpc neurons at the age of 15 months, before the detection of increased apoptotic DA neurons and a significant reduction of DA neurons in the SNpc. Together, these findings demonstrate a critical importance of microglia and microglial LRRK2 in the protection of DA neuronal function and survival during aging in a non-cell autonomous manner.

Disclosures: A. Shahapal: None. **S. Yim:** None. **J. Shen:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.05/U5

Topic: C.03. Parkinson's Disease

Title: Inflammatory activation organizes LRRK2-Rab10 signalling at pericentrosomal trafficking compartments

Authors: *F. FILIPPINI[1], C. GIAMBALVO[2], E. GREGGIO[1,3];
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Abstract: Inflammatory activation of LRRK2 is increasingly recognized as a mechanism linking immune signalling to Parkinson's disease-relevant defects in intracellular trafficking. Interferon-γ enhances LRRK2 expression and promotes phosphorylation of Rab GTPases, including Rab10, but how this signalling response is spatially organized remains poorly understood. Here, we investigated endogenous LRRK2-Rab10 signalling in A549 cells using replicated immunofluorescence experiments, matched genetic controls, and rescue conditions. Following interferon-γ stimulation, phosphorylated Rab10 accumulated in a discrete perinuclear compartment rather than displaying a diffuse increase throughout the cell. These phosphorylated Rab10-positive structures were positioned in close proximity to centrosome-associated markers, suggesting that inflammatory activation of LRRK2 promotes signalling at a defined pericentrosomal trafficking hub. Targeted perturbation of centrosome-associated trafficking and lysosome-linked membrane regulation altered the organization of this interferon-γ-induced phosphorylated Rab10 compartment, supporting a role for both processes in spatially organizing inflammatory LRRK2 signalling. These exploratory findings suggest that interferon-γ does not simply increase bulk LRRK2 kinase activity, but promotes the formation of a spatially restricted signalling domain at the interface between inflammatory signalling, lysosomal homeostasis, and centrosome-associated trafficking. This work identifies a previously underappreciated level of spatial regulation in inflammatory LRRK2 signalling and provides a framework for understanding how immune activation may engage Parkinson's disease-relevant trafficking pathways in cells.

Disclosures: F. Filippini: None. **C. Giambalvo:** None. **E. Greggio:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.06/U6

Topic: C.03. Parkinson's Disease

Support: NIH/NINDS R01NS112506
R21AG094032
UConn Health Startup fund

Title: Retrograde Transport of β-Glucocerebrosidase (GCase) in Parkinson's Disease

Authors: *Z. GALDENZI, S. CHEN, Y. XIONG;
Neurosci., UConn Hlth., Farmington, CT

Abstract: Parkinson’s disease (PD) is the second most common neurodegenerative disease, however, there is currently no curative treatment. Mutations in *GBA1*, encoding the lysosomal enzyme β-Glucocerebrosidase (GCase), are the most common genetic risk factor for PD. Despite this well-established link, the mechanisms of how these mutations contribute to the disease are unknown. Proper membrane trafficking is vital to GCase function. GCase is synthesized in the endoplasmic reticulum (ER), transported to the Golgi, then moved to the lysosome where it is mature and active. Mutations in *GBA1* result in misfolded GCase that becomes retained in the ER, leading to loss of its function and accumulation of its substrates in the lysosome. Throughout the trafficking process, glycosylation modifications occur on GCase which are crucial for its function, resulting in various-sized forms of GCase occurring at different subcellular locations. To identify candidates for modifiers of GCase, we performed an unbiased siRNA knockdown screening. Alterations in genes implicated in retrograde transport were consistently found to shift GCase size. Further immunoprecipitation experiments revealed binding of the corresponding protein complex to GCase. Despite the important role of membrane trafficking in GCase function, little is known about its retrograde transport. As alterations in machinery required for this transport alter GCase modifications, our data suggests that GCase may undergo transport beyond its canonical anterograde processing. It is possible that this process is implicated in the ER retention of GCase, ER stress, and decrease in GCase activity found in PD. This work further suggests protein interactions that have not yet been characterized. In future research, we will investigate the physical interaction of GCase and this complex, how GCase localization and function are affected by alterations to these proteins, and how these processes are implicated in PD pathogenesis.

Disclosures: Z. Galdenzi: None. **S. Chen:** None. **Y. Xiong:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.07/U7

Topic: C.03. Parkinson’s Disease

Support: NIH Grant R01NS064934

Title: Immune-cell LRRK2 regulates neuroinflammation and dopaminergic neurodegeneration in an α-synuclein mouse model of Parkinson's disease

Authors: S. STRADER[1], ***M. KATYAL**[1], A. B. WEST[2];
[2]Pharmacol., [1]Duke Univ., Durham, NC

Abstract: Parkinson’s disease (PD) is a progressive neurodegenerative disorder characterized by α-synuclein pathology, neuroinflammation, and the loss of nigral dopaminergic neurons. Leucine-rich repeat kinase 2 (LRRK2) is a major genetic contributor to PD susceptibility, with pathogenic mutations linked to altered kinase activity and prominent expression in monocytes,

neutrophils, and macrophages from different myeloid-lineage immune cells. How peripheral-originating immune cells may influence α-synuclein-induced neuroinflammation and neurodegeneration remains incompletely understood. To investigate this question, we generated bone marrow chimeric mice with donor-derived immune-cell LRRK2 deletion or LRRK2 overexpression. Following confirmation of donor engraftment, human α-synuclein was expressed in the substantia nigra using adeno-associated viral delivery. Nigral dopaminergic neuron survival, α-synuclein pathology, myeloid activation, and T-cell accumulation were analyzed by immunohistochemistry and immunofluorescence at early and late post-injection time points. Bone marrow-derived LRRK2 deletion reduced early myeloid activation following α-synuclein expression and was associated with decreased accumulation of CD3-positive and CD8-positive T cells in the substantia nigra at later time points. These neuroimmune changes were accompanied by increased preservation of tyrosine hydroxylase-positive nigral dopaminergic neurons. Conversely, bone marrow-derived LRRK2 overexpression was associated with enhanced myeloid activation, increased T-cell accumulation, and greater dopaminergic neuron loss. Together, these findings identify LRRK2 in bone marrow-derived immune cells as a regulator of α-synuclein-induced neuroimmune responses and dopaminergic neurodegeneration. These results support further investigation of immune-cell LRRK2 signaling as a potential therapeutic axis for modifying inflammatory mechanisms that contribute to PD progression.

Disclosures: S. Strader: None. **M. Katyal:** None. **A.B. West:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.08/U8

Topic: C.03. Parkinson’s Disease

Support: NIH R01 NS105432

Title: Lysosomal swelling is a convergent trigger for LRRK2-mediated Rab phosphorylation

Authors: *T. MALANKHANOVA[1], Z. LIU[2], S. STRADER[3], W. WANG[6], B. LEI[7], A. DROZMAN[4], Z. LI[7], S. M. FERGUSON[8], A. B. WEST[5];
[1]Pharmacol. and Cancer Biol., [2]PCB, Duke Univ., Durham, NC; [3]Duke Univ., DURHAM, NC; [4]Duke Univ., Durham, NC; [5]Duke Univ., Durham, NC, ; [6]Duke university, Durham, NC, ; [7]Durham, NC, ; [8]Yale Univ., New Haven, CT.

Abstract: LRRK2 is a multidomain kinase that phosphorylates a subset of Rab GTPases to regulate vesicle trafficking and lysosomal homeostasis. Mutations in *LRRK2* are the most common genetic cause of Parkinson's disease, with gain-of-function variants such as R1441C hyperactivating its kinase domain and disrupting endolysosomal trafficking. The physiological cues that engage LRRK2 activity are incompletely defined. Here we report lysosomal volume expansion as an upstream trigger for LRRK2-mediated Rab phosphorylation in macrophages.

Using sucrose as an indigestible osmolyte to model osmotic lysosomal swelling, we show that sucrose treatment increases LRRK2-dependent pRab10 and pRab12 in RAW 264.7 macrophages, primary mouse macrophages, and human monocyte-derived macrophages without detectable changes in lysosomal pH. LRRK2 kinase inhibition with PFE-360 or genetic deletion of *Lrrk2* reduces sucrose-induced lysosomal swelling without impairing fluid-phase uptake, demonstrating that LRRK2 actively drives pathological lysosomal enlargement downstream of osmotic stress. Independently, PIKfyve inhibition by apilimod causes lysosomal swelling, BMP lipid depletion, and robust LRRK2-dependent Rab phosphorylation. Apilimod-induced LRRK2 activation requires active V-ATPase and is partially mediated by Rab12 and GABARAP, while TRPML1 is dispensable. Lyso-IP experiments reveal increased lysosomal pRab10 without proportional LRRK2 lysosomal accumulation, suggesting LRRK2 is activated through transient membrane interactions rather than stable lysosomal recruitment. Notably, the Parkinson's disease-associated R1441C gain-of-function mutation amplifies LRRK2 activation in response to lysosomal swelling, suggesting that pathogenic LRRK2 mutations lower the threshold for lysosomal stress-induced kinase activation. As lysosomal swelling is a shared pathological feature of LRRK2-linked diseases including Parkinson's disease, neuroinflammation, and lysosomal storage disorders, these findings position LRRK2 as a lysosomal volume sensor with direct relevance to disease pathophysiology.

Disclosures: T. Malankhanova: None. **Z. Liu:** None. **S. Strader:** None. **A. Drozman:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.09/U9

Topic: C.03. Parkinson’s Disease

Support: 1RF1NS145135-01

Title: LRRK2 expression and signaling changes links to neuroimmune activation in idiopathic Parkinson's disease

Authors: *W. WANG[1], A. B. WEST[2];
[1]Duke university, Durham, NC; [2]Pharmacol., Duke Univ., Durham, NC

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder for which disease-modifying therapies remain limited. Mutations in the *leucine-rich repeat kinase 2* (*LRRK2*) gene represent one of the most common genetic contributors to both familial and sporadic PD, and pathogenic variants are known to increase LRRK2 kinase activity. As LRRK2-targeting therapeutics advance into clinical trials, understanding how LRRK2 signaling relates to disease progression and underlying pathology has become increasingly important. Results from single-nucleus RNA sequencing of Lewy pathology affected human brain regions identified donor-level LRRK2 upregulation in a trafficking-active myeloid state selectively enriched in

idiopathic PD substantia nigra. The LRRK2-high myeloid state was characterized by monocyte/macrophage-associated, chemotactic, vesicular-trafficking, and immune-interaction signatures and was associated with increased local T-cell abundance. To assess LRRK2 signaling linked biomarkers, our lab developed and validated ultra-sensitive single-molecule array (SIMOA) assays to evaluate extracellular levels of LRRK2, Rab10, and phosphorylated Rab10 (pRab10) in small volumes of biobanked biofluids. Our recent results from a longitudinal cohort of PD and control serums show that higher pRab10 to total Rab10 ratios are associated with worse disease severity over time, supporting the potential utility of peripheral LRRK2 pathway biomarkers for monitoring disease progression. Furthermore, whole-blood transcriptomic profiles and genomic data will be interrogated to identify factors that regulate LRRK2 signaling. Together, these findings suggest that higher expression of LRRK2 linked to compartment-specific neuroimmune activation within the PD brain, and higher LRRK2 activity is associated with worse disease severity. Integrating longitudinal biofluid biomarkers with transcriptomic and genomic analyses may improve disease monitoring and provide mechanistic insight into LRRK2-dependent pathways relevant to therapeutic intervention.

Disclosures: W. Wang: None. **A.B. West:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.10/U10

Topic: C.03. Parkinson’s Disease

Support: Parkinson's Foundation PF-PRF-1244721
start up funds from Department of Neurology, Duke University

Title: Leucine-rich repeat kinase (LRRK2) dependence of pathological tau-induced lysosomal events

Authors: *E. MA[1], S. YIM[1], J. ECKER[1], A. B. WEST[2], T. J. COHEN[3], S. A. BUCK[4], L. SANDERS[1];
[2]Pharmacol., [1]Duke Univ., Durham, NC; [3]Neurol., Univ. of North Carolina - Chapel Hill, Chapel Hill, NC; [4]Neurol., Duke Univ. Sch. of Med., Raleigh, NC

Abstract: Enhanced kinase activity of *LRRK2* (e.g., G2019S) is a major genetic contributor to familial Parkinson’s disease, and LRRK2 is also implicated in idiopathic PD. Postmortem brain tissue derived from *LRRK2*^{G2019S} carriers is often associated with tau pathology. Previously, we established a novel interaction between LRRK2 kinase function and tauopathies. We found phosphorylated Rab12 (pRab12) labeling of granulovacuolar degeneration bodies (GVBs), proteolytically active lysosomal structures with a dense core, that arise in neurons with early stages of pathological tau accumulation, in brain tissues across neurodegenerative diseases and a mouse model of tauopathy. Given the recruitment of LRRK2 to damaged lysosomal membranes,

we hypothesized that pathological tau engages LRRK2-dependent signaling to modulate lysosomal integrity and GVB development. We transduced primary murine cortical neurons with a pathological tau lentivirus, expressing the P301L and S320F mutations, to assess the effect of LRRK2 function on GVB formation and lysosomal stress. Cortical neurons were treated with the LRRK2 kinase inhibitor PF-360 or vehicle and analyzed by western blot for pRab12 and total Rab12, phosphorylated and total tau, and GVB markers. LRRK2 comparisons were achieved by transducing cortical neurons with adenoviruses, overexpressing either wild-type or G2019S LRRK2, and performing immunocytochemistry to ascertain GVB formation and lysosomal condition. Pathological tau expression significantly increased both pRab12 and total Rab12 in cortical neurons. Overall, the increase in pRab12 was LRRK2 kinase-dependent whereas total Rab12 elevation was independent of kinase activity. Interestingly, pRab12 within GVBs was resistant to LRRK2 kinase inhibition. Pathological tau also induced a LRRK2-kinase dependent increase in CHMP2B, a component of the membrane repair ESCRT machinery and GVB marker. Our data indicate pRab12 is retained within GVBs and remains LRRK2 kinase inhibitor-resistant, whereas recruitment of lysosomal membrane-repair machinery requires LRRK2 kinase function. Furthermore, PS19 mice, expressing the P301S tau mutation, were treated with PF-360 or crossed with LRRK2 knockouts to assess the LRRK2 dependence of GVB formation *in vivo* by western blot for the aforementioned markers. These *in vivo* studies will further identify the role of LRRK2 in GVB formation, and high-resolution imaging of membrane dynamics in tau-burdened neurons *in vitro* will be critical to define how LRRK2 kinase activity regulates lysosomal events upon tau pathology.

Disclosures: E. Ma: None. **S. Yim:** None. **J. Ecker:** None. **A.B. West:** None. **T.J. Cohen:** None. **S.A. Buck:** None. **L. Sanders:** None.

Poster

PSTR128: Parkinson's Disease: Molecular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR128.11/U11

Topic: C.03. Parkinson’s Disease

Support: D.A.D., R.A., L.P ASAP- 020600

Title: Cell-type-specific presynaptic dysfunction in Parkinson’s disease-vulnerable dopamine neurons.

Authors: *C. CHEN[1,2], Q. HE[3,2], D. A. DOMBECK[3,2], R. AWATRAMANI[4,2], L. PARISIADOU[1,2];
[1]Pharmacol., Northwestern university, Chicago, IL; [2]Aligning Sci. Across Parkinson’s (ASAP) Collaborative Res. Network, Chevy Chase, MD; [3]Neurobio., Northwestern Univ., Evanston, IL; [4]Neurol., Northwestern Univ., Chicago, IL

Abstract: Parkinson’s disease is marked by degeneration of substantia nigra pars compacta dopamine neurons, but accumulating evidence suggests that functional impairment begins at the axon and synapse well before neuronal loss. Importantly, dopamine neurons are not uniformly affected in PD; molecularly distinct subtypes show different degrees of vulnerability and resilience. This study examined how LRRK2, an important contributor to both familial and sporadic PD, affects dopamine neuron populations with distinct vulnerability profiles.
Using immunofluorescence, and proximity-labeling strategies, we found that PD-vulnerable dopamine neuron subtypes show elevated LRRK2 expression. In LRRK2 mutant mice, super resolution imaging pathogenic LRRK2 selectively disrupted presynaptic release-site organization in vulnerable dopamine axons, while comparatively sparing resilient dopamine neuron populations. These structural defects were accompanied by impaired evoked and spontaneous striatal dopamine release in vivo, in animals with LRRK2 mutations. This study identifies a cell-type-specific presynaptic mechanism of nigrostriatal dysfunction in PD and provides a framework for therapeutic strategies targeting early disease mechanisms before irreversible neuronal loss.

Disclosures: C. Chen: None. **Q. He:** None. **D.A. Dombeck:** None. **R. Awatramani:** None. **L. Parisiadou:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.01/U12

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

Support: NSF MRI Grant 2407348

Title: C. elegans as Model for Huntington's Disease: The Effect of a Small Molecule Compound on Behavior and Lifespan

Authors: N. ARTOLA, *A. J. KALLARACKAL, S. KRUEGER;
Mount St. Mary's Univ., Emmitsburg, MD

Abstract: Huntington's Disease (HD) is an incurable, rare neurodegenerative condition caused by CAG repeats in the HTT gene, leading to glutamine (polyQ) repeats in the resulting protein. Consequently, protein aggregation occurs in the neurons, deteriorating basic functions over time, like movement and speech. We developed a drug, A1, that binds to DNA to prevent transcription of this gene. To determine the efficacy of A1, protein aggregation in the neurons, lifespan, and behavioral changes are evaluated in C. elegans. C. elegans are a useful model for Huntington's Disease because they have a sequenced genome, transparent nervous system, and short lifespan. Three genotypes of C. elegans were utilized: control (0 CAG repeats), nonpathogenic (19 CAG repeats), and pathogenic (67 CAG repeats). C. elegans were maintained on plates based on genotype and condition (with or without A1), and researchers were blinded from conditions

during analysis. Three-day old (young adult) C. elegans were picked for reversal behavioral assays, which analyzed the number of times worms would reverse in a minute. After this experiment, worms were chosen to be imaged by a confocal microscope and will be analyzed using Nikon software to quantify protein aggregation. Lastly, C. elegans were examined in lifespan assays. Though statistically insignificant, results showed a positive trend between increased CAG repeats and reversals in the control condition and negative trend between CAG repeats and reversals with A1. In the lifespan assays, nonpathogenic worms with A1 showed a trend of decreased survival rates, while the pathogenic worms did not. In both these tests, trends could suggest a link between A1 effectiveness and pathogenic polyQ presence. This study could prove useful in understanding the effects of A1 as a potential treatment for Huntington's Disease, which could lead to clinical trials in the future.

Disclosures: N. Artola: None. **A.J. Kallarackal:** None. **S. Krueger:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.02/U13

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

Support: NIH Grant R15GM155985

Title: Pathogenic human huntingtin expression promotes widespread aggregation within striated muscle, leading to profound alterations in nuclear function, metabolic homeostasis, and physiological performance

Authors: T. HANA[1], ***K. G. ORMEROD**[2];
[2]Neurosciences and Psychiatry, [1]Univ. of Toledo, Toledo, OH

Abstract: Huntington’s disease (HD) is caused by expansion of a CAG repeat within the human *HTT* gene, producing a mutant huntingtin protein that misfolds and forms intracellular aggregates. Although HD is primarily characterized as a neurodegenerative disorder, mutant huntingtin is ubiquitously expressed and peripheral tissues, including skeletal muscle, exhibit pathological abnormalities. To investigate the muscle-intrinsic consequences of pathogenic huntingtin expression, we expressed a caspase-6-truncated human mutant huntingtin transgene in the body wall musculature of *Drosophila melanogaster* larvae and performed quantitative structural and functional analyses. Pathogenic huntingtin expression induced widespread intramuscular aggregate formation, with aggregate fluorescence intensity increasing as a function of aggregate size and morphology becoming progressively irregular. Delaying transgene expression until later stages of larval development markedly reduced aggregate abundance, indicating a strong temporal dependence of aggregate formation. Myonuclei were significantly enlarged, irregular in morphology, and exhibited reduced fluorescence intensity, consistent with altered nuclear organization. Huntingtin aggregates were also detected within nuclei, suggesting

disruption of nuclear proteostasis. While overall muscle morphology and sarcomere organization remained intact, mitochondrial organization was profoundly disrupted, with extensive mitochondrial aggregation throughout muscle fibers. Functional analyses revealed significant reductions in excitatory junctional potential amplitude and muscle contractile force, indicating impaired neuromuscular transmission and muscle performance. Together, these findings demonstrate that pathogenic huntingtin expression in skeletal muscle is sufficient to induce extensive protein aggregation, nuclear and mitochondrial dysfunction, and physiological impairment independent of overt muscle structural degeneration. These results highlight the importance of muscle-intrinsic pathogenic mechanisms and establish *Drosophila* skeletal muscle as a tractable model for investigating the cellular basis of peripheral pathology in Huntington's disease.

Disclosures: T. Hana: None. **K.G. Ormerod:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.03/U14

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

Support: NIH Grant R15GM155985

Title: The influence of dietary manipulation on Huntington's Disease pathophysiology

Authors: *M. HASSAN[1], T. HANA[3], K. O'CONNOR[1], O. ALSHEHAB[1], A. SHARMA[3], E. MCCONOCHA[3], H. GOINS[3], J. ROBERTSON[4], K. ORMEROD[2];
[1]Neurosci. and Psychiatry, [2]Univ. of Toledo, Toledo, OH; [3]Neurosci. and Psychology, Toledo, OH; [4]Middle Tennessee State Univ., Murfreesboro, TN

Abstract: Huntington's disease (HD) is an inherited neurodegenerative disorder characterized by progressive cognitive decline, psychiatric disturbances, and involuntary movements known as chorea. Disease onset and severity are strongly associated with the length of a polyglutamine (polyQ) repeat expansion within the *Huntingtin* (*HTT*) gene. Expansion of this CAG repeat sequence results in an abnormally long polyQ tract in the huntingtin (HTT) protein, promoting protein misfolding and aggregation. These misfolded proteins form insoluble intracellular aggregates, particularly within neurons, contributing to neuronal dysfunction and degeneration. While there is currently no cure for HD, dietary interventions have been shown to alleviate certain symptoms and may influence disease progression by modulating metabolic and cellular pathways associated with neurodegeneration. To demonstrate the neuron-intrinsic consequences of pathogenic huntingtin expression, our lab previously expressed caspase-6 truncated pathogenic human huntingtin in the nervous system of *Drosophila melanogaster* larvae and performed quantitative structural, functional, and behavioral analyses (Hana et al, 2024). Here we expand upon these studies and examine whether strategic dietary changes impact the

formation and proliferation of htt-protein aggregates in the larval NS. Our investigation then explores whether dietarily-influenced changes in htt-aggregation leads to changes in synaptic structure, metabolism, organelle trafficking, physiology, and ultimately larval crawling behavior. Collectively, these results underscore the critical role of dietary factors in modulating huntingtin aggregation dynamics and support further investigation of nutritional interventions as potential regulators of Huntington's disease pathogenesis.

Disclosures: M. Hassan: None. **T. Hana:** None. **K. O'Connor:** None. **O. Alshehab:** None. **A. Sharma:** None. **E. McConocha:** None. **H. Goins:** None. **J. Robertson:** None. **K. Ormerod:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

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

Support: China NSF Support: This work was supported by fundings from National Science foundation (82071421, and 82271902 to SHL, 8267053714 to HCT).
China NSF 8267053714 to HCT.

Title: Rhes is Important for Primate Striatum Neuronal Survival

Authors: S. XU[1], H. TONG[1], X. LI[2], *S.-H. LI[1];
[1]Jinan Univ., Guangzhou, China; [2]Human Genet., Jinan University, China, Guangzhou, China

Abstract: Rhes is Important for Primate Striatum Neuronal Survival
Shuying, Xu; Huichun, Tong; Xiao-Jiang Li and Shihua Li.Guangdong Provincial Key Laboratory of Non-human Primate Research, Key Laboratory of CNS Regeneration (Ministry of Education), Guangdong-Hongkong-Macau Institute of Central Nerve Regeneration, Jinan University, Guangzhou, China 510632
AbstractHuntington's disease (HD) is an autosomal dominant neurodegenerative disorder caused by mutations in the huntingtin gene (HTT), leading to an expanded CAG repeat sequence and the production of a toxic mutant huntingtin protein (mHTT) with a polyglutamine (PolyQ) tract. The accumulation of mHTT forms aggregates in the striatum, resulting in selective neuronal death, particularly affecting medium spiny neurons. Previous studies have indicated that Ras Homolog Enriched in Striatum (Rhes) is selectively expressed in the mouse striatum, suggesting a potential role in the selective vulnerability seen in HD. However, findings regarding Rhes's role in HD mouse models have been inconsistent. In this study, we compared Rhes expression patterns during development in mice and cynomolgus monkeys, identifying species-specific differences. We employed the CRISPR/Cas9 system to knock down Rhes in the striatum of both species. Through behavioral assays, western blotting, immunofluorescence staining, and quantitative PCR, we investigated Rhes's role under normal physiological conditions and in the context of

HD. Our results demonstrated that Rhes knockdown in CAG 140Q KI HD mice led to increased mHTT aggregation without neurodegeneration, suggesting compensatory mechanisms in mice. In contrast, Rhes knockdown in cynomolgus monkeys resulted in significant neuronal loss, glial activation, and reductions in synaptic proteins. These findings highlight the critical role of Rhes in neuronal survival within the primate brain and provide new insights into the mechanisms underlying selective neuronal vulnerability in HD pathogenesis.
Support: This work was supported by fundings from National Science foundation (82071421, and 82271902 to SHL, 8267053714 to HCT).The animal work in this study was approved by the Jinan University institutional animal care and use committee.

Disclosures: S. Xu: None. **H. Tong:** None. **X. Li:** None. **S. Li:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.05/U16

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

Title: Primate huntingtin orchestrates cytoplasmic mRNA localization and implicates a loss-of-function mechanism in Huntington’s disease.

Authors: *J. LIN[1,2], X. LI[2], S. YANG[2];
[1]Dept. of Neurol., The First Affiliated Hosp. of Guangzhou Med. university, Guangzhou City, China; [2]Jinan Univ., Guangzhou, China

Abstract: Huntington's disease (HD) is caused by an abnormal expansion of CAG trinucleotide repeats in the *HTT* gene, which encodes a large scaffold protein. Previous studies have characterized the HTT interaction network in the mouse brain. In this study, by analyzing non-human primate brain samples, we have for the first time mapped the primate-specific HTT interactome and identified its unique interactions with RNA-binding proteins within the spliceosome pathway. Notably, primate HTT specifically binds to a subset of spliceosome proteins through its proline-rich domain; however, polyglutamine expansion attenuates this interaction, suggesting that a loss-of-function mechanism of HTT may contribute to HD pathogenesis. Critically, although spliceosome proteins are canonically localized to the nucleus and HTT to the cytoplasm, their species-specific binding in primates reveals that certain HTT-interacting spliceosome proteins exhibit dual nuclear-cytoplasmic localization in primate neurons, whereas in murine neurons they are predominantly restricted to the nucleus. During embryonic development, HTT deficiency disrupts the subcellular localization of these spliceosome proteins, thereby impairing neuronal physiological functions. These findings elucidate the distinctive role of primate HTT in mRNA regulatory processes, providing novel molecular insights into HD pathogenesis and identifying potential therapeutic targets.

Disclosures: J. Lin: None. **X. Li:** None. **S. Yang:** None.

Poster

PSTR129: Huntington's Disease

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Program #/Poster #: PSTR129.06/U17

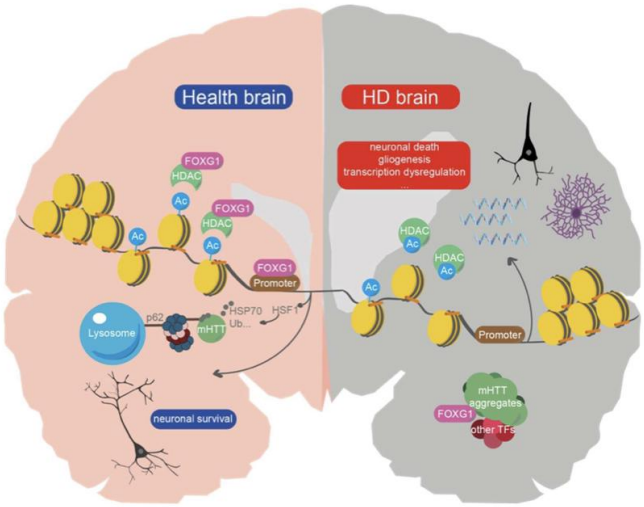
Topic: C.04. Movement Disorders Other than Parkinson's Disease

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National Key Research and Development Program of China 2021YFA0805200
National Natural Science Foundation of 536 China (82171244, 81922026, 82271902, 81830032, 82071421, 31872779, and 32170981)
Guangzhou Key Research Program on Brain Science 202007030008

Title: Striatal downregulated FOXG1 contributes to neuropathology in Huntington's Disease

Authors: *Y. CHEN[1], J. WU[2], Y. LIN[3], C. LI[3], J. WU[2], S.-H. LI[4], X. LI[3], S. YAN[5];
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Abstract: Huntington's disease (HD) is characterized by the preferential degeneration of striatal mediumspiny neurons, though the molecular drivers of this selective vulnerability remain poorly understood. While FOXG1 is a recognized key regulator of brain development, its involvement in adult neurodegeneration has been largely unexplored. In this study, we identified a selective downregulation of FOXG1 in the striatum across multiple HD species. CRISPR-Cas9.mediated knockdown of striatal FOXG1 in wild-type mice can induce schizophrenia-like behaviors, and robust gliogenesis, accompanied by the dysregulation of dopamine-related genes.Mechanistically, we demonstrate that FOXG1 functions as a key transcriptional maintainer and promotes mutant HTT degradation by regulating the HSF1/ubiquitin-proteasome system (UPS) pathway. Strikingly, knockdown of striatal FOXG1 in 12-month-old HD mice further mimics the robust striatal neurodegeneration observed in HD patients and knock-in pig models. Our findings reveal a novel role for FOXG1 in maintaining protein homeostasis and highlight it as a potential therapeutic target for HD and other misfolded protein diseases.



Schematic representation of the role of FOXG1 in the healthy and HD brain. FOXG1 is widely recognized for its crucial role in early central nervous system development, particularly in forebrain formation. However, its involvement in neurodegenerative diseases has rarely been reported. In this study, we identified FOXG1 as selectively downregulated in the striatum —a brain region vulnerable in Huntington's disease (HD)—and demonstrated that restoring FOXG1 expression alleviates key HD phenotypes, including motor deficits, neuroinflammation, and mutant huntingtin aggregation. Mechanistically, FOXG1 regulates synaptic transcription and enhances proteostasis through autophagy and ubiquitination pathways, notably via the HSF1/ HSP70/UBE3A axis. Moreover, striatal FOXG1 reduction alone induces schizophrenia-like behavior, and leads neurodegeneration in HD mice striatum. These findings establish FOXG1 as a protective modulator of striatal integrity and a potential therapeutic target in HD and related conditions.

Disclosures: Y. chen: None. **J. Wu:** None. **Y. Lin:** None. **C. Li:** None. **J. Wu:** None. **S. Li:** None. **X. Li:** None. **S. Yan:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.07/U18

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

Title: Elevated WWOX contributes to DNA damage in Huntington's Disease without affecting somatic instability

Authors: *E. GRANUCCI[1], T. PETROZZIELLO[6], A. BOUDI[10], G. FIELD[7], S. HUNTRESS[2], A. CASTILLO-TORRES[6], R. B. MONSANTO[8], M. WU[9], E. SAPP[7], M. A. POULADI[11], M. DIFIGLIA[3], K. B. KEGEL[1], J. F. GUSELLA[12], R. MOURO PINTO[4], G. SADRI-VAKILI[5]; [2]Neurol., [1]Massachusetts Gen. Hosp., Charlestown, MA; [3]Massachusetts Gen. Hosp., NEWTONVILLE, MA; [4]Massachusetts Gen. Hosp., Boston, MA; [5]Dept Neurol., Massachusetts Gen. Hosp., Charlestown, MA; [6]Neurol., Mass Gen. Brigham, Boston, MA; [8]Neurol., [7]Mass Gen. Brigham, Charlestown, MA; [9]Mass Gen. Brigham, Bronx, NY; [10]Neurol., Mass Gen.

Brigham / Harvard Med. Sch., Charlestown, MA; [11]Med. Genet., Univ. of British Columbia, Vancouver, BC, Canada; [12]Molec Neurogene Unit Ctr. Human Genet, Mass Gen. Hosp., Boston, MA

Abstract: While the genetic cause of Huntington's Disease (HD) is now well understood, the mechanisms by which neuronal degeneration occurs in HD remain incompletely characterized. Recent evidence supports a role for DNA damage and DNA repair dysfunction in HD pathogenesis, with several HD disease modifier genes involved in DNA repair mechanisms. In addition, previous studies have reported alterations in ataxia telangiectasia mutated (ATM) signaling in HD. ATM has also been linked to the WW domain-containing oxidoreductase (WWOX), a protein involved in DNA repair and genomic stability maintenance, through the E3 ubiquitin ligase ITCH. However, it remains unknown whether this pathway is altered in HD. Our analysis of post-mortem HD prefrontal cortex (PFC) revealed no significant alterations in total ATM, phosphorylated ATM (pATM-S1981), or ITCH compared to controls. Additionally, immunocytochemistry/immunofluorescence analysis of SH-SY5Y cells treated with lysates from post-mortem HD PFC demonstrated no changes in pATM-S1981 levels but revealed an increase in histone H2AX phosphorylation at S139 (γ-H2AX), a marker of DNA double-strand breaks. This suggests that HD PFC lysates can induce DNA damage signaling independent of the canonical activation of ATM. In contrast to ATM and ITCH, WWOX levels were significantly increased in post-mortem HD PFC as well as in HD embryonic stem cell-derived cortical neurons compared to isogenic controls. Furthermore, treatment of SH-SY5Y cells with recombinant human WWOX protein or stable WWOX overexpression increased γ-H2AX levels, supporting a role for WWOX in promoting DNA damage. In order to determine whether WWOX contributes to DNA damage in HD, SH-SY5Y cells were treated with HD PFC lysates that had been depleted of WWOX. Depletion of WWOX abolished the increases in γ-H2AX induced by HD PFC lysates, implicating WWOX in HD-associated DNA damage. Finally, while WWOX overexpression in RPE1-AAVS1-CAG115 cells, a cellular model of somatic instability of CAG repeats in HD, similarly increased γ-H2AX, it did not affect CAG repeat instability. Taken together, these results demonstrate an important role of WWOX in contributing to DNA damage in HD, and that this mechanism occurs independently of activation of the ATM pathway.

Disclosures: E. Granucci: None. **T. Petrozziello:** None. **A. Boudi:** None. **G. Field:** None. **S. Huntress:** None. **A. Castillo-Torres:** None. **R.B. Monsanto:** None. **M. Wu:** None. **E. Sapp:** None. **M.A. Pouladi:** None. **M. Difiglia:** None. **K.B. Kegel:** None. **J.F. Gusella:** None. **R. Mouro Pinto:** None. **G. Sadri-Vakili:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.08/U19

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

Support: CHDI Foundation, Inc.
the Ludwig Neurodegenerative Disease Seed Grants Program at Harvard Medical School
the Harvard Medical School Department of Genetics
the National Human Genome Research Institute of the National Institutes of Health under award number R01HG006855

Title: A shared DNA-repeat toxicity threshold, reached somatically at cell-type-specific rates, unites cortical and striatal neurodegeneration in Huntington's disease

Authors: S. KASHIN[1], ***W.-S. LEE**[2], T. MCDONALD[3], K. MORRIS[5], R. HANDSAKER[1], C. MELLO[2], L. SPINA[1], N. REED[3], H. DE RIVERA[3], S. JANA[3], S. BERRETTA[6], S. MCCARROLL[4];
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Abstract: Huntington's disease (HD) affects different brain areas with distinct timing, severity, and gene-expression changes. The cerebral cortex and striatum have long been proposed to have distinct pathogenic mechanisms in HD, with one's degeneration resulting from the other's. Striatal neurons degenerate as their huntingtin (*HTT*) CAG-repeat tracts expand somatically beyond 150 CAGs. To determine what dynamics affect the cortex, we analyzed RNA expression and *HTT* CAG-repeat tracts in more than 125,000 nuclei from 12 cortical areas. Cortical neurons manifested the same sequences of cell-autonomous events as striatal neurons, with their toxicity also commencing beyond 150 CAGs; however, downstream gene-expression sequelae were specific to each neuronal type. Cortical area, cortical layer, and axonal projections played only incidental roles. Cortical and striatal neurons were also united by a key pathological feature: nuclear inclusions of aggregated HTT protein appeared in those nuclei with expansions well beyond 150 CAGs.

Disclosures: S. Kashin: None. **W. Lee:** None. **T. McDonald:** None. **K. Morris:** None. **R. Handsaker:** None. **C. Mello:** None. **L. Spina:** None. **N. Reed:** None. **H. de Rivera:** None. **S. Jana:** None. **S. Berretta:** None. **S. McCarroll:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.09/U20

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

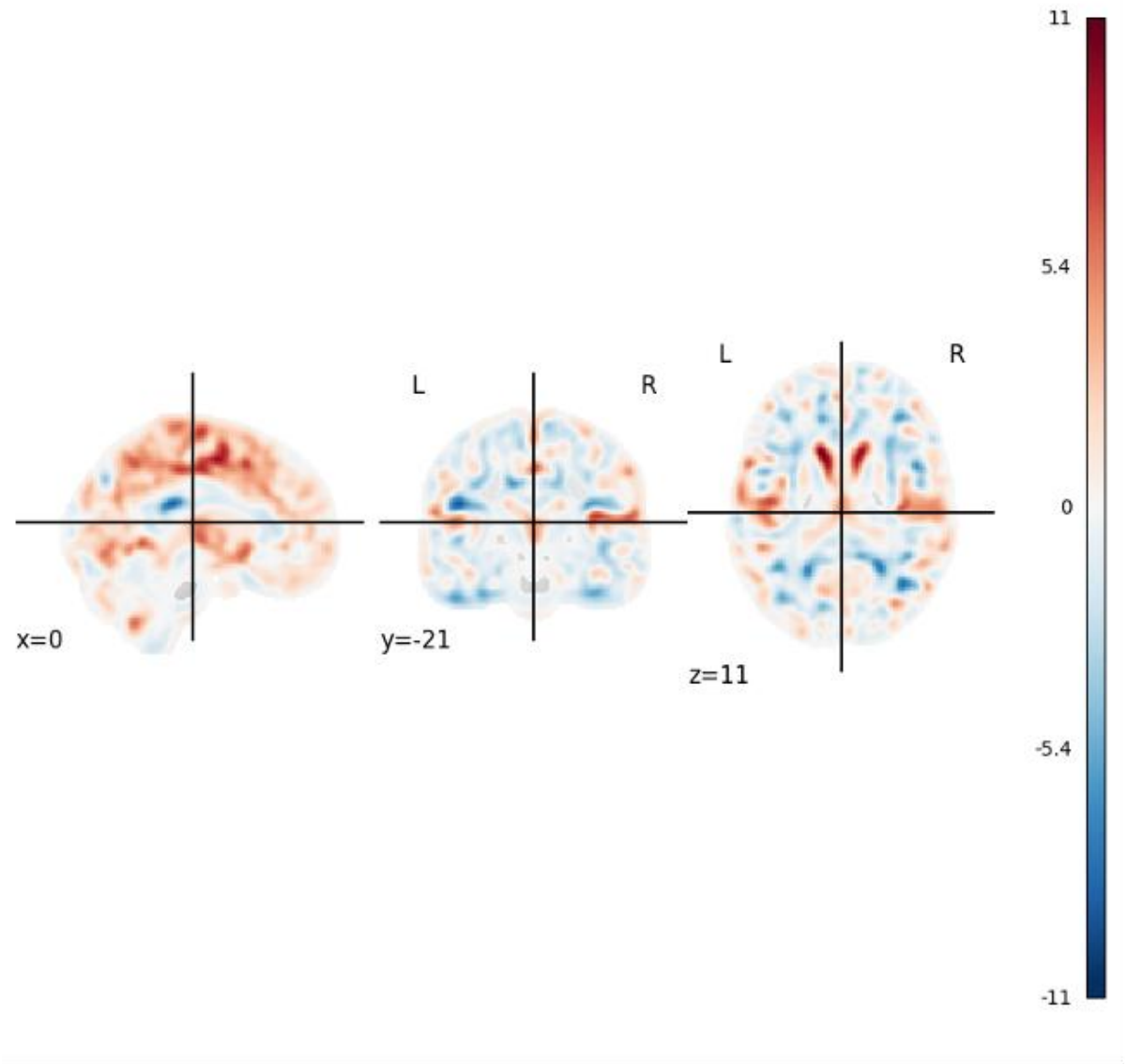
Support: NIH Grant U01NS103475
NIH Grant U01NS105509
NIH Grant R01NS040068

CHDI Grant A3917
CHDI Grant A6266

Title: Multimodal fusion of functional network connectivity and grey matter volume identifies a putative biomarker for Huntington's Disease

Authors: J. D. CLEMSEN[1], **B. T. BAKER**[1], H. J. BOCKHOLT[1], V. D. CALHOUN[2], *J. S. PAULSEN[3];
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Abstract: Background: Huntington's Disease (HD) is an autosomal dominant trinucleotide repeat disorder that transcribes and translates CAG repeats into a cumulatively pathogenic Huntingtin (HTT) protein leading to progressive neurodegeneration and decreased network integration in static functional network connectivity (sFNC). Since both motor score and sFNC have demonstrated usefulness for diagnosis, the application of multimodal fusion for biomarker discovery could provide insight into the progression of HD.
Methods: Scans from the PREDICT/PREVENT-HD dataset were preprocessed including motion correction and smoothing with 6mm FWHM in relation to the true voxel dimensions 3x3x3, flip angle of 20 degrees, TE=3, TR=18, FOV=24 cm, 124 slices matrix 256×192,3/4 phase FOV, and NEX=2. Joint independent component analysis with MCCA (MCCA+JICA) was applied to the dataset, and linear regression using Python was applied to the loading parameters and the CAG-age-product (CAP) score.
Results: The statistical results for the 60 subjects tested found one component that was significant. The eighth component GMV demonstrated a 0.002615 p value with a -2.31 t statistic (Figure 1). The sixth FNC component also showed a high p value of 0.05. However, the corresponding GMV was not with a p value of 0.38.
Conclusions: The findings suggest potential in biomarker discovery for HD with functional and structural fusion. The eighth significant component may only be the strongest and thereby most visible component for multimodal fusion.



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Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.10/U21

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

Support: Huntington's Disease Foundation Research Grant
Mercer University School of Medicine Research Grant

Title: Identification of age-associated upstream regulators to promote neuronal resilience in HD patient-derived neurons.

Authors: *S. LEE;
Biomed. Sci., Mercer Univ. Sch. of Med., Columbus, GA

Abstract: Aging is a risk factor for neurodegenerative disorders, but the molecular link between neuronal aging and neurodegeneration remains unclear. Huntington's disease (HD) is an inherited neurodegenerative disorder with adult-onset clinical symptoms. Striatal medium spiny neurons (MSNs) are mainly affected in HD, but how aging contributes to MSN degeneration remains uncertain. Using directly converted MSNs from fibroblasts of HD patients (HD-MSNs), we studied age-related pathological features, including neuronal cell death, mutant huntingtin (mHTT) aggregation, and DNA damage in HD. In this study, through transcriptomic analysis of longitudinally aged MSNs and HD-MSNs, we identified four upstream regulators, NFKB1, SOD1, IRF3, and REST, that modulate downstream gene expression in aged MSNs. Among these, knocking down NFKB1 significantly reduced HD pathologies in HD-MSNs, while overexpressing NFKB1 reversed these protective effects. Overall, these results identify NFKB1 as a key age-associated upstream regulator whose downregulation confers neuronal resilience and is a potential therapeutic target in HD.

Disclosures: S. Lee: None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.11/U22

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

Title: Transcriptomic analysis of in vitro cell models of Huntington's disease using iPSC-derived medium spiny neurons reveals disease mechanisms and therapeutic modes of action.

Authors: *S. YOSHIDA[1], M. YANO[3], K. FUKUSHIMA[2], H. OKANO[4,2];
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Abstract: Introduction: Huntington's disease (HD) is caused by a CAG repeat expansion in exon 1 of the Huntingtin gene (*HTT*), leading to widespread dysregulation of gene expression that underlies progressive neurodegeneration. While current therapeutic developments for HD largely focus on suppressing expression of mHTT, elucidating the alternative molecular mechanism of HD facilitates the discovery of novel therapeutic agents. Human induced pluripotent stem cells (iPSC)-based platforms offer opportunities to recapitulate

neurodegenerative pathologies and accelerate the identification of novel therapeutic agents. Previously, we established *in vitro* cell models of HD using iPSC-derived medium spiny neurons (MSNs) that recapitulate key neuropathological hallmarks, such as neuronal death, neurite retraction, and accumulation of HTT protein aggregates. Furthermore, we identified four lead candidates for HD through screening from existing therapeutic agents. **Objective:** We here investigated transcriptomic profiles to interrogate the molecular pathway modulated by the candidate drugs for HD. **Methods**: Three HD patient-derived iPSCs (CAG repeat length :180, 50, and 50) and 3 healthy donor-derived iPSCs were differentiated into HD-MSNs and control MSNs (CNT-MSN), respectively. We then performed RNA-seq analysis to investigate the gene expression levels quantified as transcripts per million (TPM) and the differential gene expression (DEG) using DESeq2. The prioritized gene sets were subjected to enrichment analysis via g:Profiler. **Results**: From RNA-seq data sets of our MSNs, we confirmed gene expression of DARPP32 known as the MSN marker. To clarify similarity with *in vivo*, we showed that CNT-MSNs have a high Jaccard similarity index with striatum among brain regions. Moreover, analysis of cell-type specific genes in striatum revealed that CNT-MSNs share high similarity with dopamine receptor D2-positive (DRD2+) MSN. KEGG pathway enrichment analysis revealed the distinct involvement of neuronal interaction and immune response in the HD pathogenic mechanism. Among the candidate drugs, ropinirole effectively suppressed cell death through partially normalizing the expression of dysregulated genes. KEGG pathway enrichment analysis of the genes rescued by ropinirole further clarified its mode of action, highlighting pathways associated with hyperexcitability and non-canonical cell death that resulted in promoting regenerative processes. **Conclusion**: Our *in vitro* HD-MSN models provided mechanistic insight into HD and shed light on the molecular mechanisms through which these candidate drugs exert their effects.

Disclosures: S. Yoshida: A. Employment/Salary (full or part-time):; K Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc. **M. Yano:** A. Employment/Salary (full or part-time):; K Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc. **K. Fukushima:** A. Employment/Salary (full or part-time):; K Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc. **H. Okano:** A. Employment/Salary (full or part-time):; K Pharma, Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); K Pharma, Inc..

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.12/U23

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

Title: Mitochondrial Respiratory Profiles of PBMCs in Huntington's Disease and Healthy Controls

Authors: *B. REVINA[1], R. VALANTE[2], B. JANSONE[2];
[2]Neuromedicine and Neurosci., [1]Univ. of Latvia, Riga, Latvia

Abstract: Background: Huntington's disease (HD) is an autosomal dominant neurodegenerative disease characterized by progressive motor dysfunction, cognitive decline, and neuropsychiatric symptoms. Among the multiple mechanisms underlying Huntington's disease, mitochondrial dysfunction has emerged as an important contributor where alterations in energy production may contribute to disease progression. Peripheral blood mononuclear cells (PBMCs) provide a minimally invasive model for assessing systemic bioenergetic alterations and mitochondrial function with potential biomarker value in Huntington's disease. Aim: To compare PBMC mitochondrial bioenergetics between Huntington's disease patients and healthy controls. Methods: HD group with confirmed diagnosis (52,6 ± 12,6 years; male (m) n= 6) and control group individuals (29 ± 14,3 years; male (m) n=6) without acute or chronic illnesses were tested. Age-matched controls were not available for this cohort. Approved by University of Latvia Ethics Committee (No. 13-22/179). Study participants avoided food supplements, caffeinated drinks, or substances affecting mitochondrial bioenergetics for ≥48h prior the fasting blood sampling between 9:40-10:30 a.m. PBMCs were isolated via Ficoll density gradient and followed by high-resolution respirometry (Oroboros O2k, Austria) using SUIT-002 protocol. This measured oxygen flux (JO_2, pmol/s/10^6 cells) in: ROUTINE , F-OXPHOS, FN-OXPHOS, FNS-OXPHOS, Max-ET, and ET-CII. Unpaired t-tests were performed in GraphPad Prism 8.0.2 (mean ± SD; $p<0.05$). Results: Statistically significant differences were observed in ROUTINE ($p = 0.0188$), F-OXPHOS ($p = 0.0014$), FNS-OXPHOS ($p = 0.0006$), Max-ET ($p = 0.0217$), and ET-CII ($p = 0.0089$). Limitations: small sample size and single-sex cohort limit generalizability. Conclusion: HD patients exhibited systemic bioenergetic dysfunction beyond the central nervous system. Reduced fatty acid oxidation-supported OXPHOS and Complex II-linked electron transport are consistent with mitochondrial dysfunction and impaired substrate utilization in HD. PBMCs may have potential as accessible peripheral indicators of HD-related mitochondrial dysfunction and may be useful for monitoring mitochondria targeted interventions. Conflict of interest: No conflicts of interest.

Disclosures: B. Revina: None. **R. Valante:** None. **B. Jansone:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.13/U24

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

Title: Bioenergetic profiling reveals medium dependent mitochondrial dysfunction in HTT mutant ioGlutamatergic Neurons during differentiation

Authors: *N. ROMERO[1], G. WANG[1], A. TURNER[2];
[1]Agilent Technologies, Lexington, MA; [2]bit.bio, Cambridge, United Kingdom

Abstract: Mitochondrial dysfunction is increasingly recognized as a central contributor to the pathogenesis of neurodegenerative diseases. The development of effective therapies for these conditions requires robust and human relevant in vitro disease models that can recapitulate in vivo observations. ioGlutamatergic Neurons (bit.bio) are a rapidly maturing, consistent, and functional source of human iPSC-derived glutamatergic neurons. The genetic engineered variants available provide a scalable platform to study neuronal bioenergetics and neurodegenerative disease mechanisms. Huntington's disease (HD) is an inherited neurodegenerative disorder caused by an expansion of CAG repeats in the huntingtin (HTT) gene, leading to the production of a mutant protein that drives progressive neuronal dysfunction. Mitochondrial dysfunction has emerged as a central contributor to HD pathogenesis. A 50CAG HTT expansion was engineered in ioGlutamatergic Neurons to create an isogenic HD model. Here, we optimized assay conditions for metabolic profiling of cultures of the wild-type (WT) ioGlutamatergic Neurons and the HD model to assess mitochondrial function and glycolytic dependence over time under distinct culture conditions. Metabolic profiling, including cellular ATP production rate and mitochondrial function were evaluated using the Agilent Seahorse XF Pro analyzer. Data were normalized to imaging-based live cell number using Agilent Biotek Cytation 9 multimode plate reader. Morphological assessments of iPSC-derived neurons differentiated in Neurobasal medium showed comparable neuronal development between cultures of the WT and HD model across all time points. However, metabolic profiling revealed that Neurobasal medium induced a progressive shift toward a highly glycolytic phenotype in both genotypes, accompanied by markedly reduced OXPHOS activity. In contrast, neurons cultured in BrainPhys medium preserved a predominantly oxidative metabolic phenotype over time. Under these conditions, HD model neurons exhibited reduced basal and maximal respiration, decreased spare respiratory capacity, and a compensatory increase in glycolytic contribution to energy production relative to WT controls. These findings demonstrate that culture conditions critically influence neuronal metabolic phenotypes and can either mask or reveal disease-relevant mitochondrial dysfunction. BrainPhys medium more accurately recapitulates oxidative neuronal metabolism and enables detection of HD-associated bioenergetic deficits. This platform provides a robust framework for modeling neurodegenerative disease and evaluating metabolic interventions.

Disclosures: N. Romero: A. Employment/Salary (full or part-time):; Agilent Technologies. **G. Wang:** A. Employment/Salary (full or part-time):; Agilent Technologies. **A. Turner:** A. Employment/Salary (full or part-time):; Bit.bio.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.14/U25

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

Support: Huntington's Disease Foundation
CHDI Foundation

Title: Altered MED15 localization and fatty acid metabolism in Q175/Q7 Huntington's disease mice and human HD109 neural stem cells.

Authors: *K. B. KEGEL[1], A. IWANOWICZ[1], K. SHING[4], R. ROBERTSON[1], A. BOUDI[5], E. SAPP[2], M. DIFIGLIA[3];
[1]Neurol., Massachusetts Gen. Hosp., Charlestown, MA; [2]Neurol., Massachusetts Gen. Hosp., Massachusetts General Hospital, MA; [3]Massachusetts Gen. Hosp., NEWTONVILLE, MA; [4]Neurosci., Univ. of Pennsylvania, Philadelphia, PA; [5]Neurol., Mass Gen. Brigham / Harvard Med. Sch., Charlestown, MA

Abstract: The transcription factor MED15 regulates lipogenic genes involved in fatty acid (FA) metabolism, lipid deposition and lipid droplet (LD) accumulation. MED15 was recently identified as a new genetic modifier for Huntington's disease (HD) associated with the total functional capacity score. Metabolism of FAs through beta-oxidation (FAO) in the mitochondria increases dangerous reactive oxygen species that can contribute to lipofuscin accumulation with age. MED15 has been identified by mass spectrometry in immunoprecipitates of Huntingtin. One hypothesis is that altered handling of lipids due to changed interaction of mutant Huntingtin protein with MED15 may contribute to neurons reaching a tipping point and instigating neurodegeneration. Fluorescent labeling with the LD stain Bodipy 493/503 and antibodies to cellular markers demonstrated increased LDs exclusively in neurons in Q175/7Q HD mouse caudate-putamen compared to WT (N=8 mice per group, 6 months, $p<0.05$; 12 months $p<0.05$ unpaired t-test); immunostaining for MED15 in adjacent sections showed a lower nuclear/cytoplasmic ratio in Q175/Q7 HD striatal neurons versus WT (N=7-8 mice per group, 6 and 12 months, $p<0.001$, unpaired t-test). We used human neural stem cells (NSCs) to study the effects of glucose and nutrient starvation on FAO induction and MED15 localization. In normal growth medium, the nuclear/cytoplasmic ratio of MED15 immunostaining was unchanged in non-gene carrier Control versus HD109 NSCs bearing 109 CAGs; however, HD109 NSCs had increased MED15 immunostaining in a perinuclear compartment (N=4 coverslips representing 102-108 cells per group, $p<0.001$, unpaired t-test). Metabolic labeling for FAO with a novel probe showed that in defined media containing glucose but lacking other small molecule metabolites, the mean rate of FAO for HD109 NSCs was increased compared to Control NSCs (N=98-143 cells per group, $p<0.05$, ANOVA with posthoc Tukey's test). Furthermore, nutrient starvation altered MED15 localization. Our results indicate a defect of HD109 cells to utilize glucose for energy production and suggest that MED15 localization may coerce the switch to FAO metabolism. Our data support the notion that mutant Huntingtin changes MED15 localization impacting regulation of lipid metabolism.

Disclosures: K.B. Kegel: None. **A. Iwanowicz:** None. **K. Shing:** None. **R. Robertson:** None. **A. Boudi:** None. **E. Sapp:** None. **M. Difiglia:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.15/U26

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

Title: Altered Activity-Dependent Local Protein Synthesis in Human iPSC-Derived Huntington's Disease Neurons

Authors: *T. SAROVICH[1], G. CANNESTRO[3], D. AMINEVA[1], J. WEI[2];
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Abstract: Huntington's disease (HD) is a neurodegenerative disorder characterized by early synaptic dysfunction that precedes neuronal loss. Synaptic adaptation to neuronal activity depends on activity-dependent local protein synthesis (ADLPS), a process that enables rapid, spatially restricted protein production at synapses and supports synaptic plasticity and circuit function. Although we previously demonstrated impaired protein synthesis in HD, it remains unknown whether mutant huntingtin (muHTT) disrupts ADLPS. Given the central role of ADLPS in maintaining synaptic function, impairment of this pathway could represent an important mechanism underlying early neuronal dysfunction in HD. To examine ADLPS in HD, mature control and HD human induced pluripotent stem cell (iPSC)-derived neurons were stimulated with the group I mGluR agonist 3,5-dihydroxyphenylglycine (DHPG, 100 μM, 15 min), followed by puromycin incorporation to quantify newly synthesized proteins in somatic and dendritic compartments. Under basal conditions, protein synthesis was largely comparable between control and HD neurons in both somatic and dendritic compartments, although HD neurons exhibited a modest reduction in puromycin incorporation. DHPG stimulation increased dendritic protein synthesis by 1.5-fold in control neurons ($p < 0.05$) but failed to stimulate translation in HD neurons. In contrast, increased somatic translational responses to DHPG treatment were preserved in both genotypes. To determine whether impaired ADLPS was associated with altered neuronal function, multielectrode array recordings were performed before and after DHPG stimulation. Control neurons exhibited a significant 2.5-fold increase in mean firing rate following acute DHPG treatment ($p < 0.05$), whereas HD neurons failed to exhibit a significant change in network activity in response to DHPG stimulation ($p = 0.8$).Together, these findings demonstrate that HD neurons exhibit a selective impairment in ADLPS while largely preserving basal protein synthesis, suggesting that disrupted ADLPS may contribute to early synaptic dysfunction and circuit abnormalities in HD.

Disclosures: T. Sarovich: None. **G. Cannestro:** None. **D. Amineva:** None. **J. Wei:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.16/U27

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

Support: NIH T32 MH015330

Title: Characterization of the Interaction between Huntingtin (Htt) and the N-terminus of the Huntingtin Interacting Protein 14 (HIP14)

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Abstract: The Huntingtin Interacting Protein 14 (Hip14) catalyzes palmitoyl transfer onto the N-terminus of the Huntingtin protein (Htt). This modification allows Htt to localize to cellular membranes, such as that of the Golgi apparatus. Expansion of the polyglutamine repeat within the Htt N-terminus reduces the binding affinity of HIP14, and consequently Htt palmitoylation and sub-cellular distribution. If the Htt:HIP14 binding mechanism could be understood, and the precise effects of the Htt mutation upon the interaction, it might be possible to restore the palmitoylation of Htt with long polyglutamine repeats. This would serve to re-localize Htt to cellular membranes, which would mitigate the effects of high Htt concentrations in other cellular compartments. Here, we report the general binding surface between the N-terminus of Hip14 (residues 1-288) and full-length, wild-type Htt as determined through cryo-EM. It appears that this region of Hip14 engages Htt within the first turn of its N-terminal supercoil. The structure indicated a 1:1 mol ratio between Hip14 and Htt when the Huntingtin Interacting Protein of 40 kDa (Hap40) occupies the N/C terminal groove of Htt. To further characterize the Htt:Hip14 interaction, we assembled complex of Htt 23Q, 54Q, and 79Q each with Hip14 1-288 in the absence of Hap40 at defined mol ratio. Each complex had a symmetrical elution peak, despite the apparent presence of aggregated species at higher molecular weight. We further measured the affinity of Hip14 1-288 for Htt 23Q, 54Q, and 79Q in an effort to quantitatively determine how the mutation affects HIP14 binding. The Kd for the Htt 23Q:Hip14 1-288 interaction was in the high-nanomolar range at 588.3 nM. Increase in polyglutamine length resulted in substantial increase in binding affinity; the Kd for the Htt 54Q:Hip14 1-288 interaction was 104 nM, and the Kd for the Htt 79Q:Hip14 1-288 interaction was 69.11 nM. This suggests that the initial expansion of the polyglutamine repeat increases binding affinity for the Hip14 to the extent that Htt remains soluble. Taken together, our findings describe 1. Where the Hip14 N-terminus binds to Htt, and 2. How the initial polyglutamine expansion affects Hip14 binding affinity.

Disclosures: S.G. Doll: None. **T. Ratovitski:** None. **J. Li:** None. **M. Rodriguez:** None. **M. Jiang:** None. **C.A. Ross:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.17/U28

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

Support: Taube Philanthopies

Title: Co-Activating TrkB and TrkC with PTX-BD10-3 ameliorates astrocyte dysfunction in multiple Huntington's disease mouse models

Authors: *D. A. SIMMONS[1], **R. ROBBINS**[1], T. SOUTO CAMELO[1], F. M. LONGO[1,2]; [1]Stanford Univ., Palo Alto, CA; [2]Wu Tsai Neurosci. Inst., Stanford, CA

Abstract: Huntington's Disease (HD) is a neurodegenerative disorder caused by a mutation in the *HTT* gene producing a mutant huntingtin (mHtt) protein with a polyglutamine repeat expansion. mHtt aggregates intranuclearly and causes degeneration of diverse cell types, most notably medium spiny neurons (MSNs), but also astrocytes. Astrocyte dysfunction in HD manifests as aberrant reactivity and impaired glutamate homeostasis, potassium buffering, and neurotrophic support. Astrocytes express the neurotrophin receptors TrkB and TrkC, which principally bind brain-derived neurotrophic factor and NT-3, respectively, to regulate their metabolic function and survival. Striatal TrkB/C signaling is severely disrupted in HD patients and mouse models and may contribute to astrocyte dysregulation. Thus, promoting of TrkB/TrkC activation could restore astrocyte homeostasis. We administered a novel small molecule ligand of TrkB and TrkC, PTXBD10-3 (BD10-3; 50 mg/kg, once daily, oral gavage) or vehicle (veh; water), to two mouse models of HD and their respective wild-types (WT): male Q175 were dosed for 3 months starting at ~6 months-old and male/female R6/2 for ~7 weeks starting at 4.5 weeks-old. Striatal astrocytes (S100B as a marker) were assessed for HD-related phenotypes via quantitative immunofluorescence and confocal microscopy. BD10-3 reduced astrogliosis, as evidenced by decreased area and intensity of S100B staining, and astrocytic lysosomal accumulation (S100B-LAMP1 colocalization) in both HD mouse models versus WT-veh mice. STAT signaling regulates astrocyte reactivity and proteostasis, including mHtt aggregation. S100B-STAT3 colocalization was reduced in R6/2-veh mice; BD10-3 prevented this decrease. BD10-3 reduced elevated S100B-VGLUT1 colocalization in R6/2 mice suggesting ameliorated pathological synapse elimination. Kinome profiling showed that ephrin receptors, which regulate synaptic pruning by astrocytes, were activated in Q175-veh mice; BD10-3 reduced this activation. Kir4.1 potassium channels are reduced on striatal astrocytes of R6/2-veh mice contributing to MSN excitotoxicity; BD10-3 prevented this deficit. Finally, BD10-3 normalized anxiety-like behavior, improved motor function, and reduced the size of mHtt aggregates in Q175 mice. In all, our results suggest that activating TrkB/TrkC with BD10-3 promotes a shift from reactive, dysfunctional astrocytes to a supportive phenotype in HD mouse models.

Disclosures: D.A. Simmons: None. **R. Robbins:** None. **T. Souto Camelo:** None. **F.M. Longo:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); PharmatrophiX.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.18/U29

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

Title: Amphetamine Challenge Reveals Enhanced Head Bobbing in BACHD Rats

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Abstract: Huntington's disease (HD) is an autosomal dominant neurodegenerative disorder characterized by progressive motor dysfunction. One of its hallmark symptoms is chorea, manifested as involuntary, rapid, and unpredictable movements, while later disease stages are dominated by motor impairments such as bradykinesia and rigidity. In this study, we aimed to characterize the BACHD rat model, a transgenic rat model of HD. A comprehensive behavioral and biochemical assessment was performed, including locomotor activity measured by actometer testing, sensorimotor performance evaluated using the rotarod test, sucrose preference as a measure of motivation, and striatal dopamine and metabolite levels quantified by ultra-high performance liquid chromatography. In addition, neurofilament light chain (NfL), a biomarker of neurodegeneration, was measured longitudinally using Simoa technology. Our results demonstrate that spontaneous involuntary movements are absent in the BACHD rat model. However, a significant reduction in locomotor activity and sensorimotor performance was observed from an early age, resembling motor features typically associated with later stages of HD. NfL levels remained unchanged across all assessed time points. Despite well-described dopamine dysregulation in HD, no significant differences were detected in striatal dopamine levels, dopamine metabolites, or sucrose preference between BACHD and wild-type (WT) rats. Based on these findings, we hypothesized that dopaminergic stimulation might be required to unmask additional motor readouts. Using artificial intelligence-based behavioral analysis, we investigated amphetamine-induced involuntary movements, specifically head bobbing, in WT and BACHD rats following amphetamine administration. Strikingly, amphetamine-induced head bobbing was significantly increased in BACHD rats compared with WT controls. These results indicate that involuntary, repetitive head stereotypies are not evident in the BACHD rat under baseline conditions but can be revealed following dopaminergic system stimulation. Further studies are warranted to elucidate the underlying biological mechanisms and to assess the translational relevance of these findings for HD.

Disclosures: E. Bentea: A. Employment/Salary (full or part-time):; UCB. **A. Pierre:** A. Employment/Salary (full or part-time):; UCB. **C. De Wolf:** A. Employment/Salary (full or part-time):; UCB. **J. Fréquin:** A. Employment/Salary (full or part-time):; UCB. **M. Caruso:** A. Employment/Salary (full or part-time):; UCB. **Y. Ferroudj:** A. Employment/Salary (full or part-time):; UCB. **G. Szczesny:** A. Employment/Salary (full or part-time):; UCB. **N. Pacico:** A. Employment/Salary (full or part-time):; UCB. **R. Angers:** A. Employment/Salary (full or part-time):; UCB. **E. Gillent:** A. Employment/Salary (full or part-time):; UCB. **P. Bonnaillie:** A. Employment/Salary (full or part-time):; UCB. **Z. Ali:** A. Employment/Salary (full or part-time):; UCB. **A. Michel:** A. Employment/Salary (full or part-time):; UCB.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.19/U30

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

Support: NIH Grant NINDS R01A1 NS129563
NIH Grant R01NS119208
NIH Grant R01 NS120879

Title: Huntingtin links inflammasome pathway in Huntington's disease Pathogenesis

Authors: *E. ABERLE[1], M. RODRIGUEZ[2], T. SHI[2], R. WANG[2], R. MIRYALA[2], K. BELKAS[2], G. MERCADO[2], S. G. DOLL[2], J. C. TRONCOSO[3,4], T. RATOVITSKI[2], C. A. ROSS[2,5,6,3], W. SMITH[2,5], M. JIANG[2];
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Abstract: Huntington's disease (HD) is caused by a CAG repeat expansion in the huntingtin (HTT) gene, leading to the pathogenic expansion of a polyglutamine tract in the huntingtin protein. The key pathological features include striatal medium spiny neuronal loss, and the presence of cellular inclusion bodies containing mutant HTT proteins. There is no disease-modifying treatment for HD. The pathogenesis of HD is not fully understood. Recently, studies suggest that neuroinflammation plays a critical role in HD. Here, we use HD in vitro and in vivo mouse models to investigate the roles of NLRP3-Inflammasomes in HD-linked neuroinflammation and neurodegeneration. Our results showed that mutant HTT interacted more with NLRP3 than wild-type HTT. Moreover, mutant HTT increased the activation of the NLRP3-inflammasome pathway. In contrast, knockdown of NLRP3 appears to protect against mutant HTT-induced neurodegeneration in cultured human striatal neurons. These results suggest that HTT/NLRP3-linked inflammasome pathways may play a critical role in HD pathogenesis.

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Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.20/U31

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

Support: NIH Grant R03NS114731-01A1
NIH Grant R03NS132074-01A1
OIE/OVPRED seed grant
SUNY resubmission grant

Title: Inhibition of IKKb disrupts Huntingtin (HTT) movement without affecting its motility dynamics in Drosophila larval nerves.

Authors: *J. HUANG, R. RATHNAYAKE, S. GUNAWARDENA;
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Abstract: Huntingtin (HTT) is a multidomain scaffolding protein that regulates intracellular trafficking in neurons via interactions with membranes and associated proteins. The N-terminal region of huntingtin (HTT) was found to be critical for HTT aggregation and function during Huntington's disease (HD). This domain undergoes multiple post-translational modifications (PTMs), including phosphorylation at Ser13 (S13) and Ser16 (S16), which is predicted to act as a molecular switch to regulate HTT behavior. To test the hypothesis that phosphorylation at S13 and S16 is important for the axonal transport of HTT, we examined the role of phosphomimic and phosphodeficient S13/S16 mutations in the context of physiological and pathogenic HTT. Surprisingly, both phosphomimic and phosphodeficient HTT variants rescued pathogenic HTT-mediated axonal transport defects, reduced HTT accumulation in neuronal cell bodies, and mitigated neuronal cell death in *Drosophila* larvae. These variants also restored larval crawling, mechanosensory, and chemosensory behaviors, indicating functional rescue at the organismal level. Notably, these effects were independent of overall HTT expression levels or the HTT phosphorylation state, suggesting that single amino acid substitutions may induce conformational changes that alter HTT functions independent of the phosphorylation state of HTT. To further probe how S13 and S16 phosphorylation is important for the axonal transport of HTT we examined larvae fed on the IKKβ inhibitor BMS-345541, the kinase responsible for S13/S16 phosphorylation. To verify the specificity of IKKβ inhibition, DMAT the CK-2 inhibitor was used. Compared to DMAT, BMS-fed normal and pathogenic HTT larvae showed a significant number of HTT blockages. However, no significant changes were observed in HTT motility dynamics in vivo including the average anterograde, retrograde, stalled and reversing populations, anterograde to retrograde flux ratio, or segmental velocities suggesting that IKKβ phosphorylation of HTT likely had no role in regulating HTT motility. Inhibition of IKK increased HTT intensity at cell bodies and the number of HTT puncta under normal conditions while no effect was seen for pathogenic HTT. However, these changes were independent of HTT-mediated cell death. While membrane fractionation analysis showed S13 phosphorylated HTT at membranes, perhaps inhibition of IKK is required for membrane binding during axonal transport. Taken together, our results highlight a potential regulatory mechanism by which PTMs modulate HTT function and suggest new avenues for therapeutic intervention in HD.

Disclosures: J. Huang: None. **R. Rathnayake:** None. **S. Gunawardena:** None.

Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.21/U32

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

Support: Bev Hartig Huntington's Disease Foundation
NIH RO1 NS127344
NIH RO1 NS124084
DuBose Postdoctoral Fellow Award

Title: Non-invasive focused ultrasound delivery of engineered U1 snRNA strategy for targeted suppression of CAG repeats expanded HTT in an HD mouse model

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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. We found FUS delivered U1 snRNA can alleviate the HD phenotype in behavioral test and structure MRI. 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.

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Poster

PSTR129: Huntington's Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR129.22/V1

Topic: C.05. Tauopathies, Synucleinopathies, and Other Related Diseases

Support: R01AG071512

Title: Treatment with Aminopropyl Carbazole Compound Reduces Mutant Huntingtin-associated Pathology and Improves Functional Outcomes in Huntington's Disease Models

Authors: *S. J. TRIPATHI[1], S. CHAKRABORTY[1], S. BARKER[2], E. VAZQUEZ-ROSA[3], A. A. PIEPER[4], B. D. PAUL[1];
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Abstract: Huntington's disease (HD) is a progressive neurodegenerative disorder caused by CAG repeat expansion in the huntingtin gene, resulting in the accumulation of mutant huntingtin (mHtt) and selective vulnerability of striatal neurons. Clinically, HD is characterized by motor dysfunction, psychiatric symptoms, and cognitive decline. At the cellular level, mHtt aggregates elicit widespread deleterious changes, including general proteinopathy, oxidative damage, neuroinflammation, neuronal cell death, and impaired neurogenesis, collectively driving the aforementioned symptoms. Here, we examined the therapeutic effects of an aminopropyl carbazole compound (APC) with established neuroprotective properties in a cellular and R6/2 mouse model of HD. In cellular models, APC reduces mHtt aggregation and prevents neuronal cell death. In the R6/2 mouse model, treatment decreases neuroinflammation and oxidative stress, restores dopaminergic projections to the striatum, and increases expression of medium spiny neuron markers. These molecular and cellular improvements are associated with significant rescue of motor and cognitive deficits. Together, our findings suggest that APC mitigates key pathological and behavioral features of HD and represents a potential therapeutic candidate for Huntington's disease.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.01/V2

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

Title: Activation of α7 Nicotinic Acetylcholine Receptors Ameliorate Delirium-like BSEEG abnormality in mice

Authors: *R. SAKUMA[1,2], B. AOYAMA[1,3,4], H. NGUYEN[1], S. NISHITANI[1], G. SHINOZAKI[1];
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Abstract: Delirium is a common neuropsychiatric syndrome characterized by disturbances in attention, awareness, and cognition, frequently occurring after surgery or inflammation. Despite its importance, preventive strategies remain limited. We previously developed a bispectral EEG (BSEEG) scoring method, defined as the ratio of low-frequency (3 Hz) to high-frequency (10 Hz) EEG power, to quantitatively assess delirium severity. Using LPS-induced inflammation model, we previously demonstrated significant increases in BSEEG scores consistent with delirium-like EEG changes observed in patients, accompanied by microglial activation in the cortex and hippocampus. Nicotinic receptor agonists are known to exert anti-inflammatory effects. In particular, activation of α7nAChR suppresses inflammatory responses; however, its role in delirium prevention remains unclear. Therefore, we investigated whether α7nAChR agonist attenuates delirium-like EEG changes in LPS-induced mouse model. Male C57BL/6J mice (7-8 weeks old) underwent EEG head-mount implantation followed by a 2-week recovery period. Continuous EEG recording was initiated prior to drug administration. Mice were treated intraperitoneally with LPS (1.0 mg/kg), while saline-treated mice served as control. In the treatment group, α7nAChR agonist, GTS-21 (20 mg/kg) was administered intraperitoneally 15 min before LPS injection. Mice were perfused and fixed 24 h after treatment, and brain sections were subjected to immunohistochemistry for Iba1 and CD68. Buried food test and open field test were also performed to evaluate delirium-like behaviors. We first confirmed that α7nAChR is expressed in microglia. LPS significantly increased BSEEG scores, indicating delirium-like EEG alterations, whereas GTS-21 pre-treatment attenuated these increases following treatment. Immunohistochemistry showed reduced microglial activation, including decreased Iba1 and CD68 expression in the cortex and hippocampus, in GTS-21 pre-treated mice compared with mice treated with LPS alone. Furthermore, in the buried food test, GTS-21 pre-treated mice showed reduced latency compared with LPS-treated mice. In the open field test, LPS-induced reductions in time spent in the center zone and total distance traveled were also ameliorated by GTS-21 pre-treatment. In conclusion, activation of α7nAChR attenuates delirium-like EEG abnormalities quantified by BSEEG scores, microglial activation, and behavior abnormality in an LPS-induced mouse model. Our findings suggest that α7nAChR activation may serve as a promising preventive strategy against delirium through modulation of inflammatory responses.

Disclosures: R. Sakuma: None. **B. Aoyama:** None. **H. Nguyen:** None. **S. Nishitani:** None. **G. Shinozaki:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.02/V3

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

Support: National Key R&D Program of China Brain Initiative (2021ZD0200401)

Title: Longitudinal tracking of microglial dynamics and blood-brain barrier alterations in an MK-801-induced schizophrenia model

Authors: *B. CHU[1], L. ZHU[2], Y. YU[3], W. XI[4];
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Abstract: Chronic administration of N-methyl-D-aspartate (NMDA) receptor antagonists like MK-801 is widely used to mimic schizophrenia-like phenotypes, yet the progressive longitudinal changes in the neurovascular unit cause the schizophrenia-like phenotypes remain unclear. Here, we investigated how microglia and blood-brain barrier (BBB) permeability dynamically interact during the development of behavioral deficits. C57BL/6 mice received intraperitoneal (i.p.) injections of MK-801 (0.5 mg/kg) or saline twice daily. Behavioral phenotypes were assessed via the open field test (OFT), three-chamber social interaction test, and novel object recognition (NOR) task. BBB permeability and microglial dynamics were monitored by in vivo two-photon microscopy at five time points: baseline (day 0) and days 4, 8, 12, and 15. We find that 7 days of MK-801 treatment produced hyperlocomotion in the OFT without affecting social or cognitive behaviors, whereas 14 days of treatment normalized locomotion but caused marked deficits in social interaction, social novelty recognition, and object recognition. Two-photon imaging showed that BBB hyperpermeability emerged significantly at day 8. Vessel-associated microglia increased in parallel at day 8, while microglial motility peaked at day 4 before declining sharply through day 15. Morphological analysis revealed pronounced hyper-ramification at days 8 and 15, including enlargement of cell bodies and elongation of processes. PLX5622-mediated microglial depletion reversed BBB hyperpermeability and rescued the social and cognitive deficits. Furthermore, post-modeling treatment with Fingolimod attenuated microglial activation, reduced vessel-associated microglia, restored BBB integrity, and ameliorated both social and cognitive deficits. Taken together, these results indicate that early microglial activation and subsequent hyper-ramification drive BBB disruption, precipitating the onset of social and cognitive impairments. Microglial-vascular interactions may therefore represent a tractable therapeutic target in schizophrenia.

Disclosures: B. Chu: None. **L. Zhu:** None. **Y. yu:** None. **W. Xi:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.04/V5

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

Title: Microglial cell states associated with psychiatric disorders

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Abstract: Mounting evidence suggests that microglia and neuroinflammation are implicated in schizophrenia and other psychiatric disorders. Microglia do not operate as a single uniform cell type but adopt dynamic, context dependent cellular states. Recent single cell studies have described numerous disease associated microglial phenotypes in Alzheimer's Disease and other neurodegenerative disorders. However, a lack of a consistent cell state annotations across datasets and uncertainty on which states drive disease have hindered identification of states underlying psychiatric disorders and the identification of drug targets for therapeutic intervention. The overarching goal of this work is to extend well-annotated microglia models from neurodegeneration and apply them to microglia derived from patients with psychiatric disorders. This works builds on recent microglia cell state taxonomies and will help create a transdiagnostic model of microglial cell states.
Using publicly available data from post-mortem human brain biopsies from patients with psychiatric disorders, we built a pan-psychiatric microglia cellular state atlas by selecting microglia cells and training a probabilistic model. This model was compared to a recently published model of microglia cell states in neurodegeneration, followed by characterizing relative abundance of microglia states and comparisons with expression profiles from well-defined phenotypes. This atlas will serve as a high-quality reference standard for researchers to utilize to explore microglia-mediated mechanisms of brain health and disease.

Disclosures: C. Rhodes: None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.05/V6

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

Title: Effects of stress exposure on circulating lipopolysaccharide levels in mice

Authors: *M. SUMINAGA, T. YAMANASHI, A. MIURA, N. KAJITANI, T. NISHIGUCHI, K. KOMATSU, M. NAKAMOTO, M. IWATA;
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Abstract: Recent studies have highlighted the potential involvement of inflammatory responses in the onset and exacerbation of depression. Increased translocation of lipopolysaccharide (LPS) into the circulation due to enhanced intestinal permeability has been proposed as one of the underlying mechanisms. However, observational studies in humans alone cannot clearly determine the direct effects of stress on LPS dynamics. Therefore, this study aimed to investigate the effects of stress exposure on circulating LPS levels using mouse models. Experiment 1: Male C57BL/6J mice (9-10 weeks old) were divided into three groups: a control group, a chronic social defeat stress (SD) group, and an acute immobilization stress (IMM) group. Mice in the SD group were exposed to stress for 10 consecutive days, whereas mice in the IMM group underwent a single 1-hour immobilization stress session. Blood samples were collected, and circulating LPS concentrations were measured using an enzyme-linked immunosorbent assay (ELISA). Experiment 2: To examine whether age and sex influence stress-induced changes in circulating LPS levels, three groups of mice were studied: young adult male mice (C57BL/6J, 10 weeks old), young adult female mice (C57BL/6J, 10 weeks old), and aged male mice (C57BL/6J, 52 weeks old). Each group was further divided into control and IMM groups. Mice in the IMM groups underwent a single 1-hour immobilization stress session, and circulating LPS concentrations were measured as described above.
In Experiment 1, both chronic SD stress and acute IMM stress significantly increased circulating LPS concentrations. Furthermore, the increase in LPS levels was greater following chronic SD stress than following acute IMM stress. In Experiment 2, acute IMM stress significantly increased circulating LPS concentrations in young adult males, young adult females, and aged males. Baseline circulating LPS levels (control groups) were higher in aged male mice than in young adult male mice. In contrast, no significant sex differences in circulating LPS concentrations were observed.
These findings suggest that both acute and chronic stress promote the translocation of LPS derived from the gut microbiota into the circulation. Furthermore, aging appears to increase intestinal permeability, resulting in elevated baseline circulating LPS levels. Elevated basal LPS levels may contribute to systemic inflammation and increase susceptibility to depression and other inflammatory-related disorders.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.06/V7

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

Title: Allopregnanolone ameliorates social avoidance and neuroinflammation induced by chronic social defeat stress in mice

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Abstract: In recent years, the "brain inflammation hypothesis," which proposes that inflammatory and immune abnormalities contribute to the pathophysiology of major depressive disorder (MDD), has attracted increasing attention. Allopregnanolone (ALLO), a neurosteroid, has been reported to exert antidepressant and anti-inflammatory effects; however, the relationship between its antidepressant effects and brain inflammation remains unclear. In this study, we investigated stress-induced changes in brain inflammation using a social defeat stress (SDS) mouse model of chronic stress and examined whether the antidepressant-like effects of ALLO are associated with suppression of brain inflammation. In Experiment 1, 9-week-old male C57BL/6J mice were assigned to either a non-stressed control group or an SDS group. Mice in the SDS group were exposed to SDS for 7 days, after which social avoidance behavior was evaluated using the Social Interaction Test (SIT). The mice were then re-exposed to SDS, and the prefrontal cortex (PFC) and hippocampus (Hip) were collected. mRNA expression levels of inflammatory markers, including interleukin-1β (IL-1β), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), ionized calcium-binding adapter molecule 1 (Iba1), and brain-derived neurotrophic factor (BDNF), were measured by real-time PCR. In Experiment 2, mice underwent SIT following 7 days of SDS exposure, and those exhibiting social avoidance behavior received ALLO or saline while SDS exposure continued for an additional 7 days. During the final 3 days, the Open Field Test (OFT), SIT, and Forced Swim Test (FST) were performed. After behavioral testing, the PFC and Hip were collected, and mRNA expression levels of inflammatory factors, Iba1, and BDNF were analyzed. In Experiment 1, SDS-exposed mice showed reduced social interaction time and exhibited social avoidance behavior compared with control mice. In addition, mRNA expression levels of IL-1β and IL-6 were increased in both the PFC and Hip, suggesting that SDS induced brain inflammation. In Experiment 2, ALLO treatment ameliorated SDS-induced social avoidance behavior, indicating antidepressant-like effects. Moreover, ALLO suppressed the SDS-induced upregulation of IL-1β and IL-6 mRNA expression in both the PFC and Hip. Chronic social defeat stress increased the expression of inflammation-related genes in the PFC and Hip, indicating the induction of brain inflammation. Since ALLO improved social avoidance behavior while suppressing the upregulation of IL-1β and IL-6, its antidepressant-like effects may be mediated, at least in part, through the suppression of neuroinflammatory responses.

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report that research relationship even if those funds come to an institution.; Shionogi & Co. **A. Miura:** 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.; Shionogi & Co. **N. Kajitani:** 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.; Shionogi & Co. **T. Nishiguchi:** 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.; Shionogi & Co. **K. Komatsu:** 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.; Shionogi & Co. **M. Suminaga:** 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.; Shionogi & Co. **T. Aoki:** 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.; Shionogi & Co. **M. Iwata:** 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.; Shionogi & Co..

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.07/V8

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

Support: NIH Grant R01 HL149864-01A1

Title: Subcortical Vascular Calcification Induces Disease-Associated Microglial Gene Expression in eTNAP Mice

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Abstract: Introduction: Like humans, aged mice develop subcortical vascular calcification (VC) associated with increased vascular *ALPL* expression (Yang et al., 2020). The pathophysiologic role of VC in brain microcirculation remains unclear. Studies in mice have shown that microglia

regulate VC by a mechanism similar to the clearance of beta-amyloid (Aβ), dependent on expression of Triggering Receptor Expressed on Myeloid Cells 2 (*TREM2*) (Zarb et al., 2021; Keren-Shaul et al., 2017; Sayed et al., 2021). *TREM2* expression induces transcriptomic changes characteristic to a subgroup of activated microglia, termed disease-associated microglia (DAM) (Keren-Shaul et al., 2017). Using our model of "age-related" VC by endothelial overexpression of tissue-nonspecific alkaline phosphatase (eTNAP), we aimed to (1) determine if intracranial VC in eTNAP mice induced DAM, and (2) compare glial gene expression across brain regions in eTNAP and age-matched control mice.
Methods: Micro-CT imaging and histologic analyses characterized brain VC and microgliosis in eTNAP and controls (n=4/group, 16-wk old male C57BL/6J). We isolated RNA from cortical, subcortical, and hippocampal regions in fresh collected brain tissue. DAM gene expression (*TREM2, CST7, CD11C*) was measured by qRT-PCR. We compared mRNA levels across brain regions and between groups by two-way ANOVA with post-hoc pairwise comparisons. To further examine differential gene expression, we conducted spatial transcriptomic imaging (NanoString CosMx) on 12-20-wk-old eTNAP mice and age-matched controls (n=3/group).
Results: The eTNAP model demonstrates the phenotype of age-related subcortical calcification in disease-free, 2-yr-old C57BL/6J mice. Calcifications and gliosis are prominent throughout the subcortex in eTNAP mice but not in controls (Fig. 1A-D). Expression of *CD11C* and *CST7* was significantly increased in the VC-prone subcortices of eTNAP mice; *CD11C* expression was also significant in eTNAP hippocampi (Fig. 1E). Spatial transcriptomic analyses identified significant differential expression of DAM genes in calcification-prone brain regions of eTNAP vs. controls (Fig. 2).
Discussion: *TREM2* variants, such as $TREM2^{R47H}$, are implicated in late-onset Alzheimer's disease. *TREM2*-dependent DAM genes are expressed in our model of age-related VC. Spatial transcriptomic analyses in our model demonstrate that DAM surround calcifications. Ongoing studies in our lab using mice carrying $TREM2^{R47H}$ +/- *APOE4* aim to characterize VC-associated gliosis and clarify whether $TREM2^{R47H}$ behaves as a loss of function in microglial activation triggered by VC.

Disclosures: K.A. Borges: None. **A. Charest:** None. **R.F. Stout:** None. **R.L. Ramos:** None. **O.V. Savinova:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.08/V9

Topic: B.09. Glial Mechanisms

Support: SECIHTI 4047856

Title: Modulation of Hippocampal Astrocytes, Microglia, and the NLRP3 inflammasome by 10 Hz rTMS in an Animal Model of Depression

Authors: *R. ACOSTA-LUNA[1], L. VERDUGO-DIAZ[2], D. SALAZAR[3];
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Abstract: Repetitive Transcranial Magnetic Stimulation (rTMS) is a non-invasive neuromodulatory technique used to treat treatment-resistant depression. While its therapeutic efficacy is established, the mechanism of action of this treatment is poorly understood. Recent studies suggest that rTMS modulates glial function and neuroinflammatory pathways, which may underline its antidepressant effects. The aim was to evaluate the effect of 10 Hz rTMS on depressive-like behaviors in a Wistar rat model of chronic stress and to assess its impact on neuroinflammation, specifically astrocytic reactivity, microglial activation, and the NLRP3 inflammasome pathway in the hippocampus. We exposed for 4 weeks to the CUMS protocol in male 200 g Wistar rats. To measure these symptoms, forced swimming, sucrose preference test, open field, and elevated plus maze tests were used. rTMS was applied daily for 15 days (10Hz, 10min/day) using an eight-coil. Hippocampal tissue was analyzed by immunofluorescence to quantify astrocytic density (GFAP+) and microglial activation (Iba-1+); to observe the expression of NLRP3 via Western blot. The CUMS model successfully induced depressive-like behaviors, which were significantly reversed by the 10 Hz rTMS treatment. rTMS-treated animals exhibited a distinct modulation of glial cells compared to the sham group. Specifically, we observed an altered density of GFAP+ cells across the dentate gyrus, CA1, and CA3 regions. Furthermore, rTMS treatment attenuated CUMS-induced neuroinflammation, evidenced by a reduced Iba-1+ cell expression and downregulation of the NLRP3 inflammasome. These results demonstrate that 10 Hz rTMS exposure induces cellular responses in astrocytes and microglia that correlate with behavioral recovery. Finally, the inhibition of the NLRP3 inflammatory pathway and the modulation of astrocytic reactivity could indicate a potential mechanism of action of rTMS.

Disclosures: R. Acosta-Luna: None. **L. Verdugo-Diaz:** None. **D. Salazar:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.09/Web Only

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

Title: Cannabidiol Alleviates Chronic Stress-Mediated Cognitive and Mood Impairments Associated with Astrogliosis and Microgliosis

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Abstract: Major Depressive Disorder (MDD) is a debilitating neuropsychiatric condition characterized by persistent mood and cognitive impairments, frequently associated with neuroinflammation. Chronic stress (CS) is a key contributor to the pathogenesis of MDD, promoting activation of neuroinflammatory pathways, including astrogliosis and microgliosis, as well as impaired neurogenesis and neuronal loss in brain regions involved in mood regulation. Cannabidiol (CBD), a non-intoxicating phytocannabinoid derived from Cannabis sativa, possesses anti-inflammatory, neuroprotective, and anxiolytic properties. CBD modulates the endocannabinoid system and acts on several molecular targets, including serotonergic (5-HT1A) receptors implicated in mood regulation and anxiety-like behaviors. To evaluate the therapeutic potential of CBD, a rat model of chronic stress was developed to recapitulate cognitive and mood deficits associated with MDD. Male Wistar rats were subjected to restraint stress for six hours per day over 21 days. CBD (60 mg/kg, oral) was administered once weekly for 5 weeks, with 3 doses during the stress paradigm and 2 doses after stress exposure. After treatment, animals were assessed using a comprehensive battery of neurobehavioral tests, including hippocampal-dependent cognitive tasks (object location, pattern separation, and novel object recognition), as well as tests evaluating depressive-like behavior (forced swim and sucrose preference tests) and anxiety-like behavior (novelty-suppressed feeding test). CS-exposed rats receiving vehicle treatment exhibited impairments in object location memory, pattern separation, and novel object recognition tasks, all of which were markedly improved in CS-exposed rats receiving CBD treatment. Treatment with CBD also prevented CS-induced forced helplessness, anhedonia, and anxiety-like behavior observed with forced swim, sucrose preference, and novelty-suppressed feeding tests. Immunohistochemical analyses revealed astrogliosis and microgliosis in the hippocampus, lateral habenula, and medial prefrontal cortex of CS-exposed rats receiving vehicle, whereas CBD treatment significantly attenuated these neuroinflammatory changes. The findings demonstrate that CBD treatment during and after chronic stress can protect the brain from cognitive and mood impairments, while reducing neuroinflammation. This study also suggests CBD as a prophylactic candidate for preventing or reducing depression- and anxiety-like behaviors caused by chronic stress.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.10/V10

Topic: B.09. Glial Mechanisms

Support: DOD Grant AR210111 F
Advancing Women in Science and Medicine (AWSM) awards (AMW, LB)
NIH T32 5T32AI155392

Title: Rescuing microglial mitochondrial function in a mouse model of autism spectrum disorder (ASD)

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Abstract: Autism spectrum disorder (ASD) etiology is multifactorial and includes both genetic and environmental factors. A subset of mothers of children with ASD were previously found to harbor anti-Caspr2 antibodies; Caspr2 is encoded by the autism risk gene *Ctnap2*. In a murine model of autism spectrum disorder (ASD), pregnant mouse dams are immunized with human Caspr2. Male, but not female, offspring of dams harboring polyclonal anti-human Caspr2 antibodies ("Anti-Caspr2") demonstrate ASD-like behavioral phenotypes, including social deficits and repetitive behavior, compared to male offspring of dams immunized with adjuvants only (“Control”). Male, but not female, Anti-Caspr2 mice demonstrated increased microglial reactivity and reduced dendritic spine density in the CA1 hippocampus at postnatal day 21; these changes persisted into adulthood. Hippocampal microglial scRNA-seq revealed lower expression of OXPHOS- and mTOR-related transcripts in Anti-Caspr2 male mouse microglia relative to Control microglia, suggesting that mitochondrial dysfunction may underlie the reactive phenotype of the microglia. Treatment with captopril, a blood-brain-barrier (BBB)-crossing ACE inhibitor, restored Anti-Caspr2 male mouse microglial homeostasis relative to saline-treated Anti-Caspr2 male mice. Captopril treatment also increased social behavior in male Anti-Caspr2 mice to levels similar to Controls. However, the mechanism by which captopril affects male Anti-Caspr2 mice is not understood. Additionally, the effect of captopril on microglial mitochondrial dysfunction in male Anti-Caspr2 mice is unknown. Using Seahorse metabolomics, Oroboros respirometry, and qPCR, we show that hippocampal CA1 microglia from Anti-Caspr2 male mice have reduced mitochondrial function relative to Control. Anti-Caspr2 male mouse mitochondria microglia show reduced *mt-ATP6* transcription and OXPHOS deficits. Captopril treatment rescues male Anti-Caspr2 mitochondrial function, restoring ATP production and OXPHOS capacity. Mitochondrial dysfunction appears to fuel the male Anti-Caspr2 phenotype, whereas captopril treatment restores mitochondrial function and leads to improvements in social behavior.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.11/V11

Topic: B.09. Glial Mechanisms

Support: RO1 MH132680
T32 DA50558
T32 NS121727
P50 MH096889
The Bren Foundation

Title: Do microglia contribute to paraventricular thalamus activation during early-life adversity?

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Abstract: Background Early-life adversity (ELA) disrupts brain development, increasing vulnerability to cognitive deficits and psychiatric disorders later in life. Microglia play an essential role sculpting neural circuits during development, selectively pruning weak or excess synapses through phagocytosis. Microglia surveillance and pruning of synapses were disrupted by ELA in the paraventricular nucleus of the hypothalamus (PVN), (Bolton et al., 2022). This led to augmented excitatory synapses and hyperactivity of PVN neurons that express corticotropin-releasing hormone (CRH^{+}), associated with altered stress sensitivity. We have identified the paraventricular thalamus (PVT), as a potential mediator of the enduring consequences of ELA on reward behaviors. PVT neurons were selectively and robustly activated by ELA, and chemogenetic manipulation of these same early-life-engaged neurons in adult mice normalized reward behavior. Here, we test whether, similar to their role in PVN, impaired microglia function is critical to dysregulated activity of early-life-engaged PVT neurons. **Methods** On postnatal day 2 (P2), litters are randomly assigned to LBN or control rearing. Pups are perfused on P6 (the middle epoch of the LBN paradigm) and tissue is processed for fluorescent immunocytochemistry. In 40 micron-thick free-floating tissue sections, we stain for the microglia marker Iba-1 and the neuronal activity marker c-Fos. Sections are then imaged using confocal microscopy. Microglia number (i.e., density) and contact with Fos-expressing neurons in the PVT is quantified. **Results and Conclusions**
These experiments are currently ongoing. Results will determine whether ELA leads to increased or reduced recruitment of microglia to the PVT, potentially in a subregion and sex-dependent manner, and whether microglia preferentially contact activated neurons during this critical period of development. These results may hint at a potential mechanism by which the activity of early-life-engaged neurons becomes disrupted.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.12/V12

Topic: B.09. Glial Mechanisms

Support: NIMH K99/R00 Pathway to Independence Grant #MH120327
NARSAD Young Investigator Grant #31308
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Title: The sex-specific role of microglial glucocorticoid receptors in the effects of early-life adversity on synaptic pruning and later threat-response behavior

Authors: *J. SHEHU[1], F. MROUE RUIZ[2], S. CALL[1], J. L. BOLTON[3];
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Abstract: Early-life adversity (ELA) is a major risk factor for developing neuropsychiatric disorders later in life, since environmental stimuli can have a long-lasting impact on brain development. We have previously reported that ELA increases excitatory input onto corticotropin-releasing hormone (CRH)+ neurons in the stress-sensitive paraventricular nucleus of the hypothalamus (PVN) at postnatal day (P)10 by decreasing the amount of synaptic pruning by microglia, thus increasing stress reactivity. However, the mechanisms by which ELA impairs microglial function during development are unknown. Here, we aimed to determine the role of microglial glucocorticoid receptors (GR) in the effects of ELA on microglial function and later behavior. We used CX3CR1-Cre+::GRfl/+ to achieve a microglia-specific heterozygous deletion of GR (mGR-HD) in combination with the limited bedding and nesting model of ELA. We assessed the effects of genotype, ELA, and sex on synapse number, microglial engulfment, and behavioral outcomes. For synapse number, we quantified the colocalization of pre- and post-synaptic markers in the PVN at P10. Microglial engulfment was quantified by measuring the amount of synaptic puncta colocalized with CD68+ lysosomes. In a separate cohort of adult animals, we used the looming-shadow test to measure the threat response, which is dependent on excitation of PVN-CRH+ neurons, as well as the elevated zero-maze test for anxiety-like behavior. Our analyses revealed sex-specific effects of both ELA and mGR-HD. In males, mGR-HD altered the effects of ELA on excitatory synapse number at P10, reducing excitatory synapse number in ELA mGR-HD animals. Consistently, mGR-HD increased microglial engulfment of vGlut2+ puncta at P8, suggesting enhanced synaptic pruning. ELA increased microglial complexity in males at P8, including greater branching, filament length, and Sholl intersections, whereas several of these effects were attenuated by mGR-HD. In adulthood, ELA increased anxiety-like behavior in males, whereas females exhibited increased risk-taking behavior and heightened responsiveness to threat-related stimuli. Notably, several behavioral effects of ELA

were recapitulated by mGR-HD in both males and females, though in opposite directions, suggesting that disruption of mGR signaling is sufficient to mimic certain aspects of ELA programming. Together, our findings may suggest a role for mGR in negative feedback on the hypothalamic-pituitary-adrenal axis. In the future, our findings may provide promising targets for the development of therapeutics for at-risk children.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.13/V13

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

Support: NIH Grant R01-NS-120960
Klingenstein-Simons Fellowship in Neuroscience
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Title: Microglia replacement normalizes pathological macrophage states in Krabbe Disease

Authors: *W. H. AISENBERG[1], F. YAQOOB[2], C. O'BRIEN[2], Y. ZHANG[4], B. TEMSAMRIT[5], E. LEVITT[2], S. I. LOMBROSO[3], K. NEMEC[2], D. KANCHEVA[6], K. MOVAHEDI[7], M. L. BENNETT[5], F. C. BENNETT[2];
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Abstract: Loss of function mutations in the lipid hydrolase GALC cause Krabbe disease, a pediatric leukodystrophy characterized by toxic lipid accumulation, and demyelination. Among the hallmark pathologic features of disease is profound macrophage derangement, including the appearance of large multinucleated lipid-laden macrophages called globoid cells. Neither the function nor pathogenesis of these cells are well understood. However, hematopoietic stem cell transplantation reduces globoid cell numbers and extends survival, implicating macrophages in both disease pathogenesis and treatment. To better understand the responses of both pathological and therapeutic macrophages in this condition, we characterized the origins and functional states of brain macrophages in the Twitcher model of Krabbe disease using single-cell RNA sequencing, genetic fate mapping, and microglia replacement.

We found that microglia dysfunction begins prior to symptom onset with induction of interferon-responsive genes and progresses through distinct transcriptional states as disease advances. From these analyses, we identified a molecular signature of globoid cells that was validated in human Krabbe disease tissue. Notably, globoid cells expressed markers associated with both resident microglia and bone marrow-derived macrophages, suggesting contributions from multiple ontogenetic sources. Consistent with this, genetic fate mapping revealed infiltration of peripheral macrophages and their incorporation into globoid cell clusters in the diseased brain. Therapeutically, replacement of >80% of resident microglia with GALC-expressing macrophages normalized disease-associated transcriptional signatures, reduced gliosis and toxic lipid accumulation, and doubled survival. Together, these findings reveal dynamic remodeling of the CNS macrophage compartment in response to metabolic dysfunction and identify microglia replacement as a promising therapeutic strategy for neurodegenerative disease.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.14/V14

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

Support: ISF Grant 2330/23
Kaye-Einstein Fellowship Scholarship
ICAMH Fellowship Scholarship

Title: Activation of neuronal engrams and their interactions with local microglia represent peripheral inflammation and elicit anxiety- and depression-like symptoms

Authors: *L. NAGGAN[1], S. MERON ASHER[1], E. ROBINSON[2], E. DINUR[1], Y. WEINSTEIN[1], I. GOSHEN[1], R. YIRMIYA[3];
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Abstract: Inflammation profoundly affects brain function, altering physiological, behavioral, emotional, and cognitive processes. These effects are causally linked to symptoms of depression and anxiety observed in infectious, stress-related, and neuropsychiatric conditions. In this study, we induced peripheral inflammation in 3 months old male mice using intraperitoneal LPS

injection (330 μg/kg) and stained their brains for cFos to identify regions exhibiting increased neuronal activity at the peak of the inflammatory response. We observed elevated cFos labeling in the central amygdala (CeA) and dorsal hippocampus of LPS-injected mice, as compared with saline controls. We then examined whether these regions are reactivated by subsequent LPS exposure using Ai14xTRAP2 male mice. Re-exposure to LPS three weeks after the initial injection increased the density of neurons co-expressing the TRAP2 reporter and cFos, indicating that peripheral inflammation induces stable neuronal engrams in these regions. Next, we selectively targeted LPS-activated engram neurons in the CeA and dorsal hippocampus using a combination of viral vectors, which enabled the expression of the hM3Dq excitatory chemogenetic receptor strictly in activated neurons that expressed cFos. Chemogenetic reactivation of LPS-engram neurons with Clozapine-N-oxide (CNO) in the CeA induced anxiety-like behavior in the open field and elevated plus maze tests, as well as impaired contextual memory in the fear conditioning paradigm, but it had no effect on hedonic or social behaviors. On the other hand, CNO-induced reactivation of LPS-engram neurons in the dorsal hippocampus reduced social interest and induced anhedonia, as reflected by decreased sucrose preference, but it had no effect on anxiety-related behavior. In addition, CNO treatment of LPS-engram neurons significantly increased microglial density in both the CeA and dorsal hippocampus compared to saline controls. Together, these findings suggest that peripheral inflammation is encoded by distributed neuronal engrams that mediate distinct anxiety- and depression-like symptoms. Moreover, reactivation of these inflammation-related engrams alter local microglia populations, supporting a role for neuron-microglia interactions in the neural representation of peripheral immune activation and its behavioral consequences.

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Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

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Program #/Poster #: PSTR130.15/V15

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

Support: R00 DA044838 (DWW)
R01 DA052859 (DWW)
U01 DA058527 (DWW)
Emory University Summer Undergraduate Research Experience (SURE)

Title: Regulation of Peripheral Immune Cells by Cocaine and Cannabidiol Co-Exposure and Implications for Reward-Addiction Neuroimmune Pathways

Authors: *J. DIETRICH[1], R. COLÓN-ORTIZ[2], S. KNERLER[3], A. MERCADO[4], A. ELLISON[3], J. ROSADO-FRANCO[3], L. MAMUN[3], D. W. WILLIAMS[3];

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Abstract: Substance use disorders (SUDs) are a persisting global health concern associated with addictive behaviors and chronic neuroinflammation. Emerging evidence suggests that peripheral blood mononuclear cells (PBMC), including monocytes and T-cells, contribute to neuroinflammation during SUDs by increasingly migrating across the blood-brain barrier (BBB). During this process, brain microvascular endothelial cells (BMVECs) use chemokine signaling to bind and recruit PBMC at the BBB. This adhesion step, a critical checkpoint in immune cell trafficking, promotes successful diapedesis across the BBB. Previous work in our lab suggests that commonly used substances such as cocaine (COC) and cannabidiol (CBD) possess immunomodulatory properties that may alter PBMC recruitment at the BBB during SUDs. However, the extent to which these compounds modulate immune cell interactions at the BBB and contribute to neuroinflammatory processes remains poorly understood. We hypothesized that COC increases monocyte, but not T-cell, adhesion to BMVEC, whereas CBD reduces immune cell adhesion. Furthermore, combined COC and CBD will neutralize their respective pro- and anti-inflammatory effects, restoring immune cell adhesion to basal non-inflammatory levels. To evaluate this, PBMC were isolated from 10 healthy donors and treated with 10 μM COC, 1 μM CBD, combined COC and CBD, or vehicle for 24 hours. PBMC were then added to BMVEC cultures and incubated for 1 hour to allow adhesion. After, nonadherent cells were removed using a phosphate-buffered saline (PBS) wash, adherent cells collected, and flow cytometry performed to enumerate adherent cells. Our findings address a critical gap in understanding how COC and CBD differentially, and in combination, regulate immune cell interactions at the BBB during SUD-associated neuroinflammation, in addition to their well-characterized behavioral effects. Ongoing studies in our lab using an in vitro transwell model of the human BBB will further elucidate COC- and CBD-mediated inflammatory responses that guide immune cell trafficking across the BBB and may influence neuroinflammatory processes associated with SUDs.

Disclosures: J. Dietrich: None. **R. Colón-Ortiz:** None. **S. Knerler:** None. **A. Mercado:** None. **A. Ellison:** None. **J. Rosado-Franco:** None. **L. Mamun:** None. **D.W. Williams:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.16/V16

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

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Japan Society for the Promotion of Science KAKENHI Grant JP21K07280
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Title: Initiation of immune reactions in response to systemic inflammation by migrating macrophages and leptomeningeal fibroblasts in the postnatal mouse brain

Authors: *A. SHIMADA[1], S. HASEGAWA-ISHII[2];
[1]Kyorin Univ., Mitaka, Japan; [2]Fac. of Hlth. Sci., Kyorin Univ., Tokyo, Japan

Abstract: Background Bacterial infection triggers inflammatory pathways that damage the preterm brain without direct bacterial invasion. However, the role of intracranial tissues in the immune response to systemic inflammation remains unknown. The present study aimed to answer three questions: Do the leptomeningeal macrophages that migrate into the brain to develop into microglia perform immune functions? If so, which cells partner with the migrating macrophages? Which cytokines and genes in which cells are upregulated? **Methods** Lipopolysaccharide (LPS) was administered with a single intraperitoneal injection into postnatal day 7 mice. After 1, 4, 12, 24, 48, and 72 h, immunohistochemistry, immunoassays of cytokine concentrations, microarray analysis, quantitative reverse transcription polymerase chain reaction assays, and in situ hybridization were performed. **Results** The leptomeningeal macrophages initiated an intracranial reaction by producing IL-1β 4 h after LPS administration. IL-1R1 was expressed by arachnoid, pial, and perivascular fibroblasts. These brain fibroblasts produced CCL2 and other cytokines, which increased the number of brain macrophages/microglia and led to their hypertrophy. The macrophages/microglia from the brains of mice with systemic inflammation showed marked expression of genes including *Saa3* and *Lcn2*. *Saa3* expression reached its peak 4 and 12 h after LPS administration and was upregulated in the macrophages, as well as fibroblasts, in the leptomeninges, choroid plexus, and perivascular space. The *Saa3*-expressing leptomeningeal macrophages continued their developmental migration to develop into parenchymal microglia. The blood-brain barrier remained intact. Expression of *Lcn2* was prominent in the perivascular fibroblasts and choroid plexus epithelial cells. It is known that early enhancement of *Saa3* plays a key role in priming inflammation, and the increased *Lcn2* sequesters the iron siderophore to limit bacterial growth. **Conclusions** In the postnatal mice, brain immune reactions in response to systemic inflammation were initiated by migrating macrophages and leptomeningeal fibroblasts. These cells partnered to secrete cytokines, including CCL2, into the brain parenchyma. The migrating macrophages and leptomeningeal fibroblasts increased the expression of genes including *Saa3*. Leptomeningeal and parenchymal perivascular fibroblasts, as well as choroid plexus epithelial cells, increased the expression of genes including *Lcn2*. The migrating macrophages and the leptomeningeal and perivascular fibroblasts immediately enhanced expression of these genes to protect the immature brain.

Disclosures: A. Shimada: None. **S. Hasegawa-Ishii:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.17/V17

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

Support: P50AA017823
R01AA030469

Title: Adolescent alcohol and concurrent corticosterone effects on HPA axis reactivity and motivational processes

Authors: *A. LUTZKE, A. GANO, A. S. VORE, S. TRAPP, D. GERACI, T. DEAK;
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Abstract: Adolescent stress and alcohol both provoke neuroimmune dysfunction, which may contribute mechanistically to motivational deficits and altered stress sensitivity later in life. The goal of these studies was to examine the interactive effects of adolescent alcohol and corticosterone (CORT) exposure on hypothalamic-pituitary-adrenal (HPA) axis reactivity and motivational processes. In addition, polyinosinic:polycytidylic (Poly I:C), which is recognized by TLR3, induces cytokine expression and HPA axis activation. The goal of Experiment 1 was to ascertain whether adolescent intermittent ethanol (AIE) and/or chronic CORT consumption during adolescence alter adult Poly I:C-induced CORT. In this experiment, male and female Sprague-Dawley rats (n=10, N=80) underwent AIE and/or CORT exposure. For AIE, rats received intragastric gavages of water or 4 g/kg ethanol once daily for two days followed by two days off. This was repeated six times for twelve total ethanol exposures. During this same period, rats consumed 25 μg/mL CORT or vehicle as their only source of fluids for 24 consecutive days. These exposures spanned adolescence (P32-56), then rats remained undisturbed until adulthood. At P87-92, baseline tail blood samples were collected, and then all rats were given Poly I:C (4 mg/kg, i.p.). Additional tail blood samples were collected 45-, 90-, 180-, 360-min, and 24-hours post Poly I:C to assess changes in serum CORT, and blood pellets were used for cytokine mRNA expression. In males, AIE significantly reduced the Poly I:C-induced CORT response throughout the time course, while in females, AIE sensitized Poly I:C-induced CORT at the peak (180-min timepoint). It was unknown whether these changes would manifest as behavioral deficits, therefore, the goal of Experiment 2 was to evaluate AIE+CORT-induced changes in adult motivation in males using an operant effort-based decision making (EBDM) task. Male rats (n=12, N=24) underwent the adolescent AIE+CORT exposure and remained undisturbed until P88 when they began food restriction. Monday-Friday, rats underwent 30-minute sessions of operant training, beginning with fixed-ratio 1 (FR-1) followed by FR-5. Next, the FR5/chow task was introduced in which rats either lever pressed on an FR-5 schedule for the highly palatable reward or consumed readily available chow. Throughout the three weeks of FR5/chow sessions, the AIE+CORT group lever pressed significantly less than controls, an effect which was exacerbated by Poly I:C challenge (4 mg/kg i.p.). Taken together, these results support that AIE+CORT induce long-term changes to HPA axis sensitivity, which may manifest as motivational deficits in adulthood.

Disclosures: A. Lutzke: None. **A. Gano:** None. **A.S. Vore:** None. **S. Trapp:** None. **D. Geraci:** None. **T. Deak:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.18/V18

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

Support: AR240033
5R21MH135128

Title: Investigating the Effects of TLR7 Activation on Placental and Neurodevelopmental Transcriptomic Pathways

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[2]Lurie Ctr. for Autism, [1]Massachusetts Gen. Hospital/Harvard Med. Sch., Charlestown, MA

Abstract: Autism spectrum disorder (ASD) is a male-biased neurodevelopmental disorder characterized by neurobehavioral and molecular profiles. Maternal autoantibody-related ASD (MAR ASD) is a subtype of ASD where elevated maternal autoantibodies passed from the mom to the offspring during neurodevelopment result in neurodevelopmental alterations. Single-stranded viruses that activate toll like receptor 7 (TLR7), such as influenza and SARS-CoV-2, are among the prenatal infectious agents strongly associated with ASD. Repeated treatment with the TLR7 agonist imiquimod (IMQ) stimulates production of anti-nuclear autoantibodies. Preliminary data from our mouse model shows that repeated maternal subcutaneous IMQ treatment during pregnancy induces robust maternal anti-nuclear autoantibody (mANA) production that is preferentially transferred to male offspring and results in male-specific ASD-like behaviors, potentially explaining why ASD is male-biased. mANAs are trafficked through the placenta, however, how the placental environment is affected by mANAs is not robustly understood. This is a critical gap in understanding the etiologies of MAR ASD as the placental environment is becoming increasingly recognized to influence prenatal neurodevelopment which could alter postnatal neurodevelopmental trajectories. We hypothesized that repeated maternal IMQ treatment alters the placenta and the embryonic brain's immunological landscape in a sex-specific manner with the effects in the brain persisting into the postnatal period. To test this hypothesis, we performed bulk-RNA sequencing on paired placenta and embryonic brains on embryonic day (E) 16.75 and single-nucleus RNA sequencing (snRNA-seq) on E16.75 brains and postnatal day (P) brains. Bulk-RNA sequencing analyses of placentas extracted from male and female embryos revealed upregulation of immunological pathways in both males and females following maternal IMQ treatment compared to vehicle controls, although the effect was more pronounced in males. Interestingly, the upregulated immune pathways are involved in viral response and motility in males and females, respectively. This analysis revealed dysregulation in the formation of placenta structural pathways in males. Bulk-RNA sequencing analysis on E16.75 brains revealed female specific downregulation in channel and receptor activity and male specific downregulation in extracellular components. snRNA-seq is currently underway. These preliminary findings highlight the importance of considering the effects of the maternal environment on the placenta when investigating offspring neurodevelopmental endpoints.

Disclosures: E. Plunk: None. **E.A. Bordt:** None.

Poster

PSTR130: Neural-Immune Signaling in Neuropsychiatric and Neurodevelopmental Disorders

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR130.19/V19

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

Support: Children's Brain Foundation
National Institute of General Medical Sciences (NIGMS) Institutional Research Academic Career Development Award (IRACDA) grant number 1K12GM146658-01
National Institute of Neurological Disorders and Stroke (NINDS) with The University of Chicago Neuroscience Early-Stage Scientist Training Program (NESSTP) grant number 5R25NS117360

Title: The impact of MCC950 on inflammasome signaling in a CLN2 mouse model of neuroinflammation

Authors: *K. SANCHEZ[1], S. ELIZALDE[2], N. B. SCHWARTZ[3], M. S. DOMOWICZ[1];
[1]Pediatrics, The Univ. of Chicago, Chicago, IL; [2]Pediatrics, The Univ. of Chicago, Elgin, IL; [3]Pediatrics & Biochem. and Mol. Biol., The Univ. of Chicago, Chicago, IL

Abstract: Neuronal ceroid lipofuscinoses, or Batten disease, are a group of pediatric neurodegenerative disorders caused by mutations in one of 13 different genes, and is characterized by the lysosomal accumulation of the fluorescent storage material lipofuscin. The classical late-infantile form of the disorder in humans is caused by mutations in the *CLN2*/*Tripeptidyl peptidase 1* (*TPP1*) gene and is diagnosed between 2 and 4 years of age with onset of symptoms. Similar to human CLN2, a knockout of the *Tpp1* gene (*Tpp1-/-*) in the mouse leads to progressive vision loss, ataxia, seizures, and premature death. We previously showed using bulk RNA-seq that reactive gliosis occurs between 3 to 4 months in this mouse. While microglia drive disease progression in the *Tpp1-/-* mouse, the involvement of microglial pathways remained unknown. For example, the inflammasome is a multiprotein complex formed by microglia, which triggers the release of interleukin-1 beta (IL1β). Here we report that genes associated with the NLRP3 inflammasome complex (*Nlrp3*, *Asc*, *Caspase-1*, and *Il1β*) are upregulated in 3 and 4-month-old *Tpp1−/−* cerebellum compared to controls. To dissect the role of NLRP3 in CLN2, we used the NLRP3 inhibitor MCC950 in an organotypic slice culture model. In slice culture, we demonstrated that *Il1β* (3.2-fold; P ****<.0001) and *Nlrp3* are also upregulated (5.1-fold; P ****<.0001). We found that MCC950 downregulates transcriptional expression of genes associated inflammasome assembly and function (*Il1β;* 2.6-fold at both 10 and 50 μM; P ****<.0001 and *Nlrp3;* 1.19-fold at 10 μM and 0.77-fold at 50 μM; P ****<.0001) in the *Tpp1-/-* brain. Genes encoding for non-NLRP3 sensor proteins were also

upregulated in the *Tpp1-/-* slices including *Aim2* (1.2-fold; P *<.05). In this model, MCC950 significantly lowered the expression of *Aim2* to 0.3-fold at 10 μM and 0.5-fold at 50 μM; P ****<.0001 in the *Tpp1-/-* mouse. Due to the success of MCC950 in culture, we administered MCC950 directly to *Tpp1+/-* (control) and *Tpp1-/-* mice through water over the course of 2-months until 4-months of age. *Il1β* is also downregulated in the cerebellum and forebrain when MCC950 is directly administered to *Tpp1-/-* mice through water in the forebrain 3.6-fold to 2.6-fold (P *<.05) and cerebellum 3-fold to 1.8- fold (P *<.01). We also found that *in-vivo* MCC950 administration lowers the expression of genes that are upregulated in the CLN2 murine model such as *Aim2* in the forebrain (2.3-fold to 0.5-fold; P **<.001) and the cerebellum (3.8-fold to 1.7-fold; P *<.05). These results suggest that anti-inflammatories like MCC950 are promising in CLN2 due to its unknown off-target effects in this model.

Disclosures: K. Sanchez: None. **S. Elizalde:** None. **N.B. Schwartz:** None. **M.S. Domowicz:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.01/V20

Topic: D.04. Brain Injury and Trauma

Support: NeuroInfusions LLC

Title: Cannabinoid ratio optimization promotes neuroprotection, behavioral recovery, and skin regeneration following traumatic brain injury

Authors: *L. K. FRIEDMAN[1,3], R. J. K. ZEMAN[1,3], H. PENG[2];
[1]Cell Biol. and Anat., [2]New York Med. Col., Valhalla, NY; [3]NeuroInfusionsL LLC, Valley Stream, NY

Abstract: Traumatic brain injury (TBI) results in destruction of primary neural tissue at the contusion site and disrupts microvascular function causing profound local hypoperfusion, ischemia, excessive release of glutamate, and excitotoxic calcium levels. An optimal ratio of cannabidiol (CBD) to tetrahydrocanabinol (THC) infused as an absorbable implant over the dura mater of the injured contusion site was hypothesized to protect against neuropathological consequences following TBI. Varied CBD:THC extract concentration implants with supplemental systemic treatments were compared with hemp CBD lacking THC (CBD_0). Neurons, glia, and parvalbumin interneurons (PV-INs) were evaluated. Weight loss was observed following high doses of THC dominant cannabis, $THC_{100:1}$. Neuroscores and vestibulomotor performance were restored most with CBD:$THC_{300:1\text{-}10:1}$. However, THC dominant treatments resulted in early onset to spontaneous seizures post-TBI. The alternating T-maze showed the $CBD_{10:1}$ group had the highest spontaneous alternation rates whereas TBI + vehicle, CBD_0, $CBD_{1:1}$, and $THC_{100:1}$ groups had the lowest. The novel object recognition

memory task showed $CBD_{300:1}$ treated animals had the best performance, while TBI or $THC_{100:1}$ treated groups had the worst. The forced swim test (FST) revealed immobility time was highest after TBI and lowest after $THC_{20:1}$ or $THC_{100:1}$ treatment post-TBI. The elevated plus maze (EPM) revealed the CBD_0 group spent the most time in closed arms. Both tests indicate that reduced anxiety was THC dependent. In the absence of TBI, $THC_{20:1}$ treatment resulted in the highest mobility. All combinations resulted in reduced injury post-TBI but $CBD_{10:1}$ and $THC_{20:1}$ afforded the most protection and $THC_{100:1}$ the least. Reduced GFAP labeling was highest with CBD dominant cannabis supporting its neuroprotective role against inflammation. Rescue of diminished bilateral PV-INs was observed within the hippocampus and medial prefrontal cortex (mPFC) with CBD dominant treatment (CBD_{300}, CBD_0) supporting their anticonvulsant effect. Loss of PV-INs with THC dominant treatment supports their proconvulsant effect. Improved skin/hair follicle regeneration was observed. CBD and THC have different beneficial therapeutic effects. Intracranial and systemic administration at an optimal concentration ratio provides a therapeutic strategy unavailable through current TBI protocols, addressing both primary and secondary neural injuries while simultaneously healing the associated external dermal wound.

Disclosures: L.K. Friedman: A. Employment/Salary (full or part-time):; Linda Friedman, New York Medical College. 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.; Linda Friedman CEO, NeuroInfusions LLC. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); New York Medical College. D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); New York Medical College. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroInfusions. F. Consulting Fees (e.g., advisory boards); NeuroInfusions. Other; NeuroInfusions. **R.J.K. Zeman:** A. Employment/Salary (full or part-time):; RIchard Zeman, New York MediCollegecal. 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.; Co-founder, NeuroInfusions LLC. **H. Peng:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.02/V21

Topic: D.04. Brain Injury and Trauma

Title: Eprosartan - Sinapic acid co-therapy alleviates traumatic brain injury-induced multi-organ dysfunction in mice: Restoration of brain-organ crosstalk

Authors: *M. THAKUR[1], S. SHARMA[2], N. VASUDEVA[3];
[1]Pharmaceut. Sci., Guru Jambheshwar Univ. of Sci. & Technology, Hisar, Haryana,

Yamunanagar, India; [2]Pharmaceut. Sci., [3]Guru Jambheshwar Univ. of Sci. & Technology, Hisar, Haryana, Hisar, India

Abstract: Traumatic brain injury (TBI) is an acute, non- degenerative neurological insult caused by external mechanical forces and presents a significant global health burden. In addition to localised brain damage, TBI initiates a systemic pathological cascade that impairs function in distant organs, including the heart, lungs, liver, and kidneys, ultimately leading to multi-organ dysfunction syndrome (MODS). This syndrome is driven by excessive systemic inflammation, episodic sympathetic hyperactivation, and progressive immunosuppression, although the precise regulatory mechanisms remain poorly understood. The present study hypothesises that a combined synthetic-herbal therapeutic approach could pharmacologically attenuate TBI-induced MODS by modulating the renin-angiotensin system (RAS), autonomic nervous system (ANS), high-mobility group box- 1 (HMGB-1), and immune checkpoint signalling via programmed death ligand- 1 (PD L-1). A weight-drop model was employed to induce injury in *Swiss albino* mice, with E + S administered orally for 21 days post-injury. Assessments included neurobehavioral performance, blood-brain barrier permeability, plasma norepinephrine levels, inflammatory mediators, organ-specific serum biomarkers, and gene expression (PDL-1 and IL-10) conducted at 24 hours and 21 days post-injury, along with histopathological examinations. Treatment with the E + S combination markedly enhanced neurological outcomes, suppressed sympathetic hyperactivity, mitigated systemic inflammation, normalised organ functions, and upregulated PDL-1 and IL-10 expression to prevent immunosuppression, accompanied by significant restoration of cellular architecture across organs. These findings suggest that the coordinated regulation of RAS/ANS/HMGB-1 and PDL-1 signalling by E + S effectively disrupts the pathological cycle driving TBI- induced MODS. Therefore, combination therapy provides superior neuroprotective and organ-protective effects compared with monotherapy, suggesting its promising use as an adjunct to current treatment.

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Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.03/V22

Topic: D.04. Brain Injury and Trauma

Title: Cellular and Structural Alterations of Brain Tissue in Severe Traumatic Brain Injury Lesions

Authors: *R. TANG[1], N. C. GONSALVES[2], L. KARUMBAIAH[2];
[2]Regenerative Biosci. Ctr., [1]Univ. of Georgia, Athens, GA

Abstract: Severe traumatic brain injury (sTBI) induced alterations in cellular composition and extracellular matrix (ECM) jointly shape tissue architecture and mechanics. Although glial scar

and ECM changes have been previously reported in sTBI lesions, the influence of cellular/ECM remodeling on nanoscale brain tissue morphology and mechanical properties remain poorly defined. We hypothesize that sTBI causes distinct changes in morphological signatures that correlate with perilesional remodeling of glial, immune, ECM, and glycan components. Sprague-Dawley rats (6-8-week-old) underwent sTBI or sham surgery of the rostral forelimb area (RFA), and were euthanized at 5-weeks post-sTBI. Perilesional brain regions were examined using scanning electron microscopy (SEM)-based surface texture analysis, immunofluorescence, and histological staining. SEM surface texture analysis revealed a significant reduction in the heterogeneity of surface topography as determined by predefined height-related parameters, indicating a smoother and spatially refined surface topography after injury when compared to uninjured controls. Cellular immunofluorescence and histological profiling studies revealed a close correlation between changes in tissue morphology and increased perilesional gliosis and inflammation as confirmed by GFAP+ astroglia area, IBA1+ (activated), CD68+, CD86+(M1-like), and CD206+ (M2-like) microglial/macrophage areas in sTBI lesions compared to sham controls. Hematoxylin and eosin (H&E) staining showed increased hematoxylin+ area, eosin+ area, and hemosiderin laden macrophages in perilesional tissue of sTBI animals when compared to uninjured controls. These findings were further supported by the detection of increased collagen deposition, as confirmed by Masson's trichrome staining; and enhanced glycosylation of perilesional tissue as confirmed by Alcian blue+ staining of sulfated glycosaminoglycan-rich regions, and altered glycoprotein abundance, sialylation, and fucosylation as determined by enhanced ConA, Mal-II, SNA-1, AAL, and UEA-I lectin reactivity. In conclusion, our results reveal a perilesional remodeling phenotype that is characterized by the presence of altered cellular, ECM, and glycosylation signatures that manifest in smoother SEM-defined surface textures 5 weeks after sTBI.

Disclosures: R. Tang: None. **N.C. Gonsalves:** None. **L. Karumbaiah:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

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Program #/Poster #: PSTR131.05/V24

Topic: D.04. Brain Injury and Trauma

Support: The Ministry of Science and Technology of Taiwan, ROC,Grant NSTC 112-2314-B-016-068-MY3
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Title: Blast-induced Traumatic Brain Injury Causes Damage in Hippocampus and Memory Impairment in a Rat Model

Authors: T.-T. KUO[1], Y.-P. CHIEN[2], P.-K. CHANG[3], B. J. HOFFER[4], L. OLSON[5], K.-Y. TSENG[6], ***Y.-H. CHEN**[7];
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Abstract: Background: Blast-induced traumatic brain injury (bTBI) is a major cause of neurological dysfunction in military personnel and civilians exposed to explosions. Although memory impairment is among the most common long-term consequences of bTBI, the temporal relationship between hippocampal pathology, functional alterations, and cognitive deficits remains incompletely understood.**Objective:** This study investigated the structural, functional, and behavioral consequences of bTBI, with a particular focus on hippocampal pathology and memory-related outcomes.**Methods:** Animals exposed to blast shock waves were evaluated at multiple post-injury time points. Histological analyses, magnetic resonance imaging (MRI), hippocampal functional assessments, mitochondrial function measurements, and behavioral tests were integrated to characterize neuroinflammation, microstructural alterations, neuronal dysfunction, and cognitive performance.**Results:** bTBI induced early neuronal and synaptic damage in the hippocampus accompanied by glial activation. MRI revealed that the hippocampus exhibited the most prominent and persistent microstructural abnormalities among examined brain regions. Mitochondrial respiratory function was significantly reduced from the acute phase and remained impaired throughout the chronic stage. Behavioral assessments showed no significant motor deficits in the open field test. However, Y-maze performance demonstrated early impairment of spatial working memory, while novel object recognition deficits emerged at day 7 and persisted through day 56. In contrast, Morris water maze testing revealed delayed learning acquisition with relatively preserved long-term spatial memory retrieval. Histological findings further suggested that dentate gyrus pathology and neuroinflammatory responses were closely associated with the observed cognitive deficits.**Conclusions:** These findings demonstrate that bTBI induces early hippocampal neuronal damage, neuroinflammation, microstructural abnormalities, and mitochondrial dysfunction, which collectively contribute to the development of time-dependent memory impairments. The hippocampus, particularly the dentate gyrus, appears highly vulnerable to blast-wave exposure and may represent a critical substrate underlying persistent cognitive dysfunction following bTBI.

Disclosures: T. Kuo: None. **Y. Chien:** None. **P. Chang:** None. **B.J. Hoffer:** None. **L. Olson:** None. **K. Tseng:** None. **Y. Chen:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.06/V25

Topic: D.04. Brain Injury and Trauma

Support: NIH NS119401

Title: Sex-dependent glymphatic impairments across acute and chronic timepoints following blast and impact traumatic brain injury.

Authors: *J. J. JANG[1], K. SUCHLAND[1], D. JANSSON[1,2], A. G. SCHINDLER[1,5,3], T. EHLER[1], J. ILIFF[1,2,4];
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Abstract: Traumatic brain injury (TBI) is a significant cause of death and disability and a risk factor for neurodegenerative diseases like Alzheimer's disease (AD). Increasing prevalence of TBI exposure in veterans following the conflicts in Iraq and Afghanistan has made the characterization of post TBI dysfunction over time a clinical priority. One possible mechanism that may contribute to the progression of disease pathology post TBI is impaired clearance of cerebrospinal fluid (CSF) solutes. The glymphatic system is a brain-wide network of paravascular spaces that facilitates the exchange and clearance of CSF and interstitial fluid, is dependent on Aquaporin-4 water channels localized to astroglial endfeet, and is sleep-active. TBI impairs glymphatic function causing accumulation of neurotoxic amyloid-beta and tau aggregates, and accelerated disease progression. However, TBI modalities vary in severity, mechanisms of injury, and pathophysiological outcomes. Thus, to better understand the impairments that accompany impact or blast injury at both the acute and chronic stages, we assessed behavior, sleep, glymphatic function, and cell specific markers of inflammation in male and female mice across multiple post TBI timepoints. C57BL/6 mice were subjected to blast or impact TBI once a day for three consecutive days under isoflurane anesthesia. Glymphatic function was then assessed via intracisternal injections of infrared and fluorescent tracers at 7 and 84 days post TBI. Activity and sleep measures were obtained at 7, 28, and 77 days post TBI using Comprehensive Lab Animal Monitoring Systems. Behavioral tests were conducted two weeks prior to injections at 84 days. Our data reveal key differences between male and female mice across multiple timepoints. At 7 days post blast TBI, disruptions in glymphatic function were observed in female mice while tracer distribution remained unaltered by injury in male mice. At 84 days post blast TBI this pattern reversed. Female mice showed no impairment while male mice displayed reduced tracer distribution. In impact conditions female mice showed no change at either time point, whereas injured male mice showed decreased glymphatic function. Sleep was also disrupted by both blast and impact TBI with alterations appearing at the earliest time point and dissipating later on. However, sleep architecture varied between sexes and injury modalities. These divergent injury response phenotypes highlight the complexity of the TBI-glymphatic function axis, and ongoing research will provide deeper insight into the mechanisms underlying the differential effects of impact and blast TBI.

Disclosures: J.J. Jang: None. **K. Suchland:** None. **D. Jansson:** None. **A.G. Schindler:** None. **T. Ehler:** None. **J. Iliff:** F. Consulting Fees (e.g., advisory boards); Chair of the Scientific Advisory Board for Applied Cognition, Inc..

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.07/Web Only

Topic: D.04. Brain Injury and Trauma

Title: Acute behavioural and structural impacts of precision 2Gy X-ray whole body irradiation on the rat brain microenvironment

Authors: M. N. WANG[1,2], C. LEITH[3,2], M. KELLY[1,2], R. J. MIDDLETON[2,4], R. B. BANATI[1], R. BOURNE[1], J. L. CORNISH[3], *P. D. CALLAGHAN[2,1,4];
[1]Univ. of Sydney, Camperdown, NSW, Australia; [2]Australian Nuclear Sci. and Technol. Organisation, Kirrawee DC, NSW, Australia; [3]Macquarie Univ., North Ryde, NSW, Australia; [4]Univ. of New South Wales, Kensington, NSW, Australia

Abstract: Brain radiotherapy dose is primarily limited by normal tissue complications (such as neurocognitive decline, necrosis, and systemic toxicities) rather than the capacity to destroy the tumour. Anxiety and depression are widely recognised as significant problems with brain irradiation and are major components of Normal Tissue Complication Probability (NTCP). We utilised an animal model pairing precision X-ray irradiation with a behavioural testing framework to evaluate locomotor activity, anxiety-related behaviours, and behaviours stimulated by drug-induced dopamine/serotonin release. Male Wistar rats (n=72) received a 2 Gy whole body dose via a XRAD320 irradiator (Precision X-Ray, CT, USA). Three days post-irradiation, animals underwent behavioural testing for anxiety like traits (open field emergence test-OFE; elevated plus maze-EPM). Monoamine-stimulated behaviours were done via a discrete pharmacological challenge: methamphetamine-induced locomotor activity (1 mg/kg IP) and 3,4-methylenedioxymethamphetamine-induced social interaction (MDMA; 5 mg/kg IP). Histology & hippocampal & striatal micro-CT were assessed post mortem to evaluate structural microenvironmental integrity. In a subset of samples, digital PCR (AbsoluteQ, Applied Biosystems, USA) quantified mRNA expression of the radiosensitive protein aquaporin-4 (AQP4), present on primarily on astrocytes. EPM data showed 2Gy irradiation significantly decreased time spent in open arms (Mann-Whitney U test: $p < 0.0001$; 2Gy: Md =18, IQR = 32.75, n = 36; sham: Md = 44.5, IQR = 23.25, n = 32). OFE data showed latency to emerge from hide box was significantly increased with 2Gy treatment (Mann-Whitney U test, $p = 0.0246$: 2Gy: Md = 27.15, IQR = 38.76, n = 33; sham: Md = 12.15, IQR = 24.25, n = 35). Thigmotaxis was significantly greater in the 2Gy treatment group (OFE time in centre region: Mann-Whitney U test, $p = 0.0064$; 2 Gy:Md = 27.9, IQR = 19.13, n = 33; sham: Md = 39.74, IQR = 23.39, n = 35). Locomotor activity bias from 2Gy treatment was not apparent in either test (OFE total beam crosses: Mann-Whitney U test, $p = 0.0715$; 2Gy: Md = 118, IQR = 93, n = 33; sham: Md = 140, IQR = 61, n = 35). However, the 2 Gy irradiation showed no significant impact on monoamine stimulated behaviours nor the AQP4 expression profiles and was insufficient to disrupt the mechanisms governing volume neurotransmission. This work validates a behavioural framework showing that low-dose irradiation induces significant anxiety-like traits without altering volume

neurotransmission, establishing a foundation to investigate the impacts of clinically relevant dose plans and mitigate neurocognitive complications in radiotherapy.

Disclosures: M.N. Wang: None. **C. Leith:** None. **M. Kelly:** None. **R.J. Middleton:** None. **R.B. Banati:** None. **R. Bourne:** None. **J.L. Cornish:** None. **P.D. Callaghan:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.09/V27

Topic: D.04. Brain Injury and Trauma

Support: U.S. Department of Veterans Affairs

Title: Sex-Dependent Responses to Blast-Related Traumatic Brain Injury

Authors: *A. LYNDAKER[1], K. BATES[1], K. DISANO[2], P. HOLTZHEIMER[2], C. NOLLER[2]; [1]Integrative Neurosci., Dartmouth Col., Hanover, NH; [2]Geisel Sch. of Med. at Dartmouth, Hanover, NH

Abstract: Shockwave-induced “blast” traumatic brain injury (bTBI) is a significant problem for military personnel. These injuries were historically studied in men; however, the growing number of women in the military necessitates research on this understudied population. Inflammation, a key feature of TBI, is thought to contribute to functional deficits, including increased risk for psychiatric impairment. It is unclear how the inflammatory and behavioral consequences of bTBI differ by sex, and more specifically by hormonal cycle phase. To address this gap in knowledge, we utilized a rodent model of bTBI to define inflammatory and behavioral consequences at seven days post-injury in adult male and female C57BL/6J mice. Our study demonstrated that bTBI induced distinct immune signatures in the blood and cerebrospinal fluid in both sexes (n = 11-18 mice/group). We found that injured female mice demonstrate less anxiety-like behavior at this acute timepoint compared to males (n = 7-16 mice/group). Early exploratory analyses suggest that estrous phase at the time of injury may mediate these outcomes. This project highlights the importance of understanding how ovarian hormones influence sex-specific outcomes following TBI.
Funding Acknowledgement U.S. Department of Veterans Affairs

Disclosures: A. Lyndaker: None. **K. Bates:** None. **K. Disano:** None. **P. Holtzheimer:** None. **C. Noller:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.10/V28

Topic: D.04. Brain Injury and Trauma

Support: U.S. Department of Veterans Affairs

Title: Effects of a Novel Cholinergic Agonist in Treating Female and Male Mice after Traumatic Brain Injury

Authors: *K. C. BATES[1], A. LYNDAKER[1], K. DISANO[2], P. E. HOLTZHEIMER[2], C. NOLLER[2];
[1]Integrative Neurosci., Dartmouth Col., Hanover, NH; [2]Geisel Sch. of Med. at Dartmouth, Lebanon, NH

Abstract: Worldwide, traumatic brain injury (TBI) contributes to more death and disability than any other trauma-related injury. TBI increases the risk of developing mood disorders, including depression and anxiety. Inflammation, a key feature of TBI, may mediate these outcomes; thus, evaluating effective immunomodulatory treatments remains an active area of investigation. There is a critical need to identify selective immunotherapies capable of modulating inflammation without inducing global immunosuppression. Moreover, known sex differences in TBI outcomes should guide the implementation of effective immunotherapies. The current study used a clinically relevant model of non-penetrating TBI to investigate the utility of a novel α7 nicotinic acetylcholine receptor agonist, GTS-21 (daily 4 mg/kg I.P.), to modulate behavioral and immune outcomes in adult female and male C57BL/6J mice (n=9-18 per study group). Following GTS-21 administration, we evaluated anxiety- and depressive-like behaviors using standardized behavioral assays and assessed immune profiles in serum and cerebrospinal fluid using multiplex immunoassays. Our study showed that TBI induces sex-specific immune profiles after acute injury. Although no treatment effect was observed in female TBI animals, GTS-21 modulated select serum cytokines in male animals. In addition, male sham GTS-21-treated animals showed reduced depressive-like behaviors when compared to untreated male shams. Conversely, both female and male mice showed more anxiety-like behavior following GTS-21 treatment in the sham condition. This poster highlights the importance of understanding how sex impacts response to novel immune-based treatment.

Disclosures: K.C. Bates: None. **A. Lyndaker:** None. **K. Disano:** None. **P.E. Holtzheimer:** None. **C. Noller:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.11/W1

Topic: D.04. Brain Injury and Trauma

Support: Congressionally Directed Medical Research Programs (CDMRP)
Virginia Commonwealth University

Title: Hyperacute seizure and epileptiform activity following severe TBI

Authors: *A. GIBSON[1], P. KOCH[2];
[1]Virginia Commonwealth Univ., Richmond, VA; [2]Dept. of Neurosurg., Virginia Commonwealth Sch. of Med., Richmond, VA

Abstract: There are currently no established early biomarkers that reliably predict the development of PTE, a key requirement in selecting patients for novel preventative anti-epileptogenic therapies. Early seizures after TBI are a known risk factor for PTE, yet treating them does not ameliorate that risk, suggesting an earlier pathological process underlying both. The hyperacute period (minutes to hours) after TBI is characterized by glutamate-mediated excitotoxic injury, yet the accompanying changes in neural circuits and their role in the development of PTE are unknown. In this study, we characterized seizure and epileptiform activity in cortical and hippocampal circuitry during the initial minutes and hours after severe TBI using the established lateral FPI model of PTE. Male rats underwent severe lateral FPI (N=5), or sham injury (N=1). A 32 channel flexible EEG grid was implanted bilaterally overlying the skull prior to FPI. Continuous EEG recordings were made before, during and up to 12 hours after impact. In a separate cohort (N=2), a 128 channel silicon probe was inserted into the ipsilateral dorsal hippocampus within several minutes of impact and removed prior to return of righting reflex. Epileptiform activity was seen on the cortical EEG grid in all 5 FPI animals beginning an average 4.5 min post-FPI. 2 FPI rats exhibited a fully-formed seizure between 60 and 70 minutes after FPI, while 1 FPI rat exhibited many seizures beginning 22 minutes after FPI and continuing for several hours. No epileptiform activity was observed in the sham rat. In the hippocampus, brief bursts of activity were seen in the dentate gyrus within 6 minutes of impact, most resembling dentate spikes. If linked to the development of late seizures, these findings could suggest a novel early biomarker of PTE and point to the hyperacute post-TBI period as a potential therapeutic target.

Disclosures: A. Gibson: None. **P. Koch:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.12/W2

Topic: D.04. Brain Injury and Trauma

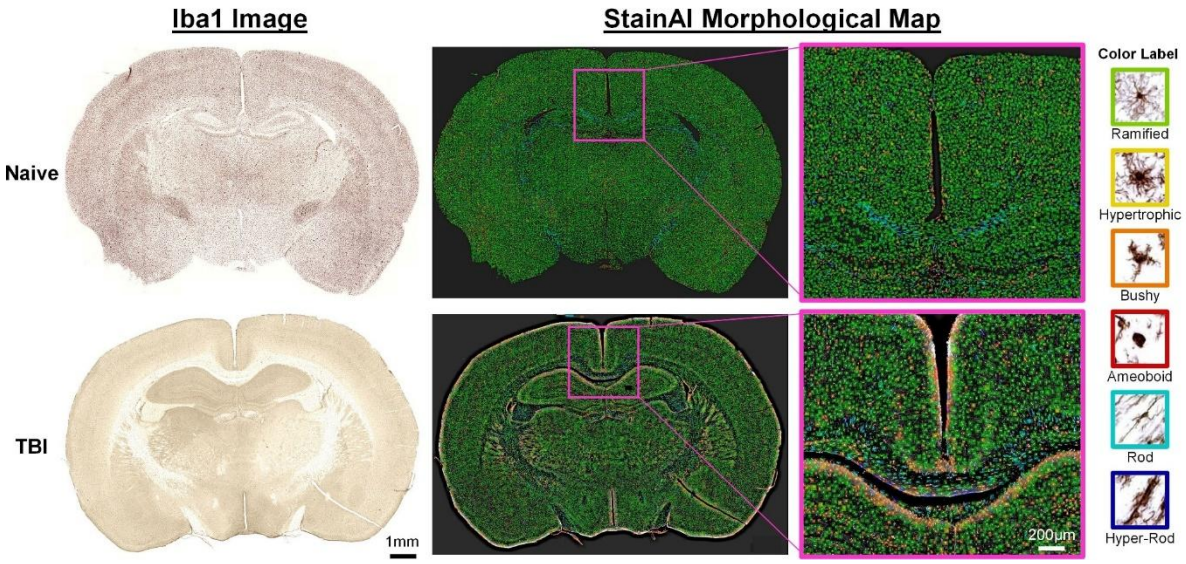
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CZI NDCF Award

Title: Region-Specific Microglial Activation Following Weight-Drop Traumatic Brain Injury

Authors: *H. ZEHRA[1], D.-Y. LIU[1], C.-H. HSU[1], T.-W. TU[1,2];
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Abstract: Microglial activation is a hallmark of traumatic brain injury (TBI), yet conventional manual or semi-automated quantification limits our understanding of brain-wide spatial distributions. To overcome these limitations, this proof-of-concept study utilized StainAI, an AI-assisted image analysis platform, to evaluate whole-slide microglial activation following weight-drop TBI and demonstrate the model's high-throughput capability. StainAI integrates a multi-stage deep learning pipeline featuring image background correction alongside YOLO-based object detection and classification of microglial cells across a spectrum of morphological phenotypes associated with resting and activated states. Adult female rats underwent a modified Marmarou closed-head injury (n=5, 2m height) and were compared to a control (n=1). Using brightfield microscopy of IBA-1-stained sections, we evaluated multiple regions of interest (ROIs): cortex, corpus callosum (CC), external capsule (EC), cerebral peduncle (CP), optic tract (OT), and cingulate cortex (Cg). StainAI quantified six morphological phenotypes: ramified, hypertrophic, bushy, amoeboid, rod-like, and hypertrophic rod-like cells, and calculated regional activation scores based on a weighted function of phenotype proportions within any given ROI. TBI elicited distinct, region-specific activation profiles, with average activation scores increasing by 55% to 104% relative to the control across a network spanning the CC, cortex, CP, OT, and Cg. Increases approached twofold in the OT and Cg, whereas the EC showed minimal change. StainAI morphological maps revealed highly heterogeneous spatial patterns of microglial activation across the brain (Fig. 1). These findings demonstrate that AI-assisted image analysis effectively maps the complex, region-specific neuroimmune landscape after brain injury. Ongoing studies are expanding our dataset to increase statistical power and evaluate varying severities of injury, providing a more comprehensive understanding of brain-wide neuroimmune dynamics following TBI.



Disclosures: H. Zehra: None. **D. Liu:** None. **C. Hsu:** None. **T. Tu:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.13/W3

Topic: D.04. Brain Injury and Trauma

Title: Mechanisms of post-TBI chronic inflammation: Interplay of Myeloperoxidase and Acrolein in the formation of foamy macrophages

Authors: *S. SCINTO[1], R. SHI[2];
[1]Ctr. for Paralysis Research, Biomed. Engin., [2]Depat. Basic Med. Sci., Purdue Univ., West Lafayette, IN

Abstract: Blast traumatic brain injury (bTBI) is caused by shock wave pressure which results in brain damage. These injuries are highly prevalent in military personnel and increasingly affect civilians. It is known that post-TBI pathology, particularly inflammation, plays a key role in the development of neurodegenerative diseases, however the mechanisms that drive the chronic inflammatory response are not well understood. In the days following injury, inflammation rises and can persist for months to years, which is exacerbated by persistent oxidative stress. Macrophage activation and subsequent polarization drive inflammation and contribute to the chronic inflammatory environment that promotes macrophage dysfunction. Specifically, lipid laden macrophages termed foamy cells develop, exhibiting impaired clearance capacity, and sustained expression of Myeloperoxidase (MPO). MPO is a pro-inflammatory enzyme that is endogenously expressed in activated macrophages, microglia, and neutrophils. Importantly, MPO is a known producer of Acrolein, a toxic aldehyde that continuously drives lipid

peroxidation which intensifies inflammation. This suggests a potential vicious feed-forward cycle in which MPO-driven acrolein production drives foam cell formation, thereby sustaining chronic inflammation following TBI. To test this hypothesis, we utilized both wildtype (WT) and mice with a genetically impaired ability to detoxify acrolein. Mice were subjected to either repeated 3-day mild bTBI or sham and assessed 7 days post injury (7 DPI). To examine MPO-acrolein-mediated foam cell formation, brain tissues were analyzed by immunofluorescence and immunoblotting to quantify Acrolein, MPO, BODIPY-labeled lipid droplets, and CD11b expression. Foamy cells ($CD11b^{+}$/$BODIPY^{+}$) are co-localized with Acrolein and MPO, which uncovers a possible mechanism of intensified lipid peroxidation. Pathological changes are exacerbated in mice with suppressed acrolein detoxification capacity, with a greater effect observed in female compared to male mice, suggesting a sex-dependent role of MPO driven acrolein production in foam cell formation, and sustained inflammation. Further, both Acrolein and MPO were elevated in mice following bTBI which suggests a synergistic mechanism that contributes to persistent neuroinflammation. These data provide insight into the mechanisms underlying the post-TBI inflammatory response and suggest therapeutic avenues for TBI, a condition for which no established treatment currently exists.

Disclosures: S. Scinto: None. **R. Shi:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.14/W4

Topic: D.04. Brain Injury and Trauma

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Title: Toward a preClinical Biomarkers, Imaging, Modifiers (pCBI-M) Framework for Preclinical Neurotrauma

Authors: R. HUIE[1], H. L. RADABAUGH[4], E. MENDOZA[2], J. S. GRETHE[5], M. E. MARTONE[6], ***A. R. FERGUSON**[3];
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Abstract: Traumatic brain injury (TBI) and spinal cord injury (SCI) comprise the major forms of neurotrauma. TBI has the highest incidence of all neurological disorders and is a major source of death and long-term disability worldwide, whereas SCI has near 'orphan disease' status as a relatively rare, but devastating condition associated with motor, sensory, and autonomic changes. Complexity represents a central challenge for developing precision therapeutics for neurotrauma. TBI and SCI consist of heterogeneous injuries superimposed on the intrinsic complexity of the mammalian CNS. From a biological perspective, they impact multiple scales of analysis from molecular and cellular pathways to neural networks, and from behavior to functional outcomes, with temporal scales that vary from milliseconds to years. Clinically, the field is working to better manage complexity by shifting away from categorization of 'mild', 'moderate', and 'severe' to a more nuanced multimodal classification of that integrates Clinical assessments, Biomarkers, Imaging, and injury Modifiers (CBI-M) into a single framework. There are early calls for the preclinical field to adopt a similar approach for experimental models to improve preclinical fidelity and translational potential. Doing so requires synthesizing data from a constellation of early functional scores, biomarkers, imaging and other features to more accurately determine injury severity in preclinical models. To this end, we have mined the 50+ published datasets currently in the NIH-supported Open Data Commons for TBI (odc-tbi.org) and SCI (odc-sci.org) to begin the process of aligning and harmonizing across the wide variety of labs and experimental designs. This rich set of data assets yielded over 3,200 variables, across 5000+ individual animal subjects. Variables were first categorized to broadly fit within 4 domains: injury (including model and parameters), subject-level metadata (including species, strain, age, sex, and weight), neurological assessment, imaging, biomarkers, and behavioral outcomes. We will present descriptive statistics detailing the extent of alignment across labs, explore multivariate approaches for harmonization, and discuss
the need for a data-driven integrative injury severity index with an eye toward bench-to-bedside translation.

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Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.15/W5

Topic: D.04. Brain Injury and Trauma

Support: Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)
Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPQ)

Title: Prenatal alcohol exposure alters brain excitability and modulates excitatory and inhibitory circuitry in the cerebral cortex of mice

Authors: *L. D. HERINGER[1], H. MENDONÇA[2], T. BASTOS DE AZEVEDO[1], T. PONTES[1], A. B. MARTINEZ[3];
[1]Federal Univ. of Rio de Janeiro, Rio de Janeiro, Brazil; [2]Inst. de Biodiversidade e Sustentabilidade NUPEM, Federal Univ. of Rio de Janeiro, Macaé, Brazil; [3]Federal Univ. of Rio de Janeiro, Rio De Janeiro, Brazil

Abstract: Prenatal alcohol exposure (PAE) is a major risk factor for Fetal Alcohol Spectrum Disorders, leading to cognitive deficits, behavioral impairments, and epilepsy. During critical periods of corticogenesis, ethanol directly interferes with GABAergic and glutamatergic neurotransmission, potentially disrupting neuronal migration, synaptic maturation, and the establishment of the excitation/inhibition balance within cortical circuits. Although several studies demonstrate that prenatal alcohol exposure is linked to cortical disorganization and increased seizure susceptibility, the cellular and synaptic mechanisms underlying the development of hyperexcitability and epileptogenesis remain incompletely understood. Therefore, the present study investigated the effects of PAE of a daily dose of 3mg/kg of ethanol through gavage in swiss pregnant mice, during a period equivalent to the human second trimester (gestational day 14 until 19), on neocortical organization, neuronal composition, synaptic content and its association with seizure susceptibility and severity. Employing immunofluorescence of S1 cortical slices, we demonstrated that PAE induces alterations in cortical circuit organization, including changes in the number and distribution of GABAergic interneurons, particularly parvalbumin-, somatostatin-, and vasoactive intestinal peptide-positive subtypes. We further observed alterations in the balance of excitatory and inhibitory synaptic sites (identified by vGluT1, PSD95, Gephryn or vGAT) into these different interneurons. Finally, PAE reduced febrile seizure vulnerability, but increased penthylenetetrazole-induced seizure severity in post-natal day 12. Taken together, our findings indicate that prenatal alcohol exposure during critical developmental windows disrupts the proper maturation of cortical microcircuits, contributing to an altered state of hyperexcitability, providing relevant experimental evidences for understanding the neurobiological mechanisms underlying epileptogenesis associated with FASD.

Disclosures: L.D. Heringer: None. **H. Mendonça:** None. **T. Bastos de Azevedo:** None. **T. Pontes:** None. **A.B. Martinez:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.16/W6

Topic: D.04. Brain Injury and Trauma

Title: rmTBI leads to cellular deficits in the entorhinal cortex in C57 wildtype mice

Authors: *A. MAREDIYA[1], T. M. SMITH[2], J. M. FLINN[1];
[1]Psychology, [2]George Mason Univ., Fairfax, VA

Abstract: Repetitive mild traumatic brain injuries (rmTBI) induce cognitive and motor impairments, yet the optimal parameters required for valid and reproducible data remain unclear. In order to examine these factors, wildtype (C57BL/6J) mice (n = 97, 14 weeks) were randomly selected for fur shaving (shaved, not shaved) and velocity (0 m/s, 3 m/s, 4 m/s) conditions and received 5 rmTBIs across 10 days using a Leica Impact One Stereotaxic Model. Behavioral outcomes measured include time-to-righting (TTR) and time-to-ambulation (TTA) to assess injury severity, along with motor deficits and anxiety-like behaviors through the Rotarod and Elevated Zero Maze (EZM). Cell and white matter density were assessed via Cresyl Violet and Luxol Fast Blue staining across cortical, hippocampal and entorhinal brain regions. Mixed ANOVAs revealed that rmTBI mice showed significantly longer TTR and TTA than sham mice (TTR and TTA: $p < .001$), regardless of velocity. Fur shaving significantly amplified TTA ($p = .003$) but did not significantly affect TTR. There were no significant differences for Rotarod or EZM due to fur shaving or impact velocity. However, between-subject ANOVAs showed the entorhinal cortex had significant cell density differences, with velocity accounting for 87% of variance ($p < .001$). The corpus callosum also showed significant velocity-related cell loss ($p = .004$), and hippocampal CA1 showed a significant fur shaving and velocity interaction ($p = .034$). At this time, fur shaving and impact velocity did not consistently affect behavioral data, however, velocity did significantly affect histology in a negative direction. Notably, the pronounced entorhinal cell loss in wildtype mice without a genetic predisposition for Alzheimer's disease (AD) illustrates the potential for mild head injuries to produce cellular damage in regions associated with AD pathogenesis without producing major motor deficits. The entorhinal cortex region is the first to showcase damage from AD; future research should further assess the neurodegenerative consequences from rmTBI.

Disclosures: A. Marediya: None. **T.M. Smith:** None. **J.M. Flinn:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.17/W7

Topic: D.04. Brain Injury and Trauma

Support: Subvenció PE501084306-2023-PROCIENCIA-BM

Title: Temporal progression of axonal pathology during persistent neuroinflammation in experimental Neurocysticercosis

Authors: *D. G. DÁVILA[1], R. H. CÉLIZ[2], M. R. VERASTEGUI[3];
[1]Programa de Doctorado en Ciencias de la Salud, Facultad Medicina, Univ. Nacional Mayor de San Marcos, Lima, Peru; [2]Univ. Científica del Sur, Lima, Peru; [3]Infectious Dis. Lab. Research-LID, Univ. Peruana Cayetano Heredia, Chaclacayo, Peru

Abstract: Neurocysticercosis (NCC), caused by the larval stage of *Taenia solium*, is one of the leading causes of acquired epilepsy worldwide. The disease is characterized by a sustained neuroinflammatory response that contributes to neurological dysfunction; however, whether chronic neuroinflammation is accompanied by progressive axonal pathology throughout infection remains poorly understood. This study aimed to characterize the temporal progression of axonal injury during experimental NCC. Brain tissues from experimentally infected rats were evaluated at 30, 60, 90, 180, and 360 days post-infection (dpi). Microglial activation was assessed using CD68 immunoreactivity and morphological analysis. Axonal injury was evaluated using amyloid precursor protein (APP), a marker of impaired axonal transport, and neurofilament protein (NFP), a marker of structural axonal damage. Activated microglia were consistently present throughout all stages of infection, indicating persistent neuroinflammation. Nevertheless, microglial morphology changed progressively over time, shifting from predominantly amoeboid cells at 30-60 dpi to hypertrophic morphologies at 90-180 dpi and predominantly dystrophic forms at 360 dpi. Axonal pathology followed a distinct temporal pattern. APP-positive axonal spheroids were detected at 30 dpi, indicating early disruption of axonal transport, and increased progressively as infection advanced. In contrast, NFP abnormalities were first observed at 60 dpi as a small number of axonal spheroids and progressively increased thereafter, reaching their highest levels at 360 dpi, consistent with chronic structural axonal degeneration. These findings reveal a temporal sequence of axonal injury characterized by early transport dysfunction followed by progressive structural degeneration. The evolution of axonal pathology occurred in parallel with persistent neuroinflammation and dynamic changes in microglial morphology throughout infection. Ongoing analyses of microglial phenotypes and quantitative assessments of axonal pathology will further characterize the relationship between microglial responses and distinct stages of axonal injury during disease progression.

Disclosures: D.G. Dávila: None. **R.H. Céliz:** None. **M.R. Verastegui:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.18/W8

Topic: D.04. Brain Injury and Trauma

Support: This work was supported partly by the Richard J Traystman professorship endowment (SK).

Title: Diffuse traumatic brain injury in a neonatal and pediatric rabbit model induces milestone delays and cerebellar dysfunction and neurodegeration with learning deficits

Authors: *J. ALLENDE LABASTIDA[1], P. VYAS[1], J. L. SOWERS[1], N. SAH[1], V. ARUN[3], M. TRIVEDI[4], B. T. OBODAIFIO[2], M. P. AVALOS[1], J. LIU[1], R. C. KOEHLER[1], S. KANNAN[1]; [1]Anesthesiol. and Critical Care Med., [2]Cell. and Mol. Med., Johns Hopkins Univ. SOM, Baltimore, MD; [3]Undergraduate Publ. Hlth. Studies, [4]Biomed. Engin., Johns Hopkins Univ., Baltimore, MD

Abstract: Traumatic brain injury (TBI) is the primary cause of death and disability in children. Diffuse axonal injury correlates with more severe outcomes in children. Neonatal and pediatric TBI leads to neurodevelopmental delays, and long-term cognitive and behavioral impairments. Perinatal white matter development, microglial distribution and pattern of brain growth in humans and rabbits share similarities. These characteristics make rabbits an ideal model to study early TBI to explore mechanisms of diffuse white matter injury and its effects on neurodevelopment. We developed a neonatal and pediatric traumatic brain injury model in rabbits mimicking biomechanical characteristics of accidental/non-accidental TBI's.

Neonatal (Postnatal Day, PND 5-7) and pediatric (PND 17-19) kits were randomly assigned to naive, single TBI (sTBI), or repetitive TBI (rTBI, 2 impacts, 24 hours apart) groups. Kits were subjected to different forces of impact based on age and number of injuries (1, 1.8, 4.2 and 5.5 joules in neonatal and pediatric rTBI and sTBI, respectively). All TBI-exposed groups exhibited significant growth delays and decreased weight gain. Neonatal TBI groups showed persisting circling behavior (missed milestone), and more pronounced ataxia and vestibular deficits than the pediatric group. Cerebellar injury manifested as Purkinje neuron degeneration and cognitive deficits in the eye-blink conditioning test, observed across all sTBI groups, with a notable trend in the neonatal rTBI group.

Matrix assisted laser desorption ionization (MALDI) mass spectrometry imaging revealed region-specific perturbations in key metabolites including glutamine, glutamate, N-acetylaspartate, glutathione and Taurine across various brain regions, suggesting significant impact on neurotransmission and oxidative stress pathways following TBI. We demonstrate the vulnerability of neonatal brain to diffuse axonal injury and provide novel insights into the metabolic deregulation possibly underlining short- and long-term developmental impairments. Our rabbit model shows impairments in these clinically relevant biomarkers, providing evidence for the application of this model to evaluate therapies.

Disclosures: J. Allende Labastida: None. **P. Vyas:** None. **J.L. Sowers:** None. **N. Sah:** None. **V. Arun:** None. **M. Trivedi:** None. **B.T. Obodaifio:** None. **M.P. Avalos:** None. **J. Liu:** None. **R.C. Koehler:** None. **S. Kannan:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.19/W9

Topic: D.04. Brain Injury and Trauma

Support: CIHR Grant PJT376309
CIHR Grant PJT156179
CIHR Grant PJT178059

Title: Disrupted frontal and hippocampal network connectivity in traumatic brain injury produces chronic spatial memory deficits

Authors: *J. TAN[1], S. PATEL[3,4], A. E. DORR[3], L. M. VECCHIO[2,4], I. AUBERT[4,2], C. HAMANI[4,5,6,7], B. STEFANOVIC[3,1,5], M. GOUBRAN[1,3,5,7];
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Abstract: Over 50% of traumatic brain injury (TBI) survivors experience memory impairments months to years post-injury, yet no effective treatments exist. Sensitive markers of memory function would aid monitoring of patient recovery and therapeutic development, but standard cognitive testing lacks sensitivity and is highly variable. MRI offers a sensitive, non-invasive, whole-brain assessment of injury, and the controlled cortical impact (CCI) experimental model offers more reproducibility for modeling network dysfunction. We longitudinally assessed structural and functional connectivity changes post-CCI via diffusion MRI (dMRI) and resting-state fMRI (rsfMRI).
C57BL/6 mice received CCI or sham surgeries (n=5/group) and underwent MRI assessment at baseline, subacute, and chronic injury phases (1 and 4 weeks post-CCI). Prior to injury and after the chronic MRI scan, mice were assessed for spatial memory via a location discrimination (LD) task in an operant chamber.
Structurally, there was a possible transient loss of crossing fibres in the internal capsule (IC) and fimbria, indicated by increased fractional anisotropy (IC: +20.7%, $p<0.05$; fimbria: +37.1%, $p<0.05$), maintained neurite density index, and reduced orientation dispersion index (IC:-12.3%, $p<0.05$; fimbria:-22.6%, $p<0.05$). Functionally, CCI mice showed chronic ipsilesional hypoconnectivity between the entorhinal cortex and both the CA2/CA3 (-148%, $p<0.01$) and the dentate gyrus (-87.2%, $p<0.05$). To investigate changes to whole-brain network topology, we applied graph theory to the rsfMRI connectivity matrices. CCI mice exhibited reduced global efficiency (-4.3%, $p<0.05$) and a trend toward increased mean clustering coefficient (+12.5%, $p=0.08$) at the chronic stage. This suggests local hyperconnectivity and impaired long-range integration. We then used connectome gradients to map network reorganization along continuous functional hierarchies. This revealed a chronic contraction of the frontal ($p<0.01$) and auditory ($p<0.05$) networks along the transmodal-unimodal functional gradient, suggesting network de-differentiation in CCI. Behaviorally, sham mice showed a significant improvement in LD accuracy (+24.5%, $p<0.001$), while CCI mice did not (-5.76%), suggesting a learning impairment. The increase in within-hippocampal connectivity ($R^2=0.616$, $p<0.05$), and the frontal network's shift toward the transmodal end of the unimodal-transmodal gradient axis ($R^2=0.756$, $p<0.01$) from baseline to chronic stage were correlated with the improvement in LD

accuracy score. These connectivity changes may serve as sensitive neurophysiological biomarkers of post-TBI memory recovery.

Disclosures: J. Tan: None. **S. Patel:** None. **A.E. Dorr:** None. **L.M. Vecchio:** None. **I. Aubert:** None. **C. Hamani:** None. **B. Stefanovic:** None. **M. Goubran:** None.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.20/W10

Topic: D.04. Brain Injury and Trauma

Support: CIHR Grant PJT376309
CIHR Grant PJT156179
CIHR Grant PJT178059

Title: Chronic neuroinflammation and aberrant cortical reorganization underlie memory impairment post-traumatic brain injury

Authors: *S. PATEL[1,2], J. TAN[4], T. XU[4], A. E. DORR[1], J. OSMANN[1,3], T. RABELO[2], L. M. VECCHIO[5,2], I. AUBERT[2,5], C. HAMANI[2,3,6,7], B. STEFANOVIC[1,4,3], M. GOUBRAN[4,1,3,7]; [1]Physical Sci., [2]Biol. Sci., [3]Hurvitz Brain Sci. Program, Sunnybrook Res. Inst., Toronto, ON, Canada; [4]Med. Biophysics, [5]Dept. of Lab. Med. and Pathobiology, Univ. of Toronto, Toronto, ON, Canada; [6]Div. of Neurosurg., [7]Harquail Ctr. for Neuromodulation, Sunnybrook Hlth. Sci. Ctr., Toronto, ON, Canada

Abstract: Traumatic brain injury (TBI) causes persistent memory impairment, yet the underlying cellular-scale structural, functional, and neuroinflammatory changes remain poorly characterized. Conventional histology suffers from sampling limitations and a restricted depth of field, while in vivo whole-brain modalities lack cellular resolution. To overcome these limitations, we applied tissue clearing and light-sheet fluorescence microscopy (LSFM) to a controlled cortical impact (CCI) mouse model of TBI to identify cellular changes underlying chronic memory impairment.
C57BL/6 mice received CCI or sham surgery (n=5/group) and a viral tracer injection (AAV-DJ/8.CaMKIIa.EYFP.NRN) at the injury site (1.5mm AP, 1.5mm ML, 1mm depth). Spatial memory was assessed before injury and in the chronic phase using an auditory-cued location discrimination (LD) task in an operant chamber. Brains were collected 1h after the final test session, optically cleared, immunolabelled, and imaged by LSFM.
Structurally, CCI mice showed ipsilesional axonal loss in the dentate gyrus (-72.5%, $p<0.05$) and fimbria (-72.7%, $p=0.085$). Interhemispheric connections were also reduced, with a significant decrease in signal density in the contralesional fimbria (-78.0%, $p<0.01$). Neuroinflammation in the CCI group was marked by elevated ipsilesional GFAP signal density in the hippocampus (CA1: +16.5%, $p<0.05$; fimbria:+33.8%, $p<0.01$) and superior colliculus (+24.2%, $p<0.05$),

indicating sustained astrocytic activation. Functionally, c-Fos+ cell density, a marker for neuronal activation, was decreased in the ipsilesional subiculum (-23.9%, $p<0.05$) and increased in the contralesional primary auditory cortex (+84.3%, $p<0.05$) of CCI mice. These findings suggest chronic ipsilesional hypoactivity, potential compensatory activity in the contralesional hemisphere, and disrupted transcallosal inhibition. Behaviorally, sham mice showed a significant increase in LD accuracy score (+24.5%, $p<0.001$) while CCI mice did not (-5.76%), reflecting a learning impairment. c-Fos hyperactivity in the contralesional primary auditory cortex was significantly correlated with the improvement in LD accuracy score ($R^2 = 0.596$, $p<0.01$), while increased GFAP activation in the fimbria ($R^2=0.431$, $p<0.05$) and superior colliculus ($R^2=0.495$, $p<0.05$) showed trends toward cognitive association. Together, these findings show that sustained neuroinflammation and changes in neuronal activation patterns were associated with impaired learning post-TBI, highlighting the utility of LSFM for studying brain-wide neuropathology in TBI.

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Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.21/W11

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R01AG061120-01
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Taube Stanford Children's Concussion Initiative
Wu Tsai Human Performance Agility Project Program
Grant of the Foundation of the American Society of Neuroradiology
Pac-12 Conference's Student-Athlete Health and Well-Being Initiative

Title: Impact exposure in contact sports is associated with reorganization of functional connectivity and cortical perfusion gradients

Authors: *Y. WANG[1], M. KARIMPOOR[2], J. OTTOY[5], H. MOEIN TAGHAVI[2], M. GEORGIADIS[2], S. SAMI[2], J. TOWNS[1], N. CECCHI[1], A. LIU[2], G. A. GRANT[3], C. LIU[7], D. CAMARILLO[1], M. GOUBRAN[6], M. M. ZEINEH[4];
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Abstract: Repetitive head impacts are common in contact sports, yet their cumulative effect on the large-scale cortical organization of the cortex is poorly understood. Recently, brain "gradients", probing spatial relationships, have been employed to study brain-wide organization (Bernhardt et al., Gradients in brain organization, Neuroimage 2020, for an overview). Here, we examined whether impact exposure reshapes the macroscale gradients describing cortical functional and vascular organization. Collegiate athletes from two institutions were prospectively studied in high-impact (football, wrestling, lacrosse, rugby; n=109) and low-impact (archery, badminton, golf, rowing, tennis, swimming; n=47) sports, with longitudinal follow-up (282 total MRIs with FU median 1.09 years / IQR 0.96-1.86). Gradients were computed and group differences and longitudinal changes were tested with two-sample t-tests and linear mixed-effects models (age, sex covariates; FDR-corrected). Diffusion map embedding of resting-state fMRI connectomes yielded the expected unimodal-to-transmodal (Gradient 1) and visual-sensorimotor (Gradient 2) gradients. At baseline, this embedding was contracted in high- vs low-impact athletes: the visual network shifted along both gradients, while the default mode and frontoparietal networks converged along Gradient 2, with overall architecture preserved. This co-occurred with selectively lower baseline ImPACT visual motor speed ($p=0.008$). Longitudinally, default mode and visual networks converged along Gradient 2 in low- but not in high-impact athletes (group×time: default mode $p<0.001$, visual $p=0.025$). Analysis of ASL perfusion covariance yielded a principal gradient following the anterior-posterior cerebral artery (ACA-PCA) distribution. Low-impact athletes gained ACA-PCA differentiation over time, whereas high-impact athletes showed a compressed gradient, indicating reduced vascular-territory segregation. In the visual and default mode networks, gradient change tracked visual motor speed change in opposite directions in high- vs low-impact athletes ($p<0.01$). Cumulative head impact exposure selectively repositions brain networks within gradient space: prior convergence at baseline may constrain, and repetitive impacts further delay, normative maturational refinement, with associated perfusion and cognitive changes. Because these changes are asymptomatic and track cognitive performance, this means routine subconcussive exposure can disrupt the developing brain organization before symptoms emerge, with direct implications for assessing athlete brain health and long-term neurological risk.

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Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.22/W12

Topic: D.04. Brain Injury and Trauma

Support: DoD/USAMRAA grant HT9425-24-1-0301

Title: Repetitive blast exposure and social isolation exacerbate chronic post traumatic seizure behaviors

Authors: *S. PRAJAPATI[1], G. WILBUR[2], N. EAPEN[1], H. MENTZEL[3], G. NAH[5], R. ROWE[6], B. BAUER[4], B. HUBBARD[1];
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Abstract: Blast-induced traumatic brain injury (bTBI) is a prevalent injury among military personnel and is associated with an increased risk of post-traumatic epilepsy (PTE). Although clinical evidence increasingly implicates epilepsy in bTBI, the underlying mechanisms remain largely unexplored. This study aims to develop a preclinical model of repetitive bTBI (rbTBI) and investigate long-term seizure burden and sleep-wake alterations under conditions of social isolation. Adult male and female Sprague-Dawley rats (rbTBI: males n=15, females n=15; sham: males n=7, females n=5) received sham procedures or two blast exposures 24 h apart using a helium-driven shock tube (19.69 ± 1.15 psi; impulse: 57.49 ± 2.00 psi·ms). After a 4-month latency under single housing, animals were monitored for one month in noninvasive piezoelectric cages to assess seizures and sleep. Following monitoring, brains were then collected and processed for immunofluorescence (IF) analysis of aquaporin-4 (AQP4), glial fibrillary acidic protein (GFAP), and ionized calcium-binding adaptor molecule 1 (IBA1) to evaluate astrocytic and microglial changes in cortex, hippocampus and corpus callosum. Subsequently, western blot was performed on tissues homogenate to quantify astrocytic damage and establish a correlation with the seizure burden. No differences in total sleep time were observed between rbTBI and sham groups, however rbTBI animals showed reduced light-phase sleep ($p=0.013$) and increased dark-phase sleep ($p=0.0164$) between weeks 17 and 20 post-rbTBI. Sleep percentage, mean bout length and sleep-wake transition was higher in males than females in both groups. Post traumatic ictal phase seizure behaviors majorly include arousal after seizure initiation, head clonus and nodding, freezing, agitation, clonic body jerks and wet dog shakes. These specific events occurred in 93% (14/15) of rbTBI males versus 67% (10/15) of rbTBI females, with 82% of total events occurring during the dark phase. There also was a positive correlation between total sleep % and seizure burden (Spearman rho, $\rho=0.173$, $p=0.025$). IF staining didn't show any significant difference in AQP4 and IBA1 expression in any of the brain regions. However, GFAP showed an increased expression in the cortex ($p=0.0411$). rbTBI also showed significantly higher GFAP expression than sham ($p=0.0235$) in western blot and a positive correlation with the seizure burden. Collectively, these results indicate that bTBI can result in PTE, characterized by altered sleep parameters, pronounced sex differences, significant relationships between sleep and seizure outcomes, and reactive astrogliosis.

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Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.23/W13

Topic: D.04. Brain Injury and Trauma

Support: NIH Grant R21NS135088 (IK)

Title: The cerebellum harbors the most prominent metabolic dysregulation and shows associated neuronal death in sepsis-associated encephalopathy

Authors: *N. WOLFF[1], M. TRIANTAFYLLOU[2], D. CRAWFORD[3], R. LARSON[4], A. RYAN[5], D. GRAHAM[6], P. KRATIMENOS[7], R. SUN[5], V. GALLO[8], I. KOUTROULIS[9]; [1]Children's Natl. Res. Inst., Washington, DC; [2]Children's Natl. Res. Insitute, Washington, DC; [3]Seattle Children's Res. Inst., Seattle, WA; [4]Biochem. and Mol. Biol., [5]Univ. of Florida, Gainesville, FL; [6]Graham Scientific, Maryland, MD; [7]Neurosci. and Neonatology, Children's Natl. Hospital, George Washington Univ. Sch. of Med. and Hlth. Sci., Washington, DC; [8]Ctr. for Integrative Brain Res., Seattle Children's Hosp., Seattle, WA; [9]Emergency Med., Children's Natl. Med. Ctr., Washington, DC

Abstract: Sepsis-associated encephalopathy (SAE) is a common, severe complication of sepsis, that produces brain region-dependent neurological deficits and long-term disability. Sepsis-induced energic failure is central to its pathophysiology, interplaying with neuroinflammation and mitochondrial dysfunction to drive oxidative stress and neuronal injury. However, the pathways linking metabolic dysfunction to neuronal death in SAE remain unclear. Here, we tested whether the brain region with the most pronounced metabolic dysregulation in SAE displays specific altered pathways in association with local neuronal death. Acute polymicrobial sepsis was induced in sex-balanced mice (8-12 weeks) by intraperitoneal cecal slurry injection. Controls received phosphate-buffered saline. Clinical and neurological status was scored with a Murine Sepsis Scale. We performed Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging (MALDI MSI) for spatial metabolomics at 6h and 24h (n=10/group). Neuropathology at 24h was assessed by hematoxylin & eosin (H&E) and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL, marker of cell death) immunohistochemistry (n=8-10/group). Sepsis induction produced acute central nervous system symptomatology, with the steepest status deterioration seen within the first 6 hours. At 6h metabolic changes were subtle, whereas by 24h significant metabolic alterations had emerged across multiple brain regions, with the cerebellum the most markedly dysregulated. Altered cerebellar metabolites were mainly involved in pathways of neurotransmitter signaling and metabolism, including glutamate and glycine, and activation of nucleotide synthesis and amino acid transport with concurrent impairment of protein synthesis. Region-specific changes in sphingolipid metabolism, redox homeostasis, and neurovascular coupling were additionally observed. These changes were accompanied by local neuronal death detected by morphological abnormalities and Purkinje cell loss on H&E, and increased cellular expression of TUNEL at 24h. Overall, these findings identify the cerebellum as the most metabolically vulnerable brain region in sepsis and define key metabolic pathways associated with region-specific neuronal injury. This contributes to a deeper understanding of SAE pathophysiology, and the identification of potential therapeutic targets to mitigate metabolic failure and neuronal death for the improvement of neurological outcomes after sepsis.

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

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.24/W14

Topic: D.04. Brain Injury and Trauma

Support: Ekam Imaging Inc

Title: Sensitive period of plasticity emerges after delayed psilocybin treatment for repetitive mild head injury: A preclinical MRI study

Authors: *E. K. BRENGEL[1], A. MAHESWARI[2], A. MOORE[2], E. BENNET[2], H. B. BRADSHAW[3], R. J. ORTIZ[4], P. P. KULKARNI[1], C. F. FERRIS[1];
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[3]Psychological and Brain Sci., Indiana Univ. Program in Neurosci., Bloomington, IN;
[4]Psychology, Northern Illinois Univ., DeKalb, IL

Abstract: INTRODUCTION: Psilocybin (PSI), a psychedelic 5-HT2A agonist, has garnered attention in recent years as a robust effector of neuroplasticity, underlying promising clinical trials for treatment of post-traumatic stress disorder, substance use disorder, and major depressive disorder. More recently, our lab and others have demonstrated PSI may be able to restore functional connectivity and cerebrovascular reactivity after repetitive mild traumatic brain injury (rmTBI) in rats. One crucial limitation of prior research is the timing of both treatment and data collection. Treatment with a classical psychedelic is often not practical immediately after injury, but may be more accessible months or years after a period of rmTBI, such as after retirement from sports or military service or while recovering from domestic violence. Further, readouts must be collected longitudinally and in vivo to track progress over time to ensure that therapeutic effects are not overstated, understated, or missed entirely. METHODS: In this study, middle-aged (7-8-month) female Sprague-Dawley rats (N = 15) were assigned to one of two groups: rmTBI with PSI treatment (rmTBI-PSI) or rmTBI with vehicle injection (rmTBI-VEH). Both groups underwent three scanning sessions on a 7T MRI. The first session occurred before rmTBI, serving as an internal healthy baseline (Day 0). All rats then received an awake, momentum exchange mTBI once per day for three days (Days 1-3). Two weeks post-rmTBI, three consecutive days of PSI or VEH treatment was administered (Days 14-17). On Day 21, a second scanning session was conducted, and on Day 35, a third scanning session. Each scanning session consisted of T2-weighted MRI for volumetric analysis, awake resting-state Functional Connectivity (rsFC), and awake BOLD fMRI with CO_2 challenge for measurement of cerebrovascular reactivity. RESULTS: Global hyperconnectivity was observed in rmTBI-PSI rats at Scan 2 that largely returned to baseline levels at Scan 3 ($p < .0001$),

suggesting the emergence of a sensitive period of neuroplasticity after PSI treatment. This pattern was observed in all studied regions, including the amygdala, basal ganglia, cerebellum, sensorimotor cortex, hippocampus, hypothalamus, medulla, midbrain, olfactory system, prefrontal cortex, and thalamus. FUTURE DIRECTIONS: In vivo and ex vivo analyses of long-term myelination in this cohort, now aged 18-20 months, are ongoing. These findings suggest that PSI treatment might serve to augment a multi-pronged approach to intervention alongside methods that will benefit from enhanced plasticity such as cognitive behavioral therapy, aerobic exercise, or dietary supplementation.

Disclosures: E.K. Brengel: None. **A. maheswari:** None. **A. Moore:** None. **E. Bennet:** None. **H.B. Bradshaw:** None. **R.J. Ortiz:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases, and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases, and analytical software for use in awake animal imaging..

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.25/W15

Topic: D.04. Brain Injury and Trauma

Support: Ekam imaging

Title: Investigating the combined effects of chronic herbicide exposure and repetitive mild traumatic brain injury using multimodal MRI

Authors: *A. MAHESWARI[1], S. BALAJI[1], R. AHUJA[2], T. CHUKWUEMEKA[3], S. KEDHARNATH[4], E. BENNET[1], D. WEISS[1], K. BALAJI[5], E. K. BRENGEL[6], A. MOORE[8], R. J. ORTIZ[9], P. P. KULKARNI[6], C. F. FERRIS[7];
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Abstract: Emerging evidence suggests that chronic exposure to herbicides such as glyphosate and paraquat may contribute to neurobiological changes including oxidative stress and disruption of dopaminergic signaling pathways. Similarly, repetitive mild traumatic brain injury (rmTBI) is associated with structural and functional changes in the brain. This study examines the potential synergistic effects of chronic herbicide exposure and rmTBI on neurotoxicity and neuronal

dysfunction. Female and male Sprague-Dawley rats were assigned to vehicle, paraquat or glyphosate treatment groups. Paraquat was administered orally at 10 mg/kg every third day and glyphosate at 75 mg/ kg daily for 45 Days. Diffusion weighted imaging (DWI) was performed on Day 30, after which rmTBI was induced over 3 consecutive days (Days 31 - 33) using a momentum exchange impactor delivering a mild impact at 7.4 m/s. Follow up imaging was conducted on day 45, including DWI, functional MRI (fMRI) and resting state functional connectivity. Functional MRI exhibited increased BOLD response in mid brain and forebrain regions indicative of altered neurovascular coupling. In parallel, decreased positive BOLD was observed in regions associated with reward signaling, suggesting reduced sensitivity to reward-salient stimuli. Resting state functional connectivity analysis revealed significant reduction across paraquat and glyphosate treatment groups, with pronounced disruption observed in the midbrain, amygdala, basal ganglia and hippocampus regions critically implicated in dopaminergic and limbic function. DWI revealed widespread reduction in fractional anisotropy (FA) and apparent diffusion co-efficient (ADC), indicative of restricted diffusivity and microarchitectural alterations which may reflect possible white matter tract disruption and neuroinflammation. Collectively, these findings suggest that chronic herbicide exposure combined with rmTBI induces a structural and functional brain disruption consistent with dopaminergic decline and early neurodegeneration.

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Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.26/W16

Topic: D.04. Brain Injury and Trauma

Support: EKAM Imaging Inc

Title: Therapeutic Effects of Arachidonoyl Methionine on Brain Connnectivity and Myelination After Repetitive Mild Traumatic Brain Injury

Authors: *E. M. BENNET[1], E. K. BRENGEL[2], P. P. KULKARNI[2], C. F. FERRIS[2];
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Abstract: Arachidonoyl methionine (AM), an endogenous lipoamino acid, has garnered attention as a putative effector of neuroplasticity. In prior work, circulating AM was found to rise alongside the neuroplastic and therapeutic effects of psilocybin (PSI) following repetitive mild traumatic brain injury (rmTBI); however, the effects of AM alone have not yet been tested. In

this study, short-term and lasting effects of AM treatment on brain health following rmTBI were examined using an array of preclinical assays from neuroradiology and molecular biology. Adult female Sprague-Dawley rats (N=24) were subjected to awake closed-head momentum exchange mTBI or sham injury once daily for three days, followed by subcutaneous AM or vehicle injection (1 mg/kg) administered 10-20 min after each injury, yielding three groups: Sham-Vehicle, mTBI-Vehicle, and mTBI-AM. On Day 4, rats received diffusion weighted imaging (DWI) and magnetization transfer ratio (MTR) imaging on a 7T MRI scanner for microstructural and myelin examination. On Day 21, microstructural and myelin recovery was assessed with DWI and MTR, cerebrovascular reactivity was measured by fMRI with CO2 challenge, and circuitry was measured with awake functional connectivity scanning (FC). Brains were collected for protein analysis of neurodegeneration, neuroinflammation, and neuroplasticity markers. Day 4 DWI indicates vasogenic edema is induced globally by rmTBI and reduced by AM (whole brain $p<0.0001$). This pattern was reflected in the cerebellum ($p<0.0001$), thalamus ($p<0.001$), hippocampus ($p<0.01$), somatosensory cortex, and basal ganglia ($p<0.05$). Preliminary MTR further indicates AM elevates in vivo myelination in white matter. Remaining analyses are ongoing. These preliminary findings establish a body of evidence supporting the therapeutic potential of AM for rmTBI. Future studies will define the lasting cerebrovascular, connectivity, and molecular effects of AM to further elucidate the mechanisms of PSI neuroplasticity and support the investigation of non-hallucinogenic alternatives.

Disclosures: E.M. Bennet: None. **E.K. Brengel:** None. **P.P. Kulkarni:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases, and analytical software for use in awake animal imaging. **C.F. Ferris:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); CFF and PPK have a financial interest in Ekam Imaging, a company that provides RF electronics, MRI atlases, and analytical software for use in awake animal imaging.

Poster

PSTR131: Brain Injury: Animal Models: Biomarkers and Histology

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR131.27/W17

Topic: A.06. Developmental Disorders

Support: NIH NIDA grant DA023999 to Pasko Rakic

Title: Diagnostic ultrasound and movement restriction stress produce acute mitochondrial disorder and necrosis-like cell injury in mouse embryo brain

Authors: *Y. M. MOROZOV[1], A. DUQUE[2], P. RAKIC[3];
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Abstract: Production of the correct number of neurons in the proliferative zones and their migration to proper positions are highly refined processes that follow a tight schedule to properly structure the mammalian neocortex. This electron microscopy (EM) study corroborates and expands our previous report that prenatal exposure to diagnostic ultrasound waves (USW) interferes with neuronal migration (Ang et al., 2006). Here we applied a novel immunohistochemical protocol based upon double selectivity of antibodies raised against the last 31 amino acids (L31) of cannabinoid type 1 receptor (CB1R); particularly, anti-CB1R-L31 serum, in addition to CB1R, recognizes stomatin-like protein-2 (SLP2; Morozov et al., 2013). SLP2 is a constitutive mitochondrial protein and likely present in all mitochondria making complexes with other molecules in its functional position on the matrix surface of the inner mitochondrial membrane (Wai et al., 2016). CB1R-L31 antibodies bind mostly disordered mitochondria due to dissociation of mitochondrial protein complexes making the SLP2's epitope available for immunolabeling. Hence, immuno-positive disordered mitochondria and the cells containing them are detectable in situ with light microscopy and EM (Morozov and Rakic, 2026). Our results show intensive SLP2-like immunolabeling in the mitochondrial matrix in neural progenitor cells and endothelial cells from USW and sham exposed embryos as compared to naïve controls. SLP2-like immuno-positive mitochondria-containing cells show features of necrosis-like ultrastructural pathology such as swollen mitochondria and swollen cisterns of endoplasmic reticulum. Importantly, cells undergoing necrosis-type cell death are virtually unidentifiable using biochemical or immunohistochemical methods for detecting regulated cell death like apoptosis and autophagy (Ai et al., 2024). Cells containing only immuno-negative mitochondria demonstrated normal ultrastructure of organelles (including mitochondria) characteristic of developing brain. The results indicate acute effects by stress and USW exposure during periods of neurogenesis and neuron migration and suggest that scrutiny of the safety of human prenatal ultrasound must continue.

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

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.01/W18

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Selectins as therapeutic targets for secondary spinal cord injury

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Abstract: Selectins are a family of calcium-dependent lectins that play a crucial role in the leukocyte adhesion cascade, providing immune cells the ability to enter inflamed tissues from the vasculature. E-, L- and P-selectin recognize the sialylated and fucosylated tetrasaccharide, sialyl-

Lewis ^{x} (sLe^{X}), a binding ligand. Selectins are crucial for the innate immune response. When injury or infection causes inflammation in surrounding tissues, endothelial cells express both P- and E-selectin in two phases of activation. Type one activation, which occurs within minutes after injury or infection, is mediated by histamine release, triggers P-selectin expression on platelets and activated endothelial cells. Neutrophils express P-selectin glycoprotein ligand-1 (PSGL-1), a P-selectin ligand, on the surface. Neutrophil tethering is triggered when PSGL-1 from neutrophils and P-selectin expressed in endothelial cells bind together to promote neutrophil homing to the site of inflammation through the vasculature. In addition, type two activation, a longer process that occurs within hours after the injury, promotes the expression of E-selectin in endothelial cells by altering the gene expression of Interleukin-1 (IL-1) and Tumor Necrosis Factor-α (TNF-α). E-selectin binds to sLe^{X}, which is also expressed in neutrophils. Further, during type two activation, CD4+ and CD8+ T-lymphocytes are recruited from peripheral lymph nodes to the site of inflammation to further assist in the immune response. The third selectin type, L-selectin, is expressed on naive T-lymphocytes and binds to GLYCAN-1 in high endothelial cells; this binding facilitates the movement of naive T-lymphocytes from the blood back into an afferent lymph node. Furthermore, secondary damage after spinal cord injury (SCI), which occurs within minutes to weeks of the injury, directly involves activation of the inflammation cascade response. Leukocytes and lymphocytes congregate at the site of injury in the spinal cord and carry out immune responses that exacerbate both injury and neurological deficit. Research on novel strategies for targeting mechanisms of this secondary injury are ongoing, with some researchers exploring the role of selectins in SCI. General theories consider targeting selectins to reduce homing of leukocytes to the site of SCI, thereby reducing levels of inflammation present at the site of injury and lessening the burden of secondary injury in SCI and improving neurological outcome.

Disclosures: E.E. Forsell: None. **S. Prieto:** None. **B.T. David:** None. **R.G. Fessler:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.02/W19

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Homeostatic $CX3CR1^{hi}$ microglia regulate immune cell recruitment and debris clearance following surgical decompression in chronic compressive cervical spinal cord injury

Authors: *S. BROCKIE[1], M. MOVAHED[2], M. G. FEHLINGS[3];
[1]Univ. of Toronoto, Toronto, ON, Canada; [2]Krembil Res. Inst., Toronto, ON, Canada; [3]Div. Neurosurg., Univ. of Toronto, Toronto, ON, Canada

Abstract: Degenerative Cervical Myelopathy (DCM) refers to chronic compressive spinal cord injury due to congenital or acquired arthritic changes. It is the most common cause of spinal cord impairment in adults worldwide, though its pathophysiology remains incompletely understood.

Moderate to severe DCM is treated with surgical decompression. While largely effective, decompression of the chronically compressed and ischemic spinal cord causes reperfusion injury that may impair recovery, though responses to these changes by local immune cells has not been evaluated. To study microglial responses to chronic compression and reperfusion following decompression, we used a Tmem119-Cre^{ERT2} driver line to facilitate targeted depletion of homeostatic Cx3cr1^{hi} microglia via administration of diphtheria toxin (DT), while leaving injury-responsive Cx3cr1^{lo} microglia, as well as Cx3cr1-expressing monocytes and peripheral macrophages, intact. Acutely following decompression, loss of homeostatic microglia permitted increased extravasation and accumulation of neutrophils in the parenchyma. Chronically, loss of homeostatic microglia impaired debris clearance and resulted in the development of myelin plaques in three out of five DT-treated animals which were not present in vehicle-treated controls. This was paralleled at the transcriptomic level, where lipid processing genes, like *ApoE*, were significantly upregulated. Functionally, loss of homeostatic microglia impaired injury resolution and significantly reduced grip strength by five weeks post-decompression. Together, these results illustrate the roles of homeostatic microglia in regulating immune infiltration and accumulation acutely post-injury, as well as wound containment and debris clearance long-term. These findings are the first to isolate a Cx3cr1^{lo} damage-associated microglial subpopulation and interrogate their functional phenotypes in acute and chronic injury settings. Further, this work offers a novel approach to target and deplete homeostatic microglia in order to understand and investigate their population dynamics.

Disclosures: S. Brockie: None. **M. Movahed:** None. **M.G. Fehlings:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.03/W20

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: SCI drives changes in hematopoiesis across bone marrow spaces

Authors: *N. T. REHTMEYER[1], J. BRYAN[2], M. HOOK[3];
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Abstract: Bone marrow is a central site for immune signaling, orchestrating blood cell formation and the growth and specialization of immune cells. This critical function underscores bones' importance not only as structural tissue, but also as vital immune organs. In aging, these functions are disrupted by immunosenescence, a driver of osteoporosis and increased fracture risk. Similarly, spinal cord injury (SCI) has been linked to bone marrow failure and rapid development of osteoporosis. We hypothesized that SCI-induced changes in the bone marrow may propagate across bone marrow spaces, from the site of injury to peripheral tissues and the

skull, to alter hematopoiesis and immune function after injury. To test this, young (4-8 months) and aged (16-24 months) male and female mice were subjected to a T11 spinal contusion injury. The femur, vertebrae, and calvaria were collected at 2 hours, and 1, 3, 7, and 28 days post-injury, respectively. Cells were stained with the fluorophore-conjugated antibodies: CD45, CD19, CD90.2, Ly6C, F4/80, CD11b, and CD45, and populations were quantified using a Cytek Aurora flow cytometer. The calvaria and vertebrae showed similar trends in immune responses after injury, with B- and T-cell populations rapidly decreasing before returning to baseline at 7 dpi. Myeloid cells and monocytes increased across all spaces in the aged mouse population by 3 dpi, peaking at 7 dpi, and then returning to baseline by 28 dpi. These data demonstrate that SCI rapidly alters hematopoiesis, with these changes propagating throughout the network of bone marrow sites distant from the site of injury.

Disclosures: N.T. Rehtmeyer: None. **J. Bryan:** None. **M. Hook:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.04/W21

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Comparative Transcriptomic Analysis Reveals a Conserved Cell-Cycle Signature in Adult Microglia Following Spinal Cord Injury

Authors: *S. ABOUZEKRY[1], A. S. ABOUHASHEM[2], A. A. ABDELLATIF[3];
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Abstract: Background: Microglia play a central role in the response to central nervous system (CNS) injury, yet the molecular programs that consistently characterize injury-activated microglia across transcriptomic studies remain incompletely understood. Identifying conserved microglial signatures after injury may provide insights into mechanisms underlying the limited regenerative capacity of the mammalian CNS. Methods: Two independent publicly available transcriptomic datasets (bulk RNA-seq and single-cell RNA-seq) representing adult *Mus musculus* spinal cord injury (SCI) microglia were comparatively analyzed to identify genes, biological processes and pathways consistently associated with the injury response. Microglial cells were computationally extracted from a single-cell RNA-seq dataset prior to downstream analysis. Shared differentially expressed genes were then subjected to gene enrichment analysis and network-based analyses to uncover common biological processes and molecular pathways and key regulatory genes. Results: Comparative analysis identified a core set of differentially expressed genes consistently altered across independent datasets. Functional enrichment revealed a strong overrepresentation of multiple cell-cycle-related processes. Protein-protein interaction network analysis identified highly interconnected regulatory genes involved in cell-cycle and mitotic progression. Hub gene analysis using cytoHubba highlighted key regulatory genes within

the interaction network. Several of these genes overlapped with candidate hub genes previously identified in independent analyses of CNS injury responses. Collectively, the findings indicate that activation of proliferative cell-cycle programs represents a notable and reproducible feature of adult microglial responses following SCI. Conclusions: This study identified a conserved microglial injury signature characterized by extensive enrichment of cell-cycle and mitotic pathways. The recurrent detection of cell-cycle-associated hub genes across independent analyses suggests that enhanced proliferative signaling may be a characteristic feature of the adult non-regenerative response to SCI. These findings provide a framework for future investigations into the relationship between microglial proliferation, tissue repair, and regenerative failure in the mammalian injured spinal cord.

Disclosures: S. Abouzekry: None. **A.S. Abouhashem:** None. **A.A. Abdellatif:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.05/W22

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant RO1NS122961
TIRR Foundation

Title: Spinal cord injury drives systemic changes in neutrophil maturation and lifespan

Authors: *A. TRAN, M. KIRCHHOFF, D. A. MCCREEDY;
Texas A&M Univ., College Station, TX

Abstract: The acute phase of spinal cord injury (SCI) is marked by rapid and extensive accumulation of neutrophils, which can substantially impact long-term outcomes. Despite their commonly short lifespan (~1-2 days), neutrophils can adopt heterogeneous phenotypes and functions that are partially dependent on cellular maturation state. However, neutrophil heterogeneity and maturation are poorly understood in the context of SCI. We tracked neutrophil maturation by flow cytometry in the bone marrow, blood, and spinal cord tissue following contusion SCI in male and female mice at 1, 3, 7, and 35 days post-injury (dpi). We observed a sex-dependent shift from predominantly mature neutrophils ($CD101^+$) circulating in the blood to mostly immature neutrophils ($CD101^-$) at 1 dpi before returning to a predominantly mature phenotype by 7 dpi. In the spinal cord, we observed an increase in mature neutrophils at 1 and 3 dpi followed by a predominantly immature phenotype at 7 and 35 dpi. Our data indicates that SCI triggers immature neutrophil release into circulation and that neutrophil maturation states change over time in the injured spinal cord. We also injected EdU at 1 day prior to SCI to label new neutrophils recently derived from proliferating neutrophil progenitors. Approximately 10% of both immature and mature neutrophils in the spinal cord were EdU^+ at 35 dpi while no EdU^+ neutrophils were observed in the blood or bone marrow, suggesting that neutrophils can remain

in injured spinal cord tissue for weeks after SCI. To the best of our knowledge, our findings are the first to characterize neutrophil maturation in both sexes after SCI and to identify long-lived neutrophils in the injured spinal cord tissue.

Disclosures: A. Tran: None. **M. Kirchhoff:** None. **D.A. McCreedy:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.06/W23

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Wings for Life Individual Grant, WFL-US-18/26.
National Institutes of Health (R01 NS131806-01) (ADG)
Mission Connect, a program of the TIRR Foundation

Title: Phagocytic Receptor MerTK Promotes Resolution of Inflammation and Functional Recovery After Spinal Cord Injury.

Authors: *A. R. SCHEINFELD, J. C. ALDRICH, A. PISSAY, F. C. BREMNER, A. D. GAUDET;
Univ. of Texas at Austin, Austin, TX

Abstract: Spinal cord injury (SCI) causes persistent neuroinflammation that drives secondary damage, impairs neurologic recovery, and elicits chronic neuropathic pain. Inflammatory resolution is an underexplored mechanism to support long-term recovery and is facilitated by *phagocytosis* via the receptor MerTK. While MerTK activation can benefit outcomes in inflammatory conditions such as multiple sclerosis, the role of MerTK in CNS trauma remains unclear. Here, we hypothesize that MerTK deletion (KO) in mice will exacerbate secondary damage, and functional deficits after SCI, while activation of MerTK by addition of its ligand, GAS6, will dampen inflammatory gene induction in macrophages. MerTK wildtype (WT) or KO female and male mice received moderate (65kdyn) T9 contusion SCI, then we assessed anatomical, molecular, and behavioral outcomes. Compared to WT mice, MerTK KO mice show significantly impaired locomotor recovery after SCI. In accordance, MerTK KO spinal cord epicenters had a larger lesion volume. Additionally, MerTK KO mice display increased CD11b+ cell density within the lesion core, suggesting greater immune cell accumulation. These CD11b+ cells exhibited elevated intracellular ORO staining per cell, indicating deficient lipid clearance and impaired phagocytic function. Further, MerTK KO spinal cord epicenters have increased RNA expression of potentially damaging pro-inflammatory mediators. Interestingly, WT—but not MerTK KO—mice experience heightened mechanical sensitivity however, thermal sensitivity does not differ between genotypes. Next, we added GAS6 to macrophages to activate MerTK and TAM receptors; we found that GAS6 attenuated LPS-induced inflammatory gene expression. Our results suggest that MerTK is required for dampening inflammation, promoting

repair, and enhancing locomotor recovery after SCI. Our ongoing studies are exploring MerTK activation as a novel neuroimmune therapy to enhance recovery after SCI.

Disclosures: A.R. Scheinfeld: None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.07/W24

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant R01NS131806

Title: Macrophage-specific REV-ERBα/β deletion induces a pro-inflammatory phenotypic shift following spinal cord injury.

Authors: *U. P. KANDJOZE[1,2], J. C. ALDRICH[3,2], F. C. BREMNER[3,2], S. M. ALMAN[3,2], A. R. SCHEINFELD[3,2], L. K. FONKEN[4,1], A. D. GAUDET[3,1,2,5];
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Abstract: Spinal cord injury (SCI) induces a sustained neuroinflammatory response driven by resident microglia and infiltrating macrophages, contributing to secondary tissue damage. SCI also disrupts circadian rhythms, further exacerbating immune dysregulation - yet the link between the circadian-neuroimmune axis and SCI repair remains underexplored. Inflammatory gene expression in immune cells is regulated by a core circadian transcriptional repressor, REV-ERBα/β. To elucidate REV-ERBα/β's role in SCI, we tested the hypothesis that macrophage-specific REV-ERBα/β deletion would amplify inflammatory gene expression and worsen SCI severity and locomotor recovery. We used a tamoxifen-inducible macrophage-specific (*Ccr2-CreERT2*) REV-ERBα/β knock-out (KO) model to conditionally delete REV-ERBα/β prior to T9 contusion SCI. Bulk RNA-seq was performed on spinal cord tissue at 3 days post-injury to characterize transcriptomic changes associated with macrophage-specific REV-ERBα/β deletion. RNA-sequencing revealed coordinated transcriptomic changes: Gene Set Enrichment Analysis (GSEA) identified that macrophage-specific REV-ERBα/β SCI epicenters showed a significant positive enrichment of interferon alpha response, complement activation, and antigen presentation via MHC class II gene sets compared to control epicenter. This suggests a pro-inflammatory phenotypic shift following macrophage-specific REV-ERBα/β deletion. Additionally, microglial and macrophage gene signatures were enriched following REV-ERBα/β deletion in macrophages, demonstrating a strong association between these cell populations and the loss of REV-ERBα/β. Trem2 and Fcer1g, canonical disease-associated macrophage (DAM) markers, were markedly upregulated in macrophage-specific REV-ERBα/β KO spinal cords, driving enrichment of these pathways and cell types. Moreover, circadian rhythm gene sets were negatively regulated, highlighting on-target effects of REV-ERBα/β deletion. Overall,

macrophage-specific REV-ERBα/β deletion promotes a pro-inflammatory, DAM-associated immune profile after SCI, consistent with REV-ERB's repressive role in immune signaling. Ongoing gain- and loss-of-function studies will explore REV-ERB as a promising therapeutic target for SCI.

Disclosures: U.P. Kandjoze: None. **J.C. Aldrich:** None. **F.C. Bremner:** None. **S.M. Alman:** None. **A.R. Scheinfeld:** None. **L.K. Fonken:** None. **A.D. Gaudet:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.08/W25

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant 2RF1NS094527
NIH Grant R01NS110825

Title: Ablation of the Hv1 proton channel in microglia confers neuroprotection after spinal cord injury in male mice

Authors: *Z. WANG[1], Z. LEI[2], Y. LI[2], B. KRISHNAMACHARY[2], H. LEE[3], H. LI[2], L.-J. WU[4], J. WU[2];
[1]Ctr. for Shock, Trauma and Anesthesiol. Res., Univ. Maryland Sch. of Med., Baltimore, MD; [2]Dept. of Anesthesiol. & Ctr. for Shock, Trauma and Anesthesiol. Res. (STAR), [3]Dept. of Med., Univ. of Maryland Sch. of Med., Baltimore, MD; [4]Neurol., Univ. of Texas Hlth. Sci. Ctr. at Houston, Houston, TX

Abstract: The voltage-gated proton channel Hv1 is a unique target for controlling multiple NOX activities and reactive oxygen species (ROS) production. We previously reported that Hv1 deletion—highly expressed in immune cells, including microglia—confers neuroprotection in a mouse model of spinal cord injury (SCI). Here, we hypothesized that microglial Hv1 contributes to secondary injury following SCI by modulating neuroinflammation. Using the NanoString Glial Profiling Panel, we found that genetic Hv1 deletion selectively attenuated chronic inflammatory pathways in injured spinal cord tissue (SPC), particularly inflammasome-related signaling. To determine the specific contribution of microglial Hv1 after SCI, $Hv1^{flox/flox}$ mice were crossed with $CX3CR1^{CreER}$ mice to generate microglia-specific Hv1 knockout (MG Hv1KO) mice. Following 4 weeks of tamoxifen induction, moderate contusive SCI was performed in male MG Hv1KO mice and their wild-type (WT) littermates. Bulk RNA sequencing of injured SPC revealed that microglial Hv1 deletion reduced the expression of pro-inflammatory cytokines, chemokines, and microglial activation markers, while enhancing tissue repair-associated gene expression at both acute and chronic stages after SCI. These transcriptional changes were accompanied by improved functional outcomes. Behavioral assessments, including Basso Mouse Scale (BMS) scoring and horizontal ladder testing, showed

significantly enhanced locomotor recovery in MG Hv1KO mice compared with WT controls. Consistently, histological analysis demonstrated a 47.8% increase in white matter sparing and a 20% reduction in lesion volume at the injury epicenter. Furthermore, pharmacological inhibition of Hv1 with 2-guanidinobenzimidazole (2-GBI) suppressed inflammatory cytokine release in primary microglial cultures and improved functional recovery and tissue preservation at 6 weeks post-SCI. Collectively, these findings identify microglial Hv1 as a critical regulator of post-traumatic neuroinflammation and a promising therapeutic target for reducing secondary injury and improving recovery after SCI.

Disclosures: Z. Wang: None. **Z. Lei:** None. **Y. Li:** None. **B. Krishnamachary:** None. **H. Lee:** None. **H. Li:** None. **L. Wu:** None. **J. Wu:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.09/W26

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH/NINDS 1R21NS128749-01A1 (SP/HS)
P20 GM148326/GM/NIGMS NIH HHS

Title: Time-Resolved Serum Lipidomics and Metabolomics to Identify Circulating Signatures of Metabolic Dysfunction Following Spinal Cord Injury and Sepsis

Authors: *K. IYER[1], S. KAUR[1], D. PATEL[1], A. SHANDILYA[2], T. GARG[1], K. ZAMIAR[1], S. RIPPY[3], T. A. BUTTERFIELD[4], H. SAITO[5], S. P. PATEL[2];
[1]Physiol., Spinal Cord & Brain Injury Res. Ctr., Lexington, KY; [2]Spinal Cord & Brain Injury Res. Center, Dept. of Physiol., [3]Univ. of Kentucky, Lexington, KY; [4]Athletic Training & Clin. Nutr., [5]Univ. of Kentucky, LEXINGTON, KY

Abstract: Sepsis is a life-threatening condition driven by a dysregulated host response to infection and is associated with organ dysfunction and high mortality. When it occurs acutely after spinal cord injury (SCI), it worsens survival and long-term recovery; however, the temporal systemic mechanisms underlying SCI-associated sepsis remain poorly understood. This study used a clinically relevant rodent model of sepsis following SCI to define time-dependent blood-based signatures of systemic inflammation and metabolic dysfunction.Adult rats were assigned to Control, Sepsis, SCI, or SCI+Sepsis groups. Contusion SCI was induced at T10 using an Infinite Horizon impactor, followed by intraperitoneal cecal slurry injection to induce polymicrobial infection. Supportive care, including antibiotics and fluid resuscitation, was initiated 8hrs post-insult and continued twice daily for 5 days. Blood was collected at 6 hrs, 24 hrs, 72 hrs, and 7 days post-SCI for bacteremia, complete blood count, cytokine profiling, serum metabolomics, and lipidomics.Bacteremia was detected only in SCI+Sepsis animals at 6 hrs, prior to antibiotic treatment. Hematological and cytokine analyses revealed distinct temporal

immune response patterns in SCI+Sepsis animals compared with SCI alone. Serum metabolomics demonstrated dynamic alterations in amino acid, nucleotide, carbohydrate, glutathione, taurine and nitrogen-related metabolic pathways, suggesting disruption of redox balance, energy metabolism, and systemic stress responses. Lipidomic profiling further identified time-dependent remodeling of circulating lipid species, including increased ceramides and decreased lysophosphatidylcholines at 24 hrs, with additional lipid shifts at later time points.Collectively, these findings define temporal hematological, inflammatory, metabolomic, and lipidomic signatures of SCI-associated sepsis. The integrated serum profiles suggest that acute sepsis after SCI drives coordinated immune-metabolic reprogramming characterized by oxidative stress, altered amino acid and nucleotide metabolism, inflammatory lipid signaling, and membrane lipid remodeling. These blood-based signatures may support future studies focused on early detection, disease monitoring, and therapeutic intervention in SCI-associated sepsis.

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Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.10/W27

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Mary Tucker Currie Endowment to JWG

Title: Characterizing protein changes in the adverse effects of noxious stimulation following spinal cord injury

Authors: *K. N. COLPITTS[1], V. BALENTINE[1], C. T. PHINNEY[1], N. KOBAYASHI[1], K. SANCHEZ[2], E. GILES[2], J. W. GRAU[1];
[1]Texas A&M Univ., College Station, TX; [2]Univ. of Michigan, Ann Arbor, MI

Abstract: Prior work has shown that 6 minutes of noxious electrical stimulation (shock) a day after spinal cord injury (SCI) impairs locomotor function and increases hemorrhage. RNAseq has revealed candidate genes and proteins linked to noxious stimulation and its adverse effects such as increased inflammation and hemorrhage after SCI. Bradford assays on spinal cord samples collected three hours after noxious stimulation have routinely reflected increased protein content at the site of injury. This may result from *de novo* protein synthesis and/or infiltrating cells. To evaluate whether the former drives nociceptive-induced adverse effects following SCI, we examined the effect of inhibiting protein synthesis during noxious stimulation. Male and female rats were subjected to a T11 moderate contusion injury and epidural catheter placement. One day later, a protein synthesis inhibitor (cycloheximide; CXM) was administered 30 minutes prior to shock. Hindlimb locomotor function was assessed hourly for 3 hours, after which a 1-cm section

of the spinal cord encompassing the area of injury was collected for cellular assays. Effective protein inhibition was confirmed with western blotting for c-Fos. Shock treatment impaired locomotor function and this effect was attenuated by CXM. Both spectrophotometry and western blotting confirmed that noxious stimulation induced hemorrhage in vehicle treated animals. Spectrophotometry suggested an effect of CXM treatment on nociception-induced hemorrhage, while western blotting found minimal evidence for this. Additional targets are being assayed. Factors related to *de novo* protein synthesis contribute to the loss of behavioral function after noxious stimulation while hemorrhage remains largely unaffected. On-going work is examining the extent of hemorrhage and protein products underlying factors.

Disclosures: K.N. Colpitts: None. **V. Balentine:** None. **C.T. Phinney:** None. **N. Kobayashi:** None. **K. Sanchez:** None. **E. Giles:** None. **J.W. Grau:** None.

Poster

PSTR132: Spinal Cord Injury: Inflammation and Pain

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR132.11/W28

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Craig H. Neilsen Foundation (1000927) to JWG.

Title: The stress of the test: Incidental procedures can amplify loss of function after spinal cord injury (SCI)

Authors: *L. F. LOPEZ VILLAGRAN, V. BALENTINE, A. TREVINO, A. AWALT, C. T. PHINNEY, J. W. GRAU;
Texas A&M Univ., College Station, TX

Abstract: Studies have shown that noxious stimulation after spinal cord injury (SCI) can increase tissue loss, foster the development of neuropathic pain, and impair long-term behavioral recovery (Grau, 2017, J Neurotrauma, 34, 1873). In a typical experiment, nociceptive (pain) fibers are engaged a day after animals received a lower thoracic (T11) contusion injury using electrical stimulation applied to a dermatome caudal to injury or via an intradermal injection of capsaicin (3%) applied to one hind paw. Six minutes of intermittent stimulation, at an intensity that engages unmyelinated (C) pain (nociceptive) fibers, produces an acute loss in locomotor function and increased hemorrhage/cell death at the site of injury. Engaging nociceptive fibers with capsaicin, which activates nociceptive fibers that express the TRPV1 receptor, has the same effect. Both treatments induce acute and long-term adverse effects. While performing experiments to examine the cellular processes underlying these effects, we have observed that our test procedures sometimes have a comparable adverse effect. Three examples are reported here. Prior to drawing blood from contused rats, the animal's tail was warmed using 50 °C water for approximately 1 min. Thermal treatment induced an acute loss in locomotor function. A similar effect was observed when contused rats underwent tail-flick testing, which assesses a

spinally mediated reflex using a transient thermal stimulus applied to the tail. Lastly, a subset of contused animals placed in Plexiglas tubes to restrict movement during the blood pressure assessment exhibited “spastic” like behavior that was accompanied by a persistent drop in locomotor function. This spastic response was accompanied by a spike in blood pressure and has not been observed in the absence of restraint. Further work is being conducted to assess the effect of these treatments on hemorrhage and cell death at the site of injury. The findings imply that relatively subtle behavioral/test procedures following injury to the spinal cord can affect locomotor recovery. The findings are consistent with other work demonstrating that routine procedures after SCI (e.g., stretching; Caudle, 2015, Neurorehab Neural Repair, 29, 268) can have unintended consequences.

Disclosures: L.F. Lopez Villagran: None. **V. Balentine:** None. **A. Trevino:** None. **A. Awalt:** None. **C.T. Phinney:** None. **J.W. Grau:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.01/W29

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: FAPESP Ph.D Scholarship: 2024/09098-8
FAPESP SI Scholarship: 2025/16144-9
FAPESP Grants: 2023/02615-4
FAPESP Grants: 2023/16415-7
FAPESP Grant: 2022/06609-6

Title: Transient Glial Responses in the Primary Motor Cortex Triggered by Proximal Spinal Motoneuron Axotomy in Mice

Authors: *K. SILVA MULLER[1], M. JUNIOR[2], A. L. OLIVEIRA[2], L. P. CARTAROZZI[2]; [1]Structural and Functional Biol., Univ. of Campinas, Campinas, Brazil; [2]Structural and Functional Biol., Univ. of Campinas - Lab. of Nerve Regeneration, Campinas, Brazil

Abstract: Ventral root crush (VRC) induces the loss of up to 50% of axotomized spinal motoneurons within the first month after injury. Although lesion-induced reactive gliosis and synaptic remodeling in the spinal cord have been characterized, the cortical repercussions of VRC remain poorly understood. Here, we investigated the time course of motoneuron survival and glial responses in the spinal cord and primary motor cortex (M1) following unilateral L4-L6 VRC in female C57BL/6JUnib mice. Animals were analyzed at 1, 3, 5, 7, 14 and 28 days after injury (dpi) (n=5/group; CEUA-UNICAMP: 6521-1/2024). Motoneuron survival was assessed by Nissl staining and cell counting, while microglial and astroglial responses were assessed by immunoistochemistry using Iba-1, GFAP, and S100β. Glial reactivity was quantified by integrated density of pixels and expressed as ipsilateral/contralateral ratios. VRC induced

progressive spinal motoneuron degeneration, reaching 20% loss at 7 dpi and 51% at 28 dpi. In the spinal cord, microglial activation increased sharply at 3 dpi (3.7-fold) and 7 dpi (4.0-fold) before partially declining by 28 dpi (2.1-fold). From 5 dpi onward, microglial processes formed persistent perineuronal sheaths around axotomized motoneuron somas. Astrogliosis peaked at 7 dpi (3.9-fold) and remained increased up to 28 dpi (2.6-fold). In contrast, no neuronal loss was detected in M1 at any time point. Nevertheless, a cortical glial response was observed. Astrogliosis emerged at 1 dpi (1.3-fold), peaked at 5 dpi (1.5-fold), and remained elevated through 28 dpi. Microglial activation was detected at 3 dpi (1.6-fold), and peaked at 7 dpi (1.7-fold), returning to baseline by 14-28 dpi. These findings reveal distinct but temporally coordinated glial responses along the spinal-cortical axis after VRC. Whereas spinal motoneurons undergo progressive degeneration accompanied by sustained gliosis, the motor cortex displays a retrograde glial response, characterized by transient microglial activation and prolonged astrogliosis.

Disclosures: K. Silva Muller: None. **M. Junior:** None. **A.L. Oliveira:** None. **L.P. Cartarozzi:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.02/W30

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant R01NS126468
NSF Grant 100824

Title: Role of ATG5-Dependent Autophagy in Endothelial Responses to Myelin Debris Following Spinal Cord Injury

Authors: S. A. BELJIC[1], S. LOPEZ[2], G. DE JESUS[3], S. SALIB[3], G. HAMMEL[4], ***R. S. NOWAKOWSKI**[2];
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Abstract: Spinal cord injury (SCI) initiates a secondary injury cascade characterized by blood-spinal cord barrier disruption, vascular dysfunction, and chronic inflammation. Endothelial cells play an important role in maintaining vascular integrity after injury, however the lesion-associated factors that drive endothelial dysfunction remain unclear. One potential contributor is myelin debris, which accumulates when the myelin sheath is damaged or destroyed during SCI. Previous work from our laboratory has demonstrated that endothelial uptake of myelin debris activates TGF-β1 signaling and promotes endothelial-to-mesenchymal transition (EndoMT)-associated phenotypes, suggesting that myelin debris alters endothelial function after injury. ATG5 is a key regulator of autophagy, a cellular pathway involved in the degradation and

recycling of intracellular material. In vivo studies from our laboratory have shown that ATG5 knockout mice exhibit improved functional recovery and increased vascular remodeling following SCI. These findings raise the question of whether ATG5-dependent autophagy influences endothelial responses to myelin debris. To address this, primary endothelial cells from wild-type and an ATG5 knockout cell line were exposed to myelin debris; evaluated using transendothelial electrical resistance (TEER) measurements and analysis of endothelial junctional proteins show reduced endothelial dysfunction. Together these data show that loss of ATG5 reduces myelin debris induced endothelial dysfunction, resulting in improved endothelial migration and preservation of barrier integrity. Additional experiments using transwell permeability assays and scratch wound-healing assays are in progress. Understanding the role of ATG5-dependent autophagy in endothelial cells may identify mechanisms that contribute to secondary injury following SCI and reveal potential therapeutic targets to improve recovery.
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Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.03/X1

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NSFC Grant 82401616

Title: Recapitulating developmental tip-cell-guided sprouting promotes functional vascular regeneration after spinal cord injury

Authors: *S. YU[1], J. XU[2], Z. LI[3], Y. LI[4];
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Abstract: Functional vascular regeneration remains limited after spinal cord injury (SCI), but the basis of this failure remains unclear. We hypothesized that vascular repair after SCI fails because it does not reactivate developmental angiogenic programs. During embryonic spinal cord development, vascular networks are established through tip-cell-guided sprouting angiogenesis. In contrast, adult SCI lesions contained enlarged, disorganized, and poorly perfused vessels with minimal sprouting activity, indicating pathological vascular remodeling rather than regenerative angiogenesis. To determine whether developmental vascular programs can be re-engaged after injury, we transplanted embryonic spinal neural tissue into injured adult or postnatal day 10 (P10) mouse spinal cord. Vascular architecture, hemodynamics, ultrastructure, and spatial molecular organization were examined using whole-mount imaging,

functional ultrasound localization microscopy (fULM), two-photon imaging, transmission electron microscopy (TEM), lineage tracing, and spatial transcriptomics. Analyses were performed in n = 3-5 mice per group across independent cohorts, with blinded quantification. Embryonic grafts promoted host-vessel ingrowth, increased endothelial tip-cell formation, and restored endothelial-pericyte organization. In P10 hosts, vascular regeneration extended throughout the lesion and rebuilt integrated microvascular networks. In adult hosts, recovery remained spatially restricted, with improved vascular remodeling in graft centers but incomplete integration at graft-host boundaries. fULM and two-photon imaging demonstrated restoration of effective perfusion following grafting, whereas injury-only lesions exhibited flow stasis and impaired hemodynamics. TEM further revealed recovery of mature vascular ultrastructure. Lineage tracing showed that regenerated vessels were derived predominantly from host cells, indicating that embryonic grafts act primarily as organizers of vascular repair rather than direct vascular donors. Spatial transcriptomic analysis identified a pro-angiogenic microglial population enriched at graft-host interfaces. Microglial depletion impaired boundary vascular remodeling, whereas microglial supplementation improved vascular integration, indicating that host microglia actively support regenerative vascular repair. Together, these findings demonstrate that functional vascular regeneration after SCI requires re-engagement of developmental tip-cell-guided angiogenesis and identify host microglia as key regulators of graft-host vascular integration.

Disclosures: S. Yu: None. **J. Xu:** None. **Z. Li:** None. **Y. Li:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.04/X2

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: RS-2025-25459402
RS-2025-16070516
BK21 R&E Initiative for Advanced Precision Medicine

Title: Engineering an injectable hydrogel to modulate the ECM microenvironment to facilitate wound healing and functional recovery following spinal cord injury

Authors: *B. JANG[1,2,3], H. PARK[5], H. SEO[7,3,2], H. KIM[6,3], Y.-M. KIM[8], B. G. KIM[9,2,3,4]; [2]Neurosci. Grad. Program, Dept. of Biomed. Sci., [3]BK21 R&E Initiative for Advanced Precision Med., [4]Dept. of Neurol., [1]Ajou university, Suwon, Korea, Republic of; [5]Dep. of Brain Sci., [6]Biomed. Sci., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of; [7]neuroscience, ajou university, suwon, Korea, Republic of; [8]Ctr. for Biomaterials, Korea Inst. of Sci. and Technol., seoul, Korea, Republic of; [9]Dept. of Brain Sci., Ajou sch of medicine, Suwon, Korea, Republic of

Abstract: Traumatic spinal cord injury (SCI) does not heal spontaneously, often resulting in permanent tissue defects with the formation of cystic cavities. These tissue defects present a formidable barrier to regenerative therapies by preventing the growth of regenerating axons and the integration of transplanted stem/progenitor cells. We previously showed that injection of imidazole-poly(organophosphazene) hydrogel (I-5) bridges cystic spaces by assembling a fibronectin-rich extracellular matrix (ECM) mediated by an imidazole moiety that interacts with macrophages. However, hydrogel-created ECM contains numerous inflammatory cells surrounded by scar-forming astrocytes, which may contribute to the degeneration of growing neuronal processes and the failure of axonal regeneration through the ECM. The present study aimed to develop a strategy to engineer the hydrogel to regulate the hostile and pro-inflammatory microenvironment within the hydrogel-created ECM. To this end, we conjugated Mannose, a ligand for CD206 (also known as the mannose receptor), a marker of M2 macrophages that promote wound healing, to the organophosphazene backbone via polyethyleneimine as a linker. In a rat spinal cord contusion model, this PEI-Mannose hydrogel injection effectively suppressed cystic cavity formation. FACS-isolated macrophages showed significant upregulation of CD206 gene expression. Immunohistochemical analysis also revealed a higher proportion of macrophages expressing CD206 and Arginase 1, another canonical marker of M2 macrophages. Furthermore, angiogenesis within the remodeled ECM was markedly enhanced, as shown by increased RECA-1-positive blood vessel density in the caudal spinal cord. Over an 8-week period, the PEI-Mannose hydrogel-injected group exhibited a significantly lower error rate in the ladder rung walking test than animals injected with hydrogel conjugated PEI alone without Mannose or injury-only controls, demonstrating substantial locomotor recovery with the PEI-Mannose hydrogel. Taken together, the PEI-Mannose hydrogel leverages its thermo-responsiveness and microenvironmental regulatory capabilities to attenuate inflammation, promote wound healing, and functional recovery following SCI. These findings establish this hydrogel as a powerful injectable biomaterial platform for optimized healing of injured CNS tissue and functional repair following CNS injury.

Disclosures: B. Jang: None. **H. Park:** None. **H. Seo:** None. **H. Kim:** None. **Y. Kim:** None. **B.G. Kim:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.05/X3

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NSF Center for Engineering Mechanobiology (CEMB)- #1548571

Title: A biodegradable piezoelectric scaffold promotes axon growth in a neuron-astrocyte co-culture model of reactive astrogliosis

Authors: *S. S. J. CHOWDHURY[1], M. OUDEGA[2,3,4], T. ARINZEH[1];
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Abstract: Functional recovery following spinal cord injury (SCI) remains unachievable due to limited endogenous axon regeneration and the restrictive physical and chemical barriers of the glial scar. While piezoelectric biomaterials may hold promise by providing self-powered electrical stimulation to facilitate spinal cord repair, conventional synthetic piezoelectric materials lack biodegradability, optimal mechanical properties, and may have biocompatibility issues. We addressed this gap by developing a biodegradable, fibrous gelatin scaffold that promotes axon growth and evaluated it in an *in vitro* model of reactive astrogliosis. Aligned gelatin fibers were prepared by electrospinning using a rotating collector and crosslinked to increase hydrolytic stability. Fibers were highly aligned (89.4±7.8% alignment) with an average fiber diameter of 647±88 nm. The scaffolds were further processed by electric poling to render them piezoelectric and designated as poled positive (P+) or poled negative (P-), depending upon the direction of the electric field applied. The piezoelectric coefficient (d_{33}) of P+ and P- demonstrated opposite polarities and were significantly higher in magnitude than the non-piezoelectric gelatin (non-piezo) (n=5 per group). Under physiologically relevant cyclic tensile loading, P+ and P- scaffolds generated 26.92±7.1 $mV_{(p-p)}$ and 30.59±4.5 $mV_{(p-p)}$ electrical outputs, respectively, whereas the waveform from non-piezo was undetectable. To assess scaffold mediated axon growth in conditions that more closely represent SCI, an in-vitro reactive astrogliosis model was established with co-cultured reactive astrocytes (221.5 K cells/cm^2) and axotomized dorsal root ganglion (DRG) from embryonic day 17 rat embryos. Embryos from at least two pregnant Sprague-Dawley rats were used, and 20 axons per DRG (n=7 DRGs per group) were analyzed. Reactive astrocytes grown on tissue culture plastic (TCP) demonstrated chondroitin sulfate proteoglycan (CSPG) staining, hypertrophy, significant cell proliferation, upregulation of neurotoxic and axon growth cone inhibitory genes (C3 and Slit2, respectively), and downregulation of homeostatic marker (Slc1a3) compared to serum-free resting astrocytes. While all scaffolds supported axon growth in co-culture with reactive astrocytes, axons appeared dystrophic and fragmented on TCP controls. Axon length on the P- scaffolds was 1.7-fold higher than non-piezo controls ($p<0.05$). These findings demonstrate that piezoelectric fibrous gelatin scaffolds promote axon growth in an inhibitory reactive astrogliosis environment, offering a promising scaffold for use in spinal cord repair.

Disclosures: S.S.J. Chowdhury: None. **M. Oudega:** None. **T. Arinzeh:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.06/X4

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: the Ministry of Trade, Industry, and Energy (MOTIE), Korea, under the "Global Industrial Technology Cooperation Center(GITCC) program" supervised by the Korea Institute for Advancement of Technology (KIAT).(Task No. P0028319) RS-2024-00419269

Title: Multi-channel scaffold promotes TUJ1-positive axonal ingrowth and locomotor recovery in complete transection spinal cord injury models

Authors: *A. SONG[1], B. CHOI[2], S. CHOI[2], J. HYUN[3];
[1]Ajou Univ., Suwon-si, Korea, Republic of; [2]Wiregene, Chunju, Korea, Republic of; [3]Physical Med. & Rehabil., Ajou Univ. Sch. of Med., Suwon, Korea, Republic of

Abstract: Spinal cord injury (SCI) is characterized by neural circuit disruption, tissue loss, inflammation, and glial/fibrotic scar formation, resulting in limited spontaneous recovery. Complete transection SCI produces a defined tissue gap and complete axonal tract disruption, making it suitable for evaluating scaffold-based strategies for structural bridging and axonal guidance. In this study, we investigated whether a multi-channel scaffold could promote TUJ1-positive axonal ingrowth and locomotor recovery in a rat complete transection SCI model, with supporting validation in a minipig SCI model. In rats, a 3-mm gap complete transection injury was induced at the T9 level of the thoracic spinal cord, followed by implantation of a 2-mm-diameter and 5-mm-long multi-channel scaffold into the lesion gap. The scaffold was designed to bridge the transected spinal cord and provide internal channels for directional axonal extension. Locomotor recovery was evaluated using the Basso, Beattie, and Bresnahan (BBB) locomotor rating scale. Immunohistochemistry was performed on sagittal cryosections to assess TUJ1-positive axonal fibers within and around the scaffold. For supporting large-animal validation, an 8-mm-diameter and 5-mm-long multi-channel scaffold was implanted in a minipig SCI model. In the rat complete transection model, the implanted scaffold was maintained within the 3-mm lesion gap and provided a structural bridge across the injured spinal cord. TUJ1-positive axonal fibers were observed extending from the surrounding host spinal cord into the internal scaffold channels, suggesting scaffold-guided axonal ingrowth across the lesion site. BBB assessment also showed improved locomotor recovery in the scaffold-implanted group compared with the control group, indicating that scaffold-mediated axonal ingrowth may contribute to functional recovery after complete transection SCI. In the minipig model, scaffold implantation was technically feasible and showed supportive functional improvement. These findings demonstrate that implantation of a 2-mm-diameter and 5-mm-long multi-channel scaffold in a rat T9 complete transection SCI model promotes TUJ1-positive axonal ingrowth into scaffold channels and improves BBB locomotor recovery. The supporting minipig results further suggest the translational feasibility of this scaffold-based approach. Overall, the multi-channel scaffold may serve as a structural bridge and axonal guidance platform for promoting axonal ingrowth and functional recovery after complete transection SCI.

Disclosures: A. Song: None. **B. Choi:** None. **S. Choi:** None. **J. Hyun:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.07/X5

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Daniel and Ada Rice Foundation

Title: Immune Response in SCI Rats treated with FPLG Scaffold

Authors: *D. A. GARCIA PRADA[1], S. PRIETO[2], E. FORSELL[2], R. G. FESSLER[2], B. T. DAVID[3];
[1]Rush Univ., Chicago, IL; [3]Neurolog. Surgery, [2]Rush Univ. Med. Ctr., Chicago, IL

Abstract: Spinal cord injury (SCI) is characterized by a primary mechanical injury followed by a secondary injury cascade involving inflammation, oxidative stress, and apoptosis. Secondary damage is largely driven by overactivation of the immune system. Research into the immune profile following SCI has revealed a complex and dynamic interplay between innate and adaptive immune responses that contribute to both neurodegeneration and repair. After injury, there is an acute infiltration of neutrophils and macrophages, leading to the release of pro-inflammatory cytokines exacerbating tissue damage. In rodent models, macrophage activity peaks approximately at 7 and 60 days post-injury (dpi), influencing inflammation and repair. Scaffolds made from poly(lactic-co-glycolic) acid (PLG), a bioresorbable polymer, have emerged as a promising strategy for promoting regeneration and modulating inflammation. This study explores the effects of a highly porous form of PLG, Fluffy PLG (FPLG), at various timepoints after injury to assess its effects.Female wild-type Sprague Dawley rats underwent a bilateral moderate contusion at the ninth thoracic vertebral level (T9) or a laminectomy at the same level. At 1 dpi, a subset of rats underwent a myelotomy at the site of injury, after which a subset of those rats received an implantation of FPLG scaffold. Following repeated behavioral tests, rats were sacrificed at 2, 5, 7, or 56 dpi for either flow cytometric analysis or immunohistochemistry. The results suggest that the FPLG scaffold appeared to not only help preserve spinal cord structural integrity, but also induce a sub-acute anti-inflammatory shift at 7 dpi, highlighting FPLG's potential to modulate inflammation and support tissue preservation in SCI.

Disclosures: D.A. Garcia Prada: None. **S. Prieto:** None. **E. Forsell:** None. **R.G. Fessler:** None. **B.T. David:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.08/X6

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: SECIHTI-Mexico, Fronteras #2019-727996

Title: Carbon nanotubes scaffolds as nanobiocables for the interconnection of neurons

Authors: *J. MENDEZ[1], Y. BASTIAN[2];
[1]Univ. Autonoma De San Luis Potosi, San Luis Potosi, Mexico; [2]Univ. Autonoma De San Luis Potosí, San Luis Potosí, Mexico

Abstract: Every year, millions of people worldwide are affected by traumatic axonal injuries, either centrally in the brain or the spinal cord, as well as in the peripheral nervous system. This might lead to mild clinical symptoms up to functional impairment and disabilities, or even death. When a central neuronal axon is transected in the adulthood, there is a null probability of recovery in the spinal cord. However, in the peripheral nervous system, some level of structural recovery could be present, though the probability of full functional recovery is also small. Taking into consideration that carbon nanotubes (CNTs) are highly conductive materials and have a greater surface area, allowing a stronger charge injection capacity with a lesser interfacial impedance, we explored the possibility of using CNTs as nanobiocables to allow the interconnection of electrically excitable cells like cardiomyocytes and neurons. Here we show that pristine-, nitrogen-doped-, or carboxylated-CNTs, either oxidized or not, can be fluorescently labeled using Alexa fluorophores, and furthermore, can be myelinated using spinal cord purified myelin. Exposing these CNTs to mesencephalic dopamine cultures, they showed different levels of biocompatibility, being the oxidized nitrogen-doped CNTs the most biocompatible CNT. These CNTs were used to build scaffolds on poli-L-lysine-coated PDMS surfaces, and mesencephalic cultured neurons were placed on both sides of the scaffolds with the help of patch clamp pipettes. Upon placement of the second cell on the scaffold, both neurons became electrically synchronized as the action potential fired by one of the neurons was mirrored by the other. By placing CNTs as conductive units between pairs of neurons, our work shows that CNTs have the intrinsic ability to work as nanobiocables and transmit electrical signals from one cell to the other.

Disclosures: J. Mendez: None. **Y. Bastian:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.09/X7

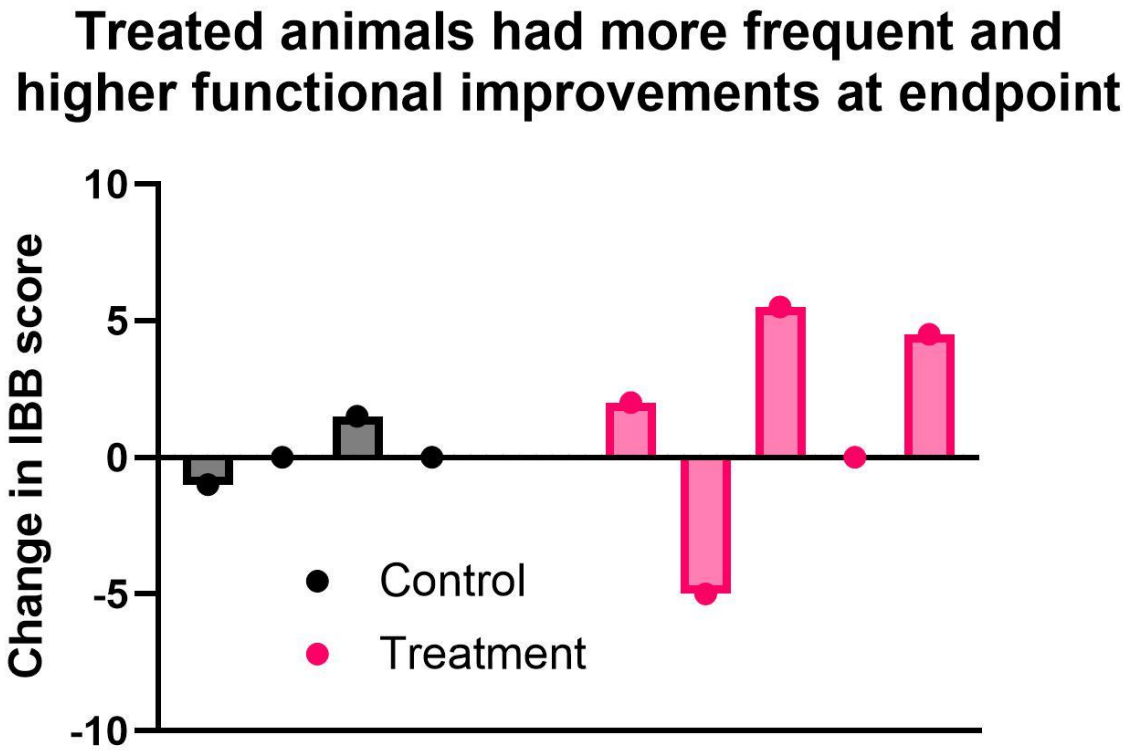
Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: NIH Grant R01NS117103-01
NIH Grant R01AI148076
NIH Training Grant T32TR004371

Title: Biomaterial Implants Improve Functional Recovery After Spinal Cord Injury

Authors: *S. SCHWARTZ[1], B. M. SMILEY[1], B. ROSS[2], B. J. CUMMINGS[3], A. J. ANDERSON[4], L. SHEA[2];
[1]Biomed. Engin., [2]Univ. of Michigan, Ann Arbor, MI; [3]Physical Med. & Rehab, [4]PM&R, Univ. of California, Irvine, Irvine, CA

Abstract: Spinal cord injury (SCI) results in persistent functional deficits affecting millions worldwide. Current treatments manage the symptoms of SCI, but no treatments promote regeneration in the chronic phase of injury. Due to the complexity of the injury, a multifaceted approach may be necessary to promote regeneration and functional recovery. We have developed polyethylene glycol microporous annealed particle tubes (PEG tubes) that are implanted directly into an injury cavity to promote axon growth across the injury and enhance functional recovery. Additionally, Epothilone D (Epo) supports axon growth in SCI. We tested chronic PEG tube implantation combined with Epo to promote functional recovery after SCI. Twelve Long Evans rats were subjected to a 75-kdyne left unilateral contusion injury with 5 s dwell at the C5 level. In a random subset of animals, 4 weeks after injury, the lesion site was re-opened and three PEG tubes (2 mm, 400 μm outer diameter) were placed into the chronic cavity space. Animals that received PEG tubes also received Epo by intraperitoneal injection every 7 days for 4 total administrations (treatment group). Control animals received no PEG tubes or Epo. The Irvine, Beatties, and Bresnahan test for forelimb function was administered 7 days prior to implant, and 7, 35, and 70 days post implant, blind to treatment. One rat did not complete the full study and 2 were classified as outliers due to a lack of functional deficit following injury or improper tube placement identified by histology, leaving n = 4-5 / condition. Holm-Šídák corrected multiple comparison testing at each timepoint did not identify significant improvement above $p = 0.05$, however, there was a trend towards significance at the endpoint of the study ($p = 0.159$). Interestingly, 60% of treated animals and only 25% of controls demonstrated functional improvement from baseline, with a range of improvements in the treated animals and minor improvement in the control group. Future studies will investigate axon growth and myelination, and include additional control groups such as PEG tube only and Epo only treatments.



Disclosures: S. Schwartz: None. **B.M. Smiley:** None. **B. Ross:** None. **B.J. Cummings:** None. **A.J. Anderson:** None. **L. Shea:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.10/X8

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Title: Microglia instruct neuronal fate for functional circuit integration after spinal cord injury

Authors: *Z. LI[1], S. YU[2], J. XU[3], Y. LI[4];
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Abstract: Neural stem cells (NSCs) transplantation is thought to provide new neurons for neural circuit repair after complete spinal cord injury (SCI), yet locomotor recovery has been limited. How host and graft properties contribute to the integration of functional relays that restore locomotion remains unclear. Here, we show that identical NSCs transplanted into postnatal day

10 (P10), but not adult, complete SCI mice hosts restore voluntary locomotion. In this permissive P10 host, graft-derived Zfhx3$^+$ long-range projection neurons are enriched and directly relay supraspinal inputs to lumbar motor circuits. Single-cell transcriptomic and functional analyses revealed embryonic-like microglia in P10 SCI hosts that instruct graft neuronal differentiation toward Zfhx3$^+$ neurons. Microglial depletion impaired Zfhx3$^+$ neuronal generation in P10 host grafts. Conversely, embryonic microglia co-transplantation into adult SCI hosts recapitulated this permissive niche, promoting Zfhx3$^+$ neuronal differentiation and restoring voluntary locomotion. Mechanistically, multi-omics analyses revealed that embryonic-like microglia relieved a DNMT3A-dependent epigenomic barrier to Zfhx3$^+$ neuronal fate. Pharmacological DNMT3A inhibition with the FDA-approved agent decitabine promoted Zfhx3$^+$ neuronal differentiation and functional recovery after NSCs transplantation in adult SCI. Together, these findings identify embryonic-like microglia as host niche instructors of graft neuronal fate and reveal a pharmacologically tractable strategy for NSC-mediated circuit repair.

Disclosures: Z. Li: None. **S. Yu:** None. **J. Xu:** None. **Y. Li:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.11/X9

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: VA CDA-1 IK1RD000676-01A2

Title: Improving Connectivity Between Host and Neural Stem Cell Grafts After Spinal Cord Injury

Authors: *R. LEVY-MYERS[1], M. H. TUSZYNSKI[2];
[1]UCSD, La Jolla, CA; [2]Neurosci., UCSD Dept. of Neurosciences, La Jolla, CA

Abstract: Recovery following spinal cord injury (SCI) is limited by the poor regenerative ability of axons in the CNS. The Tuszynski lab has developed a system where neural progenitor cells (NPCs) are grafted into sites of SCI. This significantly improves motor outcomes in mice, rats, and non-human primates by forming neural relays across the lesion. Graft-derived neurons extend axons into distant host tissue and receive synapse from regenerating corticospinal tract (CST) axons. These regenerating CST neurons form synapses specifically with graft-derived motor-related interneurons while avoiding sensory-related interneurons. To identify molecular determinants of this target selection, we developed a transsynaptic viral labeling and sequencing approach that isolates graft-derived neurons receiving CST input. This strategy reveals gene expression programs associated with CST-connected graft neurons. We also map downstream connectivity between graft-derived neurons and host interneurons caudal to the lesion. Together, these data define the molecular and circuit-level rules by which adult regenerating CST neurons

choose appropriate synaptic partners within developing stem cell derived grafts, providing insight into mechanisms that support functional recovery after SCI.

Disclosures: R. Levy-Myers: None. **M.H. Tuszynski:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.12/X10

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Japan Agency for Medical Research and Development (AMED), Grant Number 24bm1223008h0002

Title: Epidural electrical stimulation-based rehabilitation promotes clinical relevant human iPSC neural graft integration, caudal axonal extension and off-stimulation motor recovery in chronic severe spinal cord injury

Authors: *Y. ICHIHARA[1], N. NAGOSHI[1], M. SHINOZAKI[2], J. KOHYAMA[3,1], H. OKANO[2], M. NAKAMURA[1];
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Abstract: Introduction: Chronic severe spinal cord injury (SCI) remains a major therapeutic challenge, with few effective options available to promote meaningful neurological recovery. Human iPSC-derived neural stem/progenitor cell (hiPSC-NS/PC) transplantation can provide a neuronal substrate for repair, but transplantation alone is often insufficient in chronic severe SCI, where the host spinal cord may not support long-distance axonal growth and circuit integration. We tested whether epidural electrical stimulation-based rehabilitation (EES-rehab), which activates lumbar circuits, enhances clinical-grade hiPSC-NS/PC transplantation.
Materials/Methods: Clinical-grade hiPSC-NS/PCs were transplanted into immunodeficient rats 6 weeks after complete thoracic forceps-compression SCI (BBB score ≤4). EES-rehab alone showed no significant locomotor benefit in a preliminary sham-controlled experiment. Rats were assigned to PBS, transplantation only, or combination groups; EES-rehab began 1 week after transplantation and continued for 7 weeks. Behavioral recovery was assessed off stimulation by BBB score and gait kinematics, and MEPs were recorded. Circuit reconstruction was examined by immunohistochemistry, CLEM, G-deleted rabies tracing, graft-cell single-nucleus RNA-seq and host bulk RNA-seq. **Results:** Combination therapy significantly improved EES-off BBB locomotor scores compared with PBS and transplantation only at days 91 and 98 after injury; at day 98, scores were 4.91 in Combination, 2.08 in transplantation only and 1.82 in PBS controls. Gait kinematics improved and showed distinct locomotor patterns. MEPs were detected only in the combination group, suggesting descending reconnection. Rabies tracing suggested host-to-

graft connectivity involving brainstem reticulospinal neurons. In the lumbar enlargement, STEM121-positive graft-derived fibers were 2.02-fold greater in the combination group than in the transplantation only group ($p<0.05$). CLEM confirmed ultrastructural synaptic contacts between graft-derived axons and V2a interneurons. Single-nucleus RNA-seq showed profiles related to neurite extension and synaptic integration, while host bulk RNA-seq showed reduced ECM programs and increased axon guidance/synapse formation-related programs. **Conclusion:** EES-rehab enhanced hiPSC-NS/PC transplantation in chronic severe SCI by promoting graft-derived axonal extension, lumbar circuit integration and off-stimulation motor recovery, supporting a translational strategy to improve stem cell-based repair.

Disclosures: Y. Ichihara: None. **N. Nagoshi:** None. **M. Shinozaki:** None. **J. Kohyama:** None. **H. Okano:** None. **M. Nakamura:** None.

Poster

PSTR133: Study of the SCI Lesion Environment , Stem Cell, and Scaffold Interventions

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR133.13/X11

Topic: D.05. Spinal Cord and Peripheral Nerve Injury and Plasticity

Support: Daniel and Ada Rice Foundation

Title: Engineered Mesenchymal Stem Cell Transplantation for Reduction of Acute Inflammation after Spinal Cord Injury

Authors: *S. PRIETO[1,2], D. A. GARCIA PRADA[3], B. T. DAVID[2], R. G. FESSLER[2];
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Abstract: Approximately 17,000 people experience a spinal cord injury (SCI) in the US each year. After a traumatic SCI, there is initially a loss of nervous tissue followed by secondary damage, driven by chronic inflammation, which is not reversible. Mesenchymal stem cells (MSC) are multipotent stem cells that have been shown to improve multiple SCI outcomes following transplantation, notably via their anti-inflammatory effects and immunomodulation. However, unlike other tissues, MSCs do not home to sites of spinal cord injury. This is due to mammalian MSCs lacking E-selectin binding activity, because their sialylated (sLeX) motif in CD44 lacks fucose, which is crucial for cell trafficking and homing. Further, other studies have shown that MSC transplantations can help reduce spinal cord inflammation and promote an anti-inflammatory (M2) macrophage polarization. Nevertheless, current methods used to perform these transplants are invasive and involve significant risk for patients. To make MSCs capable of both adhering to the endothelial barrier and being trafficked to injury sites, it was necessary to generate Hematopoietic cell E-/L-Selectin ligand (HCELL) CD44 glycoform in cells by exofucosylation (a technique pioneered in stem cells by our collaborator). We administered HCELL-MSCs directly within the vasculature to deliver MSCs to the SCI epicenter (via tail

vein) to 60 female Sprague-Dawley rats after they received a moderate SCI (T9). We compared the effect of HCELL-MSCs to unmodified MSC transplantations by measuring rats' thermosensitivity, immunohistochemistry, and flow cytometric analysis, comparing T cells, microglia, and macrophage population profiles. Past experiments have shown that MSCs reduce the expression of immune cells and promote M2 polarization. After HCELL-MSC transplantation, immune cells within the spinal cord exhibited similar levels to rats that received transplantations of normal [nonfucosylated] MSCs within the cord, but with a significant shift in anti-inflammatory (M2) macrophage polarization in the rats that were transplanted with HCELL-MSCs. Additionally, HCELL-MSCs offer a minimally invasive method of administration, enhancing their translatability. HCELL-MSCs showed promising results to modulate the immune response after SCI and enhanced the polarization of anti-inflammatory macrophages, which are known to promote tissue repair in damaged areas. Additionally, these cells offer a minimally invasive method of administration.
This work is funded by the Daniel and Ada Rice Foundation.

Disclosures: S. Prieto: None. **D.A. Garcia Prada:** None. **B.T. David:** None. **R.G. Fessler:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.01/X12

Topic: E.02. Somatosensation – Touch

Support: Test Product

Title: Autonomic Regulation of Piezoelectric Ion Channels via Haptic Technology: An Emerging Nonmedication Approach to Symptom Relief

Authors: *P. HURWITZ;
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Abstract: Overview Piezo ion channels enable interpretation of sensory information conveyed through the Somatic Nervous System (SNS) of the Peripheral Nervous System (PNS) to be communicated between neurons in the brain, and also bidirectionally between the brain and the PNS. Piezo channels allow electrical current to pass through them. In this way, ion channels enable neurons to communicate with each other, so that the brain's neural networks can properly function. Haptic Vibrotactile Trigger Technology (VTT) prompts a sensory response by using electrical current-producing vibrations to stimulate the skin's mechano-receptors and is communicated via the PNS to the brain. Outcomes from several IRB-approved randomized clinical trials evaluated the efficacy of a non-drug, topical patch with VTT in patients with sleep disorders, pain, stress/anxiety, and balance issues, in addition to evaluating fatigue, improved performance and endurance in elite athletes. **Methods** Subjects were provided a topical patch

with VTT, or a placebo patch without VTT. Over 14 days, responses to validated scales were collected and functional measurements were taken to evaluate the efficacy of the VTT patch and any change in athletic performance. Subjects were provided a topical patch with VTT or a placebo patch without VTT (REM Patch, n=33, FREEDOM Patch , n=64) LIBERTY Patch (n=68), VICTORY Patch (n=70); (Super Patch Company, Toronto, Canada). Over 14 days, responses to validated scales (e.g., Pittsburgh Sleep Quality Index (PSQI), Insomnia Severity Index (ISI), Falls Efficacy Scale (FES), Brief Pain Inventory (BPI)) were collected and functional measurements were taken to evaluate the efficacy of the VTT patch and any change in sleep, insomnia, fatigue, and athletic performance as compared to a placebo patch. **Results** Outcomes demonstrated the statistically significant reduction ($p< 0.001$) of insomnia, fatigue, and nighttime awakenings, including improvement in sleep, decreases in anxiety, stress, depression, pain severity and interference, improvement of balance and stability, and improved athletic strength and performance. **Conclusion** The bi-directional sensory communication promoted by VTT may be able to boost the functioning of the piezoelectric channels. Evolving VTT treatments may be beneficial in people with diminished functioning of their piezoelectric channels and lead to breakthrough, minimally invasive, and drug-free approaches for treating various disorders as well as improving athletic performance, endurance, and prevention of injuries.

Disclosures: P. Hurwitz: C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); SuperPatch Company.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.02/X13

Topic: E.02. Somatosensation – Touch

Title: Psychophysically-Defined Haptic Laterality Potentially Disambiguates Dermatome Maps of the Toes

Authors: *D. S. V. CHOPP, M. F. WESNER;
Psychology, Lakehead Univ., Thunder Bay, ON, Canada

Abstract: Previous haptic, multisensory studies revealed a tactile sensitivity difference between the second (Toe 2) and fourth toe (Toe 4) from the big toe (Wesner et al. 2017; 2018). We hypothesized dermatomal map overlap as a possible cause. Few studies show overlapping dermatome boundaries on drawn maps. However, more recent evidence-based mappings point to a large overlap on Toe 2, determined by S1/L5 pathways versus Toe 4 which is determined primarily by S1 pathways (Lee et al., 2008). Our lab investigated the sensitivity effects of overlapping tactile dermatome boundaries using a percent-correct haptic discrimination task. Thirty-nine participants aged 18-35 were screened for conditions affecting sensation. Participants wore headphones and sat at a computer monitor displaying an orange crosshair against a black

background, with their left foot resting out of view. Using a 2-Alternative Forced Choice design we tactilely presented five Von Frey Monofilaments of varying target bending weights ranging from .04 to 300 gm (log iterations). Participants used contralaterally-mapped right-hand finger responses to indicate which of their two toes (Toe 2 or Toe 4) was stimulated. Medial (towards the big toe) and lateral (away from the big toe) sites 1-2cm apart were marked on the dorsal surface of each toe (4 sites total) mid-length down the middle phalanx. A 500ms, 500hz tone preceded stimulation; a 2-beep error tone indicated an incorrect response. Weibull fits were used to plot participant percent correct responses as a function of filament weight. Lateral Toe 2 presentations showed decreased sensitivity compared to the medial side with a greater sensitivity shift for filament weights above threshold (75% correct). No significant difference in performance was seen between lateral/medial Toe 4, or between lateral/medial Toe 4 and medial Toe 2 supporting a strong territory dominance by a single dorsal root ganglion (S1). The sensitivity shift across Toe 2, however, supports the idea that areas of high overlap (i.e., S1/L5) produce greater uncertainty (lower efficiency slopes of the psychometric function) along with a loss in tactile sensitivity. Additionally, we argue for haptic discrimination interference due to lateral inhibition in areas represented by overlapping dermatome pathways. Researchers using haptic paradigms must be aware of potential confounds caused by overlapping territories. Psychophysical methodology may be an effective way to illuminate the relative representation of adjacent dermatomes, specifically in the distal extremities. Further research plans to explore the role of lateral inhibition in tactile dermatomal processing is discussed.

Disclosures: D.S.V. Chopp: None. **M.F. Wesner:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.03/X14

Topic: E.02. Somatosensation – Touch

Support: ANR REMASS

Title: Investigation into slowly-adapting type I and II mechanoreceptor firing and adaptation to sustained pressure using microneurography in humans

Authors: L. THRACE, J.-M. AIMONETTI, *R. ACKERLEY;
CRPN, CNRS - Aix-Marseille Univ., Marseille, France

Abstract: Slowly-adapting low-threshold Aβ mechanoreceptors are found all over the skin of the body, where the type I (SA-I) and type II (SA-II) afferents encode a vast range of touch events, especially those relating to sustained pressure. We investigated the responses of single slowly-adapting afferents in human skin, where microneurography recordings were mainly from the hairy skin of the lower leg. The study was approved by an ethical committee and conformed to the Declaration of Helsinki. All participants gave written, informed consent. We tested single SA

unit responses to the indentation of a range of calibrated monofilaments (0.14 - 180 g) to obtain force-response curves, as well as to sustained indentation to high pressure (300 g) to explore their adaptation properties for up to 5 minutes of stimulation. We recorded from a total of 19 slowly-adapting units, where n = 15 SA-I and n = 4 SA-II and both types could be distinguished by differences in their coefficient of variation during sustained indentation. Two units were spontaneously active, and these were both SA-IIs. About half the units showed an 'off' response to the removal of the monofilament. The force-response curves showed stronger responses with increasing force for all units, although this plateaued earlier for some. For the sustained indentation, the type of slowly-adapting unit (SA-I or SA-II) did not affect whether it adapted during prolonged pressure. For the SA1s units, 9 adapted and 5 did not adapt, whereas for the SA2s, 1 adapted and 3 did not adapt. Overall, there was variability between the times to adaptation, but there was no difference between SA-I and SA-II units. The minimum time to adaptation was 6 s and the maximum was 5 minutes (where the unit did never fully adapted to the indentation). There was a significant decrease in the firing of the units that adapted by 40 s of stimulation (multiple comparison corrected $t = -3.2$, $p = 0.008$), whereas no significant decreases were found for the non-adapting units, which continued to fire at a slowly-decreasing rate (average 1% change every 10 s) over many minutes. These results show that SA-I and SA-II mechanoreceptors share similar properties, in that their time-to-adaptation does not distinguish between the two types, yet there was a lot of variability overall in the whole group. We are continuing to explore other skin sites, as well as investigating more thoroughly variability and time-frequency aspects of the responses.

Disclosures: L. Thrace: None. **J. Aimonetti:** None. **R. Ackerley:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.04/X15

Topic: E.02. Somatosensation – Touch

Support: European Union - NextGenerationEU PNRR – BRIEF "Biorobotics Research and Innovation Engineering Facilities" PNRR M4C2, Cod. IR0000036, CUP J13C22000400007
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ADJOINT2 project N. PR23-PAS-P4 funded by INAIL (Istituto Nazionale per l'Assicurazione contro gli Infortuni sul Lavoro)

Title: Large-scale characterization of identified human tactile afferents using targeted microneurography and intra-neural microstimulation

Authors: *M. STATACHE[1], S. BALLANTI[1], N. FRAGAPANE[1], G. D'ALESIO[2], M. BELLINI[3], S. DALISE[3], C. CHISARI[3], S. TADDEI[3], M. FILOSA[1], C. ODDO[1];
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Abstract: Microneurography (MNG) and intra-neural microstimulation (INMS) provide a unique opportunity to directly access and functionally interrogate single tactile afferents in awake humans. These techniques enable the characterization of individual mechanoreceptive fibers and the investigation of their contribution to tactile perception. However, large datasets of identified human tactile afferents remain scarce because of the technical complexity and limited success rates associated with single-unit recordings and selective stimulation. Here, we report a large-scale dataset of targeted recordings and stimulations of single-unit tactile afferents within the median nerve of healthy participants. Under medical supervision, tungsten microelectrodes were inserted percutaneously at the wrist to combine MNG recordings and INMS. Following single-unit isolation, afferents were classified as Slowly Adapting type I (SAI), Slowly Adapting type II (SAII), Fast Adapting type I (FAI), or Fast Adapting type II (FAII) according to receptive field properties, adaptation characteristics, and response thresholds to natural skin stimulation. Across the healthy subjects, we identified and characterized 29 single tactile afferents, including 17 SAI, 5 SAII, 2 FAI, and 5 FAII fibers. Units were recorded from multiple digits innervated by the median nerve. Receptive field characteristics were consistent with the expected properties of each afferent class, with SAI units exhibiting small and well-defined receptive fields and SAII and FAII fibers displaying larger receptive territories. Selective INMS was successfully delivered in 79% of identified fibers, with stimulation thresholds ranging from 2 to 14 μA (6.0 ± 2.8 μA). Stimulation elicited localized and natural percepts whose qualitative characteristics were generally consistent with the physiological identity of the stimulated afferents in 57% of successful INMS trials. Among characterized units, SAI afferents represented the largest fraction of the dataset. Although FAI fibers are known to constitute a major population of cutaneous mechanoreceptors, their successful characterization was comparatively less frequent, likely reflecting the increased difficulty of isolating and maintaining stable recordings from these units. These results demonstrate the feasibility of obtaining reproducible single-unit recordings and selective stimulation across a relatively large cohort of participants. The resulting dataset provides a valuable resource for investigating the neural basis of human touch and for developing biomimetic sensory feedback strategies for closed-loop neuroprosthetic systems.

Disclosures: M. Statache: None. **S. Ballanti:** None. **N. Fragapane:** None. **G. D'Alesio:** None. **M. Bellini:** None. **S. Dalise:** None. **C. Chisari:** None. **S. Taddei:** None. **M. Filosa:** None. **C. Oddo:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.05/X16

Topic: E.02. Somatosensation – Touch

Support: 1R01 AT011447-01 (D.D.G.)
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The Edward R. and Anne G. Lefler Center for Neurodegenerative Disorders (D.D.G.)
Canadian Institutes of Health Research Doctoral Foreign Study Award, 193217 (Z.K.S)
D.D.G. is an investigator of the Howard Hughes Medical Institute

Title: Structural and biomechanical basis of pacinian vibration tuning

Authors: *Z. K. SARAFIS, D. HAN, J. TURECEK, D. D. GINTY;
Dept. of Neurobio., Howard Hughes Med. Institute, Harvard Med. Sch., Boston, MA

Abstract: Pacinian neurons are low-threshold mechanoreceptors that detect high-frequency mechanical vibrations. Their sensitivity and tuning to vibration arise from the Pacinian corpuscle, a specialized end organ found in deep tissues across species, which consists of a central axon surrounded by concentric lamellar layers. Pacinian neurons have a range of vibration tuning and sensitivities. It remains unclear how the corpuscle structure enables exquisite tuning to vibration, and whether variations of vibration tuning and sensitivity across Pacinian neurons reflects corpuscle shape, size, and location. Additionally, while individual Pacinian neurons project centrally to the brainstem, relatively little is known about how high-frequency information is processed in this region. Using mouse genetic tools, whole tissue clearing for anatomical and structural analyses, and in vivo electrophysiology, we assessed the relationship between the structure and location of individual mouse Pacinian corpuscles and their functional tuning across the hindlimb, forelimb, and digits. We found a wider than expected distribution of Pacinian corpuscles across these body regions. Moreover, we observed anatomically organized heterogeneity in corpuscle and axonal structure within the hindlimbs and forelimbs. Electrophysiological recordings revealed that both corpuscle location and structure may account for variance in Pacinian vibration tuning properties. In addition, local tissue biomechanical properties dictate the sensitivity and tuning of Pacinian neurons. Specifically, Pacinian corpuscles are situated between two tissue interfaces, such as bone and muscle, and this placement is required for Pacinian neurons' responses to vibration stimuli. Lastly, we find electrophysiological evidence for convergence of digit and limb Pacinian neurons onto second order neurons of the brainstem. These findings suggest that multiple variables, including end organ structure, location, intrinsic properties, and local tissue mechanics shape Pacinian sensory neuron tuning, and these sources of variance may underlie a Pacinian population coding scheme for the central representation of mechanical vibration stimuli.

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Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.06/X17

Topic: E.02. Somatosensation – Touch

Support: F31 NS135947
R01 NS136228
RF1 NS128898
DP2 NS105555
L.I.F.E. Foundation Research Award
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Title: The effect of chronic stress on inhibitory modulation of tactile sensitivity

Authors: *J. MOSKO[1], J. M. CONNER[2], E. AZIM[3];
[1]Univ. Of California San Diego, La Jolla, CA; [2]MNL-E, Salk Inst., San Diego, CA; [3]MNL-E, Salk Inst., La Jolla, CA

Abstract: The constant flow of sensory information into the nervous system is fundamental for interaction with the world. The brain's ability to flexibly adjust sensitivity to various sensory stimuli is context-dependent and can be shifted on acute or chronic time scales. This dynamic regulation can be advantageous or maladaptive; prey animals may benefit from becoming temporarily hypersensitive to sensory cues elicited by a predator, but chronic shifts in sensory processing may become detrimental and debilitating. Importantly, a chronic shift in internal state increases stress-related amygdala activity, and this can impact sensory regulation. Consequently, we find that chronic stress can lead to an aberrant increase in tactile sensitivity. However, the neural circuit mechanisms underlying this shift in responsivity to touch remain unclear. The cuneate nucleus of the brainstem is responsible for transmitting sensory information originating from the forelimbs and anterior trunk region to the thalamus and primary somatosensory cortex, among other brain regions. Our recent work showed that local inhibitory networks envelop the cuneate, and perturbing the activity of these inhibitory neurons can bidirectionally modulate the gain of tactile signaling. We are now exploring how top-down pathways from the central amygdala that target these inhibitory networks might be involved in adjusting the strength of sensory signaling on short time scales, and how the function of these circuits is affected by chronic stressful experience.

Disclosures: J. Mosko: None. **J.M. Conner:** None. **E. Azim:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.07/X18

Topic: E.02. Somatosensation – Touch

Support: NIH intramural funding NCCIH
NIH intramural funding NINDS

Title: An inherited hypomorphic variant in PIEZO2 reveals structural features of mechanotransduction

Authors: *D. J. ORLIN[1], A. NICKOLLS[2], C. MADDEN[3], M. FALGAIROLLE[4], A. T. CHESLER[5];
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Abstract: PIEZO2 is the principal mechanosensory channel for proprioception, touch, and many interoceptive processes, yet key details of how PIEZO channels convert force into electrochemical signals remain unclear. Here, we report fraternal twins with proprioceptive ataxia and scoliosis, carrying an unreported PIEZO2 missense variant (N2434K) in compound heterozygosity with a null variant. Gene-edited mice confirm N2434K is disease-causing, with in vivo recordings demonstrating deficits in mechanosensory neuron responses. Despite normal plasma membrane expression, the variant has severely reduced mechanically evoked current, suggesting defective gating. N2434 is conserved between PIEZO1 and PIEZO2 and resides in the cap-pore linker, which bridges the extracellular cap and ion-conducting pore. Computational modeling, site-directed mutagenesis, and single-molecule imaging reveal this region is essential for channel-wide conformational changes during gating. Our findings explain how a single amino acid change produces a hypomorphic PIEZO2 allele, broadening the clinical spectrum of PIEZO2 deficiency syndromes and offering structural insight into mechanotransduction.

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Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.08/X19

Topic: E.02. Somatosensation – Touch

Title: The role of proprioception in orofacial muscle control in mice

Authors: *S. MARKEL, K. UCHIMA KOECKLIN, P. LI;
Life Sci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Essential life functions such as mastication, phonation and breathing rely on meticulous control of jaw-opening and jaw-closing muscles. Disruption of these behaviors can result in health complications such as masticatory dysfunction, temporomandibular disorder, and bruxism. These motor functions are regulated by sensory inputs, primarily proprioception, the body's sense of position and movement. Despite the known health consequences of orofacial disturbances, the neural mechanisms for the proprioceptive control of motor functions in normal and pathological conditions are not yet fully understood. The mesencephalic nucleus of the trigeminal nerve (Vmes) is a unique sensory nucleus that processes proprioceptive input from the

orofacial muscles. These neurons express the *Piezo2* gene, which encodes a mechanosensitive ion channel protein crucial for proprioception and mechanosensation. Vmes neurons innervate muscle spindles, which are specialized proprioceptors in skeletal muscle that recognize changes in muscle length and the speed at which the change occurs. In the orofacial region, muscle spindles are most densely concentrated in the masseter muscles, which are responsible for jaw closing. The aim of our study is elucidating the role of orofacial proprioception in the control of orofacial function. We utilized a loss-of-function conditional knockout (cKO) mouse model to delete the *Piezo2* gene in Vmes neurons*: Vglut1-Cre cKO* (*Slc17a7*) and examined the changes in the masseter muscles. For structural analysis, masseter muscles from both cKO mice (n=2) and their littermate controls (n=2) were cryosectioned, immunostained, and imaged by confocal microscopy. Muscle spindle lengths were quantified from the images using ImageJ and statistical comparisons were performed using a t-test. For functional assessment, jaw-closing force was measured using a bite force transducer. From this model, we noticed that the *Vglut1-cre cKO* mice showed a decrease in bite force and muscle spindle abnormalities. These results suggest that *Vglut1* neurons are essential for muscle spindle function and orofacial proprioception. Our research on orofacial proprioception will advance our understanding of the neural mechanisms underlying orofacial disturbances.

Disclosures: S. Markel: None. **K. Uchima Koecklin:** None. **P. Li:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.09/X20

Topic: E.02. Somatosensation – Touch

Title: Proprioceptive control of the masticatory muscles during orofacial chewing in mice

Authors: *K. UCHIMA KOECKLIN, S. MARKEL, P. LI;
Life Sci. Inst., Univ. of Michigan, Ann Arbor, MI

Abstract: Orofacial functions, including chewing, swallowing, breathing, and phonation, require precise coordination of jaw-opening and jaw-closing muscles. Disturbances in these functions could lead to severe consequences in the individual's health. These motor activities are precisely regulated by sensory inputs, particularly proprioception, which is the body's ability to sense its location and movement. Although body proprioception has been widely studied, the neural mechanisms responsible for orofacial proprioceptive control of the masticatory muscles during both normal and pathological conditions remain incompletely understood. The masticatory muscles are innervated by the trigeminal nerve, which comprises four distinct motor and sensory nuclei in the brainstem. Among these nuclei, the mesencephalic nucleus of the trigeminal nerve (Vmes) is a unique sensory nucleus located within the brainstem that processes the proprioception from the orofacial muscles, periodontal ligament, and temporomandibular joints. The aim of this study is to elucidate the role of Vmes in the control of the jaw muscles during

orofacial function, using a mouse genetics model of loss of function. We genetically targeted the Vmes to investigate the underlying mechanisms after loss of function of these neurons during chewing in adult mice. Neural ablation by cell apoptosis was achieved by caspase3 gene expression into the targeted neurons. Adult Vglut1-cre mice were stereotaxically injected with the Cre-dependent viral vector rAAV2/Flex-taCasp3-TEVP into the Vmes to efficiently ablate these neurons (n=3). Control mice were injected with the control viral vector AAV-Ef1a-DIO-EGFP. Ablation of Vmes neurons in adulthood resulted in impaired jaw motor control and reduced biting force, while also disrupting the coordinated muscle activity pattern during chewing. Furthermore, Vmes neurons express the Piezo2 gene, which encodes a mechanosensitive ion channel protein crucial for proprioception. To further explore the role of Piezo2 in Vmes during masticatory muscle function, we generated a conditional knock-out mouse model to delete the Piezo2 gene in Vmes neurons (n=3). The results showed a similar pattern of impaired masticatory muscle function, both in jaw motor control and chewing, leading to masticatory dysfunction. These findings suggest that Vmes neurons play a significant role in the control of the masticatory muscles during chewing, which is mediated by Piezo2. Our research on the neural mechanisms controlling the masticatory muscles will improve the clinical management of disturbances in orofacial functions.

Disclosures: K. Uchima Koecklin: None. **S. Markel:** None. **P. Li:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.10/X21

Topic: E.02. Somatosensation – Touch

Support: NIH Grant U24NS135547

Title: Interactive visualizations of somatosensory neuron cell types across species and nomenclatures to aid cell type harmonization

Authors: *S. TAPPAN[1], I. ZIOGAS[2], F. T. IMAM[3], T. GILLESPIE[4], J. BOLINE[6], J. S. GRETHE[7], M. E. MARTONE[5];
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Abstract: Dorsal Root Ganglion (DRG) neurons detect mechanical, thermal, and chemical stimuli in the periphery. Large-scale spatial sequencing from DRG at multiple spinal levels and across multiple species now reveals rich genomic diversity and provides a valuable foundation for classification. However, molecular profiles alone cannot tell us where a neuron projects, its conduction velocity, or how it responds to specific stimuli. Anatomical and physiological

characterization capture properties that molecular profiles cannot, and are essential components of any robust classification strategy. Because classification criteria span multiple modalities, different studies arrive at different population structures, producing many nomenclatures that makes cross-study integration difficult. A unified classification strategy must therefore capture both the phenotypic properties of each cell type and the methods used to define them. To address this, we created a database for somatosensory cells to express cellular phenotypes in a standardized way and a complimentary tool to explore the data, facilitating cross-study comparisons while supporting multiple nomenclatures. Central to this effort is the Neuron Phenotype Ontology (NPO), a computable framework for representing neuron types as collections of normalized phenotypic properties, spanning molecular markers, morphology, electrophysiology and anatomy (Gillespie et al., 2022). Curation begins with molecular cell type data extracted from published papers, with additional phenotypic features and methods mapped to NPO-compliant terms from established community ontologies. Each cell type is assigned a unique NPO identifier independent of author-chosen names. This separates cell identity from cell naming and allows nomenclature to evolve as new data emerges. Structured reference profiles capture the defining characteristics of DRG neuron subtypes and are organized as cell cards that serve as standardized anchor points for reconciling classifications across studies with differing nomenclatures. A visualization platform integrates cross-study concordance and subtype relationships, marker gene expression, fiber types, and species data into a unified interface with five complementary views.The goal is to enable researchers to determine when cell types across laboratories represent the same or related neuronal populations, advancing community understanding of somatosensory cell types, pain research and the broader effort to map the cellular landscape of the nervous system.

Disclosures: S. Tappan: None. **I. Ziogas:** None. **F.T. Imam:** None. **T. Gillespie:** None. **J. Boline:** None. **J.S. Grethe:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc. **M.E. Martone:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SciCrunch, Inc.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR134.11/X22

Topic: E.02. Somatosensation – Touch

Support: Klingenstein-Simons Fellowship
BBRF NARSAD

Title: Exploring the unexpected role of spinothalamic circuits in motor control.

Authors: K. CRUITE[1], *A. NELSON[2];
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Abstract: Skilled behavior depends on the continuous interaction between motor commands and sensory feedback. While the spinal circuits that link sensation to action are well characterized, far less is known about how ascending sensory pathways engage motor control circuits in the brain. Here we examine the spinothalamic (ST) system, traditionally framed as a pain pathway but anatomically poised to deliver direct sensory feedback to forebrain motor centers via its broad spinal distribution and multiple thalamic targets. The organization of ST neurons, their inputs, and their cellular targets remains poorly resolved, limiting our understanding of their role in motor control. We dissected the organization of ST inputs and outputs using projection-specific viral tools. Dual retrograde tracing from functionally distinct thalamic nuclei yielded a quantitative spinal atlas of ST populations, revealing a spatial organization consistent with functional specialization, including candidate groups linked to proprioception and motor control. Intersectional anterograde tracing showed that ST populations project selectively to distinct thalamic nuclei but collateralize broadly in brainstem structures, positioning them to broadcast signals across multiple motor-related circuits. Intersectional transsynaptic tracing revealed diverse peripheral inputs: nociceptors, mechanoreceptors, and a surprisingly prominent input from proprioceptors, including proximal limb muscle spindles. ST neurons also receive descending input from multiple forebrain regions involved in forelimb motor control and sensation, with input patterns varying across defined ST populations. Together, these results uncover previously unrecognized diversity within ST circuits and suggest that the spinothalamic system integrates sensory and motor-related signals to support skilled behavior. The work provides an anatomical framework for dissecting how distinct ST pathways contribute to the coordination of sensation and action.

Disclosures: K. Cruite: None. **A. Nelson:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR134.12/X23

Topic: E.02. Somatosensation – Touch

Support: 7DP2NS136872-02

Title: Axonal spike-count regimes link spinal cord stimulation periodicity to artificial sensory detection and discrimination in rodents

Authors: T. TVRDY, J. SLACK, ***A. P. YADAV**;
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Abstract: Electrical stimulation is widely used to evoke artificial sensation, yet how temporal stimulation patterns are transformed into neural activity and perception remains poorly understood. Recent behavioral studies have shown that increasing the aperiodicity of spinal cord stimulation pulse trains alters both detection thresholds and discrimination performance despite

constant pulse counts, suggesting a role for temporal structure beyond rate alone. However, the neural mechanisms underlying these effects remain unresolved.We developed a biophysically grounded computational framework linking a finite-element model of the rodent spinal cord, conductance-based axon simulations, and observer decision models to investigate how stimulation periodicity shapes neural responses and resulting behavior. By systematically varying stimulation amplitude, frequency, and inter-pulse interval variability, we identified distinct spike-count regimes arising from interactions between stimulation timing and axonal membrane dynamics. These regimes ranged from single spikes and small volleys to sustained spike trains, and they exhibited diverse frequency- and variability-dependent trends.No single regime was able to sufficiently explain experimentally observed detection threshold trends; instead, mixtures of regimes accurately reproduced both frequency-dependent threshold behavior and trial-level variability. Extending this framework to periodicity discrimination, we show that features derived from regime mixtures contain sufficient information to recover behavioral psychometric curves. Furthermore, observer model results provide a mechanistic account of behavioral asymmetries depending on the periodicity of the reference stimulus: discrimination relative to periodic inputs relied on combined rate and timing evidence, whereas discrimination relative to aperiodic inputs was dominated by timing irregularity.These results establish a mechanistic link between stimulation temporal structure, axonal spike generation, and perceptual behavior. This framework suggests that spinal cord stimulation does not operate within a single fixed neural regime but instead engages a spectrum of spike-count regimes whose mixtures shape perception. These findings have important implications for the design of biomimetic stimulation strategies, highlighting temporal patterning as a key dimension for controlling sensory outcomes.

Disclosures: T. Tvrdy: None. **J. Slack:** None. **A.P. Yadav:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR134.13/X24

Topic: E.02. Somatosensation – Touch

Support: SECIHTI with funding number: 840356

Title: Distribution of Sensory Neurons Innervating the Rat Glans Penis and Prepuce

Authors: *M. CHAVARRIA LEZAMA[1], C. F. PASTELIN[2], M. D. OLOARTE FLORES[3], C. MORAN[4], Y. CRUZ[5];
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Mexico; [5]Neurofisiología, Ctr. Tlaxcala de Biología de la Conducta, Univ. Autonoma Tlaxcala, Tlaxcala, Mexico

Abstract: Male sexual function relies on genital sensory neural circuitries. In rats, innervation of the glans penis and prepuce is provided by the dorsal nerve of the penis, a branch of the pudendal nerve, which arise from lumbar 6 to sacral 1 (L6-S1) spinal nerves. However, information about the afferent neurons is still poor. The aim of the present study was to determine the segmental distribution of the sensory neurons innervating glans penis and prepuce in rats, by using neural retrograde tracers. Adult male Wistar rats (n=7) were used. Under sodium pentobarbital anesthesia (40 mg/kg, IP), 5 µL of True Blue (4% w/v) was injected into the glans penis (n=4) or prepuce (n=3). Ten days later, the animals were intracardially perfused with saline followed by formalin. Dorsal root ganglia from L1 to S2 were collected, cryoprotected, and sectioned on a cryostat (10 µm). Retrogradely labeled neurons were identified and quantified using epifluorescence microscopy. It was found positive TB cells from L1 to S2. Retrograde labeling from the glans penis showed that most neurons were in L6 (94.28%). The remaining neurons were sparsely distributed in L1 (0.11%), L2 (0.51%), L3 (0.34%), L4 (1.13%), L5 (1.25%), S1 (0.85%) and S2 (1.53%). Retrograde labeling from the prepuce indicated that most labeled neurons were in L6 (84.39%), followed by L5 (5.64%) and S1 (4.67%). The remaining dorsal root ganglia contributed less than 6% of the total population. Based on these findings we conclude that sensory innervation of the glans penis and prepuce mainly originates from L6, with very little contribution of rostral lumbar and S2 dorsal root ganglia.

Disclosures: M. Chavarria Lezama: None. **C.F. Pastelin:** None. **M.D. Oloarte Flores:** None. **C. Moran:** None. **Y. Cruz:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

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Program #/Poster #: PSTR134.14/X25

Topic: E.02. Somatosensation – Touch

Support: MSCA Grant 101264556

Title: Tarsal bristle mechanosensors mediate active tactile sensing and obstacle detection in Drosophila

Authors: *G. ELISHA[1], P. RAMDYA[2,1];
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Abstract: Animals navigate complex terrain using active tactile sensing, a fundamental behavior for environmental exploration that has yet to be replicated with similar fluidity in robotic systems. To gain mechanistic insights into this behavior, we investigated how the fly, *Drosophila melanogaster,* gathers information about obstacles in its environment using touch. We first video recorded animals interacting with a physical wall and, by quantifying their leg kinematics, found

that flies tap their front legs on obstacles in a manner reminiscent of active sampling - the deliberate acquisition of sensory information through self-generated movements. They typically contacted walls with their ventral tarsi, implicating distal leg mechanosensors in tactile sensing. To test this hypothesis and to identify precisely which mechanosensors mediate obstacle detection, we developed an experimental system in which flies do not interact with a physical wall but instead with a virtual wall made of light. By expressing the light-sensitive cation channel, CsChrimson, in distinct leg mechanosensory neuron populations, we could identify those which yield tapping and retreat, behavioral responses of flies when they interact with real, physical obstacle. Flies with CsChrimson expressed in the leg campaniform sensilla, chordotonal organs, and hair plates crossed through the laser wall unimpeded, a behavior seen in control animals with no CsChrimson expression. By contrast, flies expressing the optogenetic channel in leg mechanosensory bristles paused, tapped or groomed at the laser wall. To identify the contribution of distinct bristle subpopulations in this behavior, we expressed CsChrimson in leg-specific, sparse bristle driver lines. Interactions with the light wall by proximal bristles in the femur or tibia elicited grooming, while optogenetic activation of more distal, tarsal bristles yielded pausing and tapping akin to what we observed when flies encountered a real wall. Thus, tarsal bristles on the front legs are causally sufficient to reproduce obstacle contact-like behaviors. These results provide a mechanistic inroad towards identifying neural computations for active sensing and inspiring the design of algorithms for tactile navigation in robots.

Disclosures: G. Elisha: None. **P. Ramdya:** None.

Poster

PSTR134: Somatosensation: Peripheral Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: E.02. Somatosensation – Touch

Support: NIH Grant F31NS141622
NIH Grant R00NS114179
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NIH Grant U01NS131438

Title: Sensory-motor integration in a nonspiking interneuron contributes to active sensor control in Drosophila

Authors: *O. M. NUNN, M. P. SUVER;
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Abstract: An animal’s nervous system enables it to detect and respond to stimuli to navigate its environment. To enhance sensory acquisition, animals can actively position sensors, altering how they extract information from the external world. However, active sensing, and movement in general, produces sensory feedback, requiring mechanisms for integrating predictive motor

signals with externally generated sensations. Despite the importance of these mechanisms for guiding coordinated behavior, the cellular and circuit basis of motor control and sensory processing during active movements are not fully understood. Here, we determine how mechanosensory information contributes to motor output in the *Drosophila* antenna, an active sensor that can be passively deflected or actively positioned. We combine electrophysiology, quantitative behavior, optogenetics, and connectomics to characterize APN2, a nonspiking interneuron in *Drosophila* that encodes both mechanosensory stimuli and motor commands. We show that these neurons integrate higher-order motor commands with mechanosensory input to shape antennal movement. Together, this work reveals a previously uncharacterized sensory-motor circuit within the antennal mechanosensory system. These findings provide insight into how nervous systems integrate sensation with motor commands to guide the movement of active sensors, highlighting circuit mechanisms that may more broadly support sensory acquisition during movement.

Disclosures: O.M. Nunn: None. **M.P. Suver:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.01/X27

Topic: E.05. Auditory and Vestibular Systems

Support: NIH K08 NS099425
NIH R01 NS130038
NIH T35HL166206

Title: A possible role for Neuropeptide S-expressing neurons in auditory threat response

Authors: *R. ZHANG[1], S. GASPARINI[1], H. ZHU[1], J. C. GEERLING[2];
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Abstract: The parabrachial nucleus is a region of the brainstem between the midbrain and hindbrain that integrates and modulates sensory information to shape behavioral responses. A group of neurons in this region express neuropeptide S (NPS). These neurons project to brain regions implicated in threat response, circadian regulation, homeostasis, and auditory integration. Cholera toxin B injections in this region showed substantial input from auditory-related brain regions, unlike any previously described populations in the parabrachial nucleus. Rabies retrograde tracing showed Nps-expressing neurons receive input from the dorsal cochlear nucleus, inferior colliculus, and superior olivary complex. Together, the inputs and outputs of these neurons suggest a role in regulating aversive behavior in response to auditory information. To test this hypothesis, we performed preliminary experiments examining whether auditory stimulation or chemogenetic activation alters neuronal activity or behavior. Exposure to white noise produced possible Fos induction in Nps-expressing neurons in the parabrachial nucleus

compared to controls (n=2). To test if activation of these neurons drive aversive behavior, we then used deschloroclozapine (DCZ) to chemogenetically activate Nps-expressing neurons transduced with hM3Dq. In our initial cohort (n=9), we did not observe any significant difference in time spent in the center zone between DCZ and vehicle-injected mice. In a conditioned place preference assay, we found that hM3Dq-injected mice did not significantly prefer or avoid the DCZ-paired chamber (n=9). Although chemogenetic activation did not produce detectable effects in these preliminary behavioral assays, input and output connections and auditory-related induced activation support further investigation of their role in behavioral responses to auditory stimuli.

Disclosures: R. Zhang: None. **S. Gasparini:** None. **H. Zhu:** None. **J.C. Geerling:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.02/X28

Topic: E.05. Auditory and Vestibular Systems

Support: Funding sourse Collaborative Research Center SFB 1286 “Quantitative Synaptology", University of Göttingen
Funding sourse Multiscale Bioimaging Cluster of Excellence (MBExC), University of Göttingen

Title: Investigation of neuromodulation of the endbulb of Held to bushy cell synapse in the cochlear nucleus by serotonin, norepinephrine and dopamine

Authors: *M. GROSHKOVA[1,2,3,4,5], T. ALVANOS[1,2,3], Y. QI[6], F. WANG[6], C. WICHMANN[1,3,7,8], Y. HUA[6], T. MOSER[1,2,3,4,5,8];
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Abstract: Neuromodulation is a candidate mechanism to explain some of the variability in synaptic strength and plasticity, within a circuitry or a set of pre- and postsynaptic neurons. Here, we focused our research on the putative neuromodulation of the mouse endbulb of Held to bushy cell (BC) synapse in the anteroventral cochlear nucleus (AVCN) by serotonin (5-HT), norepinephrine (NE) and dopamine (DA).

We combined electron microscopy (EM) and immunohistochemistry (IHC) approaches to investigate the presence of monoaminergic projections in cochlear nucleus (CN). Additionally, we employed IHC to study the localization of monoamine receptors in the AVCN as well as in spiral ganglion neurons (SGNs). We investigated spontaneous and evoked synaptic transmission as well as short-term plasticity using whole-cell patch-clamp recordings and afferent fiber stimulation.
Our EM data provides evidence for putative monoaminergic neurites containing varicosities in both ventral and dorsal divisions of the CN. Immunolabeling against the 5-HT (SERT) and NE (NET) transporters revealed 5-TH- and NE-containing projections juxtaposed to both endbulbs and BCs. Using IHC we uncovered several monoamine receptors both in the AVCN and in SGNs. Furthermore, we observed an increase in the frequency of miniature excitatory postsynaptic currents (mEPSCs) upon application of NE but no effect was detected upon 5-HT or DA application. The amplitude of the first EPSC increased and the paired-pulse ratio decreased upon DA application at 100 Hz stimulation frequency, while evoked release was not affected by NE application.
In summary, we report evidence for the presence of monoaminergic innervation in the CN and for subtle functional NE and DA-neuromodulation at the endbulb of Held to BC synapse.

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Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.03/X29

Topic: E.05. Auditory and Vestibular Systems

Support: R01 DC12557

Title: Behavioral timescale synaptic plasticity in the mouse auditory cortex

Authors: *M. WOLLET[1], M. A. KIRCHGESSNER[2], K. MARTIN[4], R. C. FROEMKE[3]; [1]Neurosci. Inst., [3]Otolaryngology, [2]NYU Grossman Sch. of Med., New York, NY; [4]Dept. of Biol. Sci., UCSD, San Diego, CA

Abstract: Learning at the behavioral level can sometimes be ‘one-shot’ or almost instantaneous, but most studies of long-term plasticity such as long-term potentiation (LTP) seem to require dozens or hundreds of induction events yet measure outcomes minutes afterwards. However, recent studies of behavioral timescale synaptic plasticity (BTSP) show that enduring hippocampal plasticity can be induced in just a few trials in vivo and in vitro (Bittner et al. Nat Neurosci 2015, Bittner et al. Science 2017, Liao & Losonczy Annu Rev Neurosci 2024). Here we examine the potential for BTSP to occur in the mouse auditory cortex. For in vivo experiments, adult mice were head-fixed and trained on a 2-alternative forced-choice task to

distinguish pure tones of one frequency (e.g., 13 kHz) from tones of other nearby frequencies (Martin et al. Nat Neurosci 2024). We performed 2-photon imaging during behavior and observed sudden, sometimes trial-to-trial changes in frequency tuning curves. For some responsive cells, new peaks to behaviorally relevant stimuli could emerge or be suppressed, shifting overall tuning curve structure. In some cases, unresponsive cells suddenly became responsive to tones during behavioral training. Many of these sudden and enduring changes happened during the earliest phases of training. We also examined BTSP in brain slices of the adult mouse auditory cortex. In whole-cell recordings from layer 5 pyramidal neurons, we measured EPSP amplitudes before and after a BTSP induction protocol comprised of a strong postsynaptic depolarization and synchronous synaptic stimulation at 2-10 repetitions. Pairing of either layer 2/3 or layer 5 inputs led to significant synaptic potentiation compared to baseline (L2/3: 40% increase, $p=0.0007$ in paired t-test, $n=10$ cells; L5: 68%, $p=0.005$, $n=8$ cells) while current injection alone had no effect ($p=0.23$, $n=5$ cells). BTSP induction did not significantly change probability of release ($p=0.27$), input resistance ($p=0.73$), or resting membrane potential ($p=0.97$, $n=8$ cells). To identify the molecular mediators of this plasticity, we pharmacologically blocked L-type calcium channels (LTCCs) and NMDA receptors (NMDARs) during the baseline and induction period using bath application of nimodipine and D-APV, respectively. Both nimodipine (10μM) and D-APV (50 μM) inhibited potentiation of inputs (Nim: $p=0.21$, $n=3$ cells; D-APV: $p=0.71$, $n=3$ cells). This is also observed with hippocampal BTSP (Bittner et al. Science 2017), and we have determined that LTCCs and NMDARs are required for cortical BTSP induction.

Disclosures: M. Wollet: None. **M.A. Kirchgessner:** None. **K. Martin:** None. **R.C. Froemke:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR135.04/X30

Topic: E.05. Auditory and Vestibular Systems

Support: 1RF1AG083937
R01DC013073
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Beckman Institute for Advanced Science and Technology
Carl R. Woese Institute for Genomic Biology

Title: Molecular Diversity and Organization of the Mouse Inferior Colliculus Revealed by Single-Cell Spatial Transcriptomics

Authors: *E. B. TAYLOR[1], S. TURPEN[1], M. AKPUOKWE[2], S. SINGH[3], N. VAITHIYALINGAM CHANDRA SEKARAN[2], D. LLANO[4];
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Abstract: The inferior colliculus (IC) is a hub in the midbrain for processing auditory formation, integrating both ascending and descending signals from numerous brain regions. Despite its role in central auditory processing, the molecular identities and spatial organization of IC cell types remain poorly characterized. Here, we present a single-cell resolution map of the mouse IC using 10x Xenium imaging-based spatial transcriptomics, profiling over 80,000 cells across a 247-gene panel. Unsupervised cell clustering identified 18 transcriptionally distinct cell populations, including 6 excitatory and 2 inhibitory neuronal subtypes. Notably, we identified excitatory neuron subpopulations expressing parvalbumin and somatostatin, which are typically associated with inhibitory interneurons, suggesting previously under-recognized molecular heterogeneity among IC neurons. Each cell population was defined by unique molecular signatures, and their spatial coordinates allowed us to map these cell types across IC subregions, including the central nucleus (CNIC), dorsal cortex (DCIC), and lateral cortex (LCIC). Differential expression analysis revealed distinct transcriptional profiles across subregions, with the CNIC, DCIC, and LCIC each enriched for different gene sets, reflecting their connectivity and functional specialization in auditory processing. This is consistent with the CNIC's primary role in ascending auditory processing, while the LCIC and DCIC are more heavily involved in integrating descending and multisensory information. Furthermore, we found that the GABA-rich “modules” of the lateral cortex of the IC, which receive somatosensory input, showed highly distinct transcriptional profiles relative to the surrounding “matrix”. The modules were preferentially enriched for genes involved in synaptic organization, axon guidance, and structural patterning, suggesting their specialization reflects not only their distinct inputs but also how that information is received and integrated at the synaptic level. The matrix, by contrast, was enriched for neuropeptide and neuromodulatory signaling genes, as well as genes related to the extracellular matrix, pointing to differences in signaling and organization. Together, these findings reveal unexpected molecular diversity within the IC and establish a spatially resolved transcriptomic framework that links cell type identity to subregion organization and how they contribute to auditory processing and circuit modulation.

Disclosures: E.B. Taylor: None. **S. Turpen:** None. **M. Akpuokwe:** None. **S. Singh:** None. **N. Vaithiyalingam Chandra Sekaran:** None. **D. Llano:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.05/X31

Topic: E.05. Auditory and Vestibular Systems

Title: Deep-layer circuit failure in Auditory Cortex disrupts social sound processing in a mouse model of Rett Syndrome

Authors: *D. NEOPHYTOU[1,2], C. PHAM[1], F. HIGGINS[1], H. OVIEDO[1];
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Abstract: Often characterized by severe impairments in communication, Rett Syndrome (RTT) results from mutations in the gene encoding for methyl-CpG-binding protein 2 (MeCP2). Yet the cortical circuit disruptions underlying these impairments remain unclear. Given the Auditory Cortex's (ACx) critical function in decoding behaviorally relevant acoustic signals, we asked how loss of MeCP2 alters sound-evoked activity and local excitatory connectivity. Using hemizygous male MeCP2 knockout mice (MeCP2-KO), we combined sound stimulation with Fos immunolabeling and whole-brain clearing to map neuronal activation across sound categories. Compared to wild-type mice, MeCP2-KO mice showed disrupted hemispheric organization of sound-evoked activity in the ACx, with a prominent loss of deep-layer (L4-6) recruitment in the left ACx. Consistent with this phenotype, MeCP2-KO mice also showed abnormal processing of social vocalizations in behavioral assays. To identify circuit mechanisms underlying these abnormalities, we used laser scanning photostimulation with glutamate uncaging to map excitatory synaptic connectivity. We first focused on L3, a major site of spectral integration, and found that total excitatory input to L3 was reduced in the left ACx of MeCP2-KO mice. Across all cortical layers, this target-layer deficit was matched by a source-layer abnormality with reduced excitatory output from L4-6 in the left ACx. The stronger expression of both deficits in the left ACx suggests that MeCP2 loss disrupts deep-layer cortical output and normal auditory cortical specialization. Preliminary developmental results further suggest that these abnormalities emerge in the context of disrupted maturation of inhibitory and extracellular matrix-associated programs during postnatal circuit refinement. Together, these findings identify a candidate cortical circuit basis for communication deficits in RTT: a failure of deep-to-superficial circuit assembly, marked by weak deep-layer output and altered maturation of superficial target circuitry.

Disclosures: D. Neophytou: None. **C. Pham:** None. **F. Higgins:** None. **H. Oviedo:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.06/X32

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01DC018790
NIH F31DC022195
NIH R01DC022640

Title: Brief Visual Deprivation Selectively Remodels Intracortical Inputs onto Layer 6 Corticothalamic Neurons in the Primary Auditory Cortex

Authors: *A. T. COLLINS, Jr.;
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Abstract: Loss of one sensory modality can enhance processing in spared systems. Brief visual deprivation by dark exposure (DE) enhances auditory responses in primary auditory cortex (A1), increasing firing rates, frequency selectivity, and behavioral performance. This enhancement is accompanied by reduced inhibition of the auditory thalamus (MGBv) and strengthened thalamocortical and intracortical feedforward inputs. While the mechanisms coordinating cross-modal cortical and thalamic plasticity are unknown, layer 6 corticothalamic neurons (L6-CTNs) are a promising candidate given their regulation of both cortical and thalamic gain. Here, we examined how 1 week of DE in adult mice alters intracortical synaptic inputs onto A1 L6-CTNs using laser-scanning photostimulation (LSPS) and whole-cell recordings. We found DE selectively reduced excitatory intracortical connectivity onto L6-CTNs across multiple layers and weakened synaptic strength from infragranular inputs. In contrast, inhibitory inputs were largely preserved. This shift resulted in a layer-specific reduction in excitation-inhibition balance, particularly for inputs from layer 4. Although the spatial extent of inputs was unchanged, DE decreased the similarity of input patterns across neurons, indicating a reorganization of circuit structure. Together, these findings identify selective weakening of intracortical excitation onto L6-CTNs as a key feature of cross-modal plasticity. By reducing recruitment of the L6 gain-control circuit, this reconfiguration may bias cortical processing toward enhanced sensory discrimination while preserving sensitivity.

Disclosures: A.T. Collins: None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR135.07/Y1

Topic: E.05. Auditory and Vestibular Systems

Support: TSC DoD TS220016

Title: Altered Auditory Processing in Rat Model of Tuberous Sclerosis Complex

Authors: *M. INAMDAR[1], N. JAMES[2], B. D. AUERBACH[3];
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Abstract: Autism spectrum disorder (ASD) comprises a group of highly heritable neurodevelopmental disorders associated with numerous genetic risk factors. Despite substantial progress in identifying ASD-associated mutations, linking these genetic alterations to the neural mechanisms underlying clinical symptoms remains a major challenge and has hindered the development of effective therapies. A key question is whether genetically distinct forms of ASD converge on shared pathophysiological mechanisms that ultimately give rise to common

behavioral phenotypes. Previous studies demonstrated that Tsc2+/− mouse models of tuberous sclerosis complex (TSC) and Fmr1 knockout (Fmr1KO) mouse models of fragile X syndrome (FXS) share same molecular pathway but exhibit opposing synaptic and cellular phenotypes that respond to opposite pharmacological interventions. How these divergent cellular alterations produce shared behavioral symptoms remain unclear. As a first step toward addressing this question, we used an operant conditioning paradigm to assess auditory hypersensitivity and auditory processing in Tsc2+/− Eker rats. We found a sex-specific increase in auditory sensitivity, with male Tsc2+/− rats exhibiting significantly faster auditory reaction times. These findings are consistent with our previously published observations in Fmr1 KO rats and demonstrate that two genetically distinct ASD models exhibit a shared behavioral phenotype of auditory hypersensitivity.

Disclosures: M. Inamdar: None. **N. James:** None. **B.D. Auerbach:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.08/Y2

Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant DC016599
NIH Grant DC013073
NIH Grant DC02160

Title: Auditory cortical feedback modifies task-dependent state modulation in the inferior colliculus

Authors: G. XIAO[1], B. LI[2], S. GOGINENI[3], ***D. LLANO**[2,4];
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Abstract: Sensory processing in the inferior colliculus (IC) is dynamically modulated by behavioral contexts, such as active task engagement. While corticofugal projections from the auditory cortex (AC) are known to innervate the IC extensively, their precise contribution to shaping these task-dependent network states in awake, behaving animals remains poorly understood. To address this, we used two-photon calcium imaging to examine neural activity in the dorsal cortex of the IC under both active task and passive listening conditions. Mice expressing GCaMP in the IC dorsal cortex were trained on a head-fixed two-alternative forced-choice auditory discrimination task. To determine the necessity of cortical feedback, we utilized chemogenetic silencing (hM4D(Gi)) to suppress AC responses during task performance. Unsupervised clustering of IC neurons revealed distinct functional subpopulations, indicating that the awake IC parses task parameters into specialized parallel channels, including sound-

excited, sound-suppressed, and motor/sound-offset-excited profiles. Comparing active and passive states, we found that active task engagement bidirectionally modulates IC output, optimizing the signal-to-noise ratio by amplifying specific integrated signals and deepening suppression. Chemogenetic inactivation of the AC shifted this active network state toward passive baseline levels. We observed significant degradation in task-specific modulation across subpopulations of IC neurons. The disruption was most robust during the post-sound window, where both task-enhanced activation and task-driven suppression were impaired in the absence of cortical input. These findings demonstrate that the IC operates via highly specialized, intermingled subnetworks, and that auditory cortical feedback modifies these task-dependent state modulations during active behavior.

Disclosures: G. Xiao: None. **B. Li:** None. **S. Gogineni:** None. **D. Llano:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR135.09/Y3

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC016599
R01DC013073
R21DC021605

Title: Neurochemical characterization of GABAergic modules in the lateral cortex of the mouse inferior colliculus

Authors: W. DAI[1], ***E. J. SANCHEZ**[1], A. DESHPANDE[1], K. GRAVES[2], M. BHATI[1], K. ORTGIESEN[1], D. A. LLANO[3,4];
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Abstract: The inferior colliculus (IC) is a major hub in the central auditory system. Within the IC, the lateral cortex (LC) is distinguished by a unique module-matrix organization. These periodic clusters of neurons, with distinct neurochemical profiles, are thought to support auditory-somatosensory interaction in the midbrain. Despite this established organizational framework, the cellular composition of LC modules and the surrounding matrix remains incompletely characterized. The present study aimed to identify neuronal populations associated with the module-matrix organization in the LC using a panel of histochemical markers. To answer these questions, we developed a novel mouse line by crossing mice that express GFP in GAD67-positive neurons, to delineate the GABAergic modules of the LC, with CBA/CaJ mice. We assessed LC-containing sections for expression of neuropeptides (neuropeptide Y [NPY] and vasoactive intestinal peptide [VIP]), extracellular perineuronal nets (PNNs), calcium binding

proteins (parvalbumin [PV] and calretinin [CR]) and vesicular glutamate transporter 2 (VGLUT2), a marker for glutamatergic terminals. Neurons were classified based on co-expression of various markers and their spatial localization within the modules and matrix. We observed distinct trends of the various neurons identified within the LC. GABAergic cells comprised a greater proportion of neurons in modules than in matrix, consistent with prior findings. For most markers, co-expression with GAD67-GFP was higher in GABAergic cells than in non-GABAergic cells, both overall and across modules and matrix, except for CR, which was only significantly enriched in GABAergic cells within the matrix. Most GABAergic cells expressed neither PNN nor VGLUT2, though there was evidence for slight upregulation of PNNs in module neurons and VGLUT2 in matrix neurons. Notably, we found that the superficial layer of the LC was densely enriched with NPY, VGLUT2, and CR axons and termini, rather than cell bodies, potentially reflecting an input-rich zone for integration in the LC. These findings provide a neurochemical framework for identifying distinct cell types within the LC and refining our understanding of module-matrix organization in the IC.

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Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC016599
NIH Grant R01DC013073
NIH Grant R21DC021605

Title: Molecularly characterizing and mapping an auditory hypothalamotectal pathway

Authors: *S. HASHIM[1], E. ALDRICH[2], D. LLANO[3,4,5];
[1]Molec & Integrative Physiol, Univ. of Illinois Urbana-Champaign, Urbana, IL; [2]Univ. of Illinois Urbana-Champaign, Champaign, IL; [3]Molec & Integrative Physiol, Univ. of Illinois at Urbana-Champaign, Urbana, IL; [4]Carle Illinois Col. of Med., Urbana, IL; [5]Beckman Inst., Urbana, IL

Abstract: Within the central auditory pathway, the inferior colliculus (IC) is responsible for integrating and relaying ascending auditory inputs. The hypothalamus (HY), which maintains homeostasis by regulating autonomic functions and motivated behaviors, is not classically studied relative to the central auditory pathway. However, we have observed that multiple HY nuclei are implicated in this pathway by injecting a fluorescent retrograde tracer into the IC that backlabeled HY source neurons. To molecularly characterize these neurons and map their projection systems, we utilized immunohistochemistry and Cre-dependent viral anterograde tracer injections into the HY in several Cre driver lines of cell types with established HY neuron

populations. We found backlabeled neurons that were positive for orexin, somatostatin, or tyrosine hydroxylase, which are associated with arousal and metabolic state, inhibitory signaling, and catecholamine synthesis, respectively. These cell types do not colabel with each other in the HY, indicating that multiple distinct HY neuron populations innervate the IC. We then characterized the projection patterns of these cell types across IC subdivisions, including the lateral cortex of the IC, which contains GABAergic modules that distinctly receive somatosensory inputs and an extramodular matrix that is instead innervated by auditory inputs. HY orexin and somatostatin projections interdigitated in both the modules and matrix, suggesting a diverse functional relationship with stimulus type. We subsequently used a transynaptic viral anterograde tracer injection into the HY in GAD67-GFP mice, observing postsynaptic neuron labeling primarily in non-GABAergic neurons in the matrix of the lateral cortex of the IC. Together, these data identify a pathway through which HY circuits involved in homeostasis may directly modulate auditory processing in the IC in a regionally distinct manner.

Disclosures: S. Hashim: None. **D. Llano:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.11/Y5

Topic: E.05. Auditory and Vestibular Systems

Support: b

Title: Acute disruption of calcium influx alters calcium regulatory pathways in the inferior colliculus

Authors: *S. YALCINOGLU, R. D. BRAUN, A. HOLT;
OVAS, Wayne State Univ. Sch. of Med., Detroit, MI

Abstract: Calcium homeostasis is critical for maintaining neuronal excitability, synaptic transmission, and activity-dependent plasticity within the auditory system. We previously demonstrated that systemic administration of the L-type voltage-gated calcium channel blocker verapamil produces an acute loss of neuronal synchrony within the inferior colliculus (IC) (Yalcinoglu et al., 2025). The present study investigated whether transient disruption of extracellular calcium influx triggers compensatory molecular and cellular adaptations in calcium signaling pathways.Adult rats received a single systemic injection of verapamil or saline and were euthanized either 1 day or 5 days following treatment. Quantitative PCR was used to assess expression of genes involved in calcium signaling, including CACNA1C (CaV1.2), CACNA1D (CaV1.3), NOS1, RYR2, and RYR3. Immunohistochemistry was performed to evaluate CaV1.2 and CaV1.3 labeling within the IC.One day following verapamil administration, expression of CACNA1C, NOS1 ($p < 0.05$), RYR2, and RYR3 was increased, whereas CACNA1D expression was decreased relative to saline controls. By 5 days post-treatment, CACNA1C and CACNA1D

expression levels had largely returned toward control levels, NOS1 remained elevated, RYR2 expression was reduced relative to the 1-day time point, and RYR3 expression remained robustly elevated ($p < 0.05$). At 5 days there was increased CaV1.2 puncta labeling within dorsal region of the IC, accompanied by decreased CaV1.3 puncta labeling within both dorsal and ventral regions of the IC ($p < 0.05$).These findings demonstrate that inhibition of L-type calcium channel-mediated calcium influx is sufficient to engage molecular and cellular adaptations in calcium signaling pathways within the inferior colliculus. The differential temporal responses observed across calcium signaling components suggest that molecular adaptations to disrupted calcium homeostasis are not uniform, with distinct regulatory pathways exhibiting varying degrees of responsiveness following reduction of calcium entry. Together, these observations suggest that acute perturbation of L-type calcium channel activity initiates a reorganization of calcium regulatory mechanisms involving extracellular calcium influx, intracellular calcium release, and nitric oxide signaling. This work identifies potential pathways through which disrupted calcium homeostasis may influence oxidative stress-related processes that contribute to neuronal dysfunction in the auditory midbrain.

Disclosures: S. Yalcinoglu: None. **R.D. Braun:** None. **A. Holt:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Topic: E.05. Auditory and Vestibular Systems

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Centurion Foundation for All
NIH NIDCD F32DC018211 (to C.G.S.)
Pew Latin American Fellows Program (to L.G.V.)

Title: Functionally defined NDNF interneuron ensembles regulate cortical network dynamics and plasticity

Authors: *C. G. SWEENEY, L. G. VATTINO, M. THOMAS, Z. GHASEMAHMAD, A. E. TAKESIAN;
Mass Eye and Ear/Harvard Med. Sch., Boston, MA

Abstract: Behavioral state profoundly influences sensory processing and learning, yet the circuit mechanisms by which state signals modulate cortical network activity remain incompletely understood. Cortical layer 1 (L1) neuron-derived neurotrophic factor-expressing interneurons (NDNF-INs) are ideally positioned to integrate neuromodulatory, top-down, and sensory inputs and may serve as key mediators of state-dependent cortical regulation.To determine how NDNF-INs represent behavioral state, we performed two-photon calcium imaging of NDNF-IN populations in auditory cortex while monitoring pupil diameter, whisking, and locomotion.

NDNF-INs' spontaneous and sound-evoked activity were strongly modulated by behavioral state, revealing distinct functional ensembles associated with specific behavioral variables. Specific temporal patterns of ensemble activity were reproducible within and across sessions, suggesting stable organization of state-related signaling within the NDNF-IN population.We next tested whether behaviorally defined NDNF-IN ensembles exert distinct influences on cortical network activity. Using ChRmine-mediated optogenetic stimulation with spatial light modulation, we activated select NDNF-IN ensembles while monitoring network responses. Activating different ensembles produced distinct patterns of network modulation, demonstrating that functionally defined NDNF-IN populations differentially control cortical activity. Furthermore, repeated activation of select ensembles produced persistent changes in network responses, consistent with a role for NDNF-INs in experience-dependent plasticity.Together, these findings identify NDNF-IN ensembles that encode behavioral state and demonstrate that selectively recruiting these ensembles can drive both immediate and lasting changes in cortical network function. These results suggest that NDNF-INs provide a mechanism to link behavioral state to sensory processing and cortical plasticity.

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Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR135.13/Y7

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R15 DC020327
NIH R25 NS114326
NS114326

Title: Male-Specific Reproductive State Changes in Catecholaminergic Innervation of Auditory Pathways in a Vocal Fish

Authors: *A. J. SKEANS[1], Y. AZZAM[1], R. RODRIGUEZ[1], K. KOBI[2], T. QUIGLEY[3], S. GRAY[5], J. A. SISNEROS[6], P. M. FORLANO[4];
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Abstract: In seasonal breeding vertebrates, hormone regulation of catecholamines (CA), which include dopamine and noradrenaline, may function, in part, to modulate behavioral responses to conspecific vocalizations. During the early summer reproductive season, male plainfin midshipman fish produce advertisement calls that females detect and localize to mate as well as agonistic calls used during male competition for nests. While reproductive-state changes in CA

innervation of the central and peripheral auditory system is well documented in females and contributes to seasonal changes in their hearing sensitivity, it is unknown whether males experience seasonal plasticity in CA innervation within auditory and vocal-acoustic brain regions and contribute to male seasonal reproductive behaviors. To address this gap, we compared non-reproductive and reproductive males collected in winter and summer months respectively, and processed brain and saccules, the largest end organs of hearing, for tyrosine hydroxylase immunoreactivity (TH-ir), a marker of CA synthesis. Notably, summer reproductive males display greater TH-ir innervation at several levels of the ascending auditory system, including identified nuclei in the hindbrain, hypothalamus, and thalamus. No seasonal, reproductive state differences were found in the saccule, paratoral tegmentum, or the vocal-acoustic periaqueductal gray in midbrain. These results indicate male-specific patterns when compared to a previous study in females, suggesting seasonal patterns of CA innervation reflect differential function in males and females, as senders vs receivers of social acoustic signals for reproduction.

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Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Topic: E.05. Auditory and Vestibular Systems

Support: NIH Grant R01DC018353
NIH Grant F31DC023141

Title: Bidirectional serotonergic modulation of somatostatin-expressing neurons in auditory cortex

Authors: *M. G. CHAVES[1], C. G. SWEENEY[2], L. G. VATTINO[3], A. E. TAKESIAN[4];
[1]Harvard Univ., Cambridge, MA; [2]Mass Eye and Ear/Harvard Med. Sch., Boston, MA;
[3]Otolaryngology Dept., Mass Eye and Ear - Harvard Med. Sch., Somerville, MA;
[4]Otolaryngology, Massachusetts Eye and Ear, Boston, MA

Abstract: Bidirectional serotonergic modulation of somatostatin-expressing neurons in auditory cortexAuthors: M. Grace Chaves[1,2,3], Carolyn G. Sweeney[1,3], Lucas G. Vattino[1,3], Anne E. Takesian[1,31]Eaton Peabody Laboratories, Massachusetts Eye & Ear, Boston, MA; [2]Graduate Program in Speech and Hearing Biosciences and Technology, Harvard Medical School, Boston, MA; [3]Department of Otolaryngology, Harvard Medical School, Boston, MAAuditory cortex (ACtx) is strongly regulated by neuromodulatory projections that convey information about behavioral state and prior experience. These inputs dynamically alter neuronal excitability, filter incoming sensory information, and gate synaptic plasticity. Serotonin (5-HT) is a powerful regulator of cortical network function and plasticity throughout the brain and has

been implicated in experience-dependent reorganization of ACtx tonotopic maps. However, the cellular and circuit mechanisms by which 5-HT acts within the complex cortical circuits remain poorly understood. Here, we focus on somatostatin (SST)-expressing neurons, a putative locus of serotonergic modulation based on their diverse 5-HT receptor expression.
Using fluorescence-guided whole-cell recordings in thalamocortical slices of mouse auditory cortex, we measured SST neuron responses to local 5-HT application. We observed bidirectional serotonergic modulation within the SST neuron population: one subset exhibited prolonged depolarization and increased firing, whereas another showed hyperpolarization. Pharmacological experiments indicate that these opposing effects are mediated by 5-HT_{2A} and 5-HT_{1A} receptor subtypes, respectively. SST neurons are highly heterogeneous, composed of diverse morphological, electrophysiological, and transcriptomic subclasses with distinct connectivity and functional roles. Ongoing work is determining how 5-HT bidirectionally modulates these distinct SST neuron subclasses to modulate different downstream targets and control cortical dynamics. Together, these results demonstrate robust, bidirectional serotonergic modulation of SST neuron subclasses in ACtx and indicate that 5-HT can flexibly regulate inhibition through distinct SST neuron microcircuits.

Disclosures: M.G. Chaves: None. **C.G. Sweeney:** None. **L.G. Vattino:** None. **A.E. Takesian:** None.

Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

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Program #/Poster #: PSTR135.15/Y9

Topic: E.05. Auditory and Vestibular Systems

Support: NIH R01 NS082179

Title: Early Auditory Experiences Shape Neuronal Properties of Zebra Finch Auditory Forebrain

Authors: *P. N. ANDERSON[1], B. FUREST CATALDO[2], L. REMAGE-HEALEY[3];
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Abstract: Sensory experiences during development shape how the brain processes information in adulthood. Plasticity in neural circuits allows encoding of sensory signals across different contexts, which is dependent on neuronal activity. The type and magnitude of ion currents that an individual neuron expresses (i.e., its “intrinsic membrane properties”) contribute to the timing and patterns of its activity. Changes to these properties can modify network dynamics and thereby contribute to overall brain plasticity. While these changes have been studied across primary sensory modalities, intrinsic membrane properties have seldom been investigated in higher sensory association regions. Specifically, the contribution of early auditory experiences to changes in intrinsic membrane properties in higher-order auditory regions remains largely

unexplored. This project investigates how different developmental auditory environments shape intrinsic membrane properties of neurons in the caudomedial nidopallium (NCM), a region in zebra finches that is known to process and store memories of song. We used ex vivo whole-cell patch-clamp recordings to assess intrinsic properties of distinct neuronal populations in juvenile birds reared in environments with varying acoustic complexity. Birds raised in an all-female zebra finch environment (song naive) will be compared to birds raised with female and male zebra finches (song experienced). Current findings indicate that song deprivation alters action potential features related to excitability in distinct NCM neuron types, with tonic firing neurons in song-naive birds showing reduced excitability. Understanding these mechanisms will elucidate principles of plasticity related to auditory experience and inform future research on neurodevelopment and learning.

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Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

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Program #/Poster #: PSTR135.16/Y10

Topic: E.05. Auditory and Vestibular Systems

Support: NIH RO1DC009607

Title: A novel tool for studying the first-order auditory thalamocortical circuit

Authors: *M. CHANG, M. CARDOSO DE OLIVEIRA, Z. LYU, P. O. KANOLD;
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Abstract: The thalamic nuclei relay sensory information to the cortex via first- and higher-order pathways, with first-order thalamocortical axons conveying ascending peripheral information. While the first-order thalamocortical pathway is well characterized in adult sensory systems (auditory, visual, and somatosensory), the developmental sequence of axonal targeting and refinement in the auditory system remains poorly understood. A major limitation is the lack of genetic tools to selectively label the first-order thalamic pathway, distinguishing it from other higher-order thalamic pathways, thereby hindering its specific manipulation and functional studies. Here, using Tshz1-2A-FlpO;Rosa26-FSF-tdTomato mice, we introduce a genetic approach to selectively label first-order auditory thalamic neurons in the ventral division of the medial geniculate body (MGBv) and map their developmental projections in the auditory cortex from birth. The Tshz1-reporter expression is largely confined within the MGBv, defined by the calbindin-immunostained boundary, with approximately 90% of NeuN-immunopositive neurons in the MGBv expressing the reporter. Next, we employ brain-clearing approaches to preserve the intact thalamic pathway of Tshz1-MGBv axons in the auditory cortex. At birth, Tshz1-MGBv axons primarily ramified in deeper cortical layers. By postnatal day (P)3, they were detected in the middle cortex (future layer 4). From P7 onward, axonal arbors became denser in the middle

cortex with reduced arborization in deeper layers. Such innervation patterns remained similar throughout the third postnatal week, with increasing signal intensity in layer 1 and layer 4 with age, suggesting denser axonal arborization. While in normal development, axonal pruning is experience-dependent; in the absence of auditory input, will MGBv axons be preserved? To test this hypothesis, we generated a sensorineural hearing loss mouse model expressing the Tshz1 reporter. Preliminary data suggest that the auditory area innervated by Tshz1-MGBv axons is similar between deaf and control littermates at P8. We propose that the persistence of Tshz1-MGBv axons may contribute to better outcomes of early interventions in individuals with congenital deafness, as these preserved thalamic pathways can be recruited for auditory rehabilitation. Overall, although Tshz1-reporter expression was detected in other brain regions (e.g., striatum), it was selectively enriched in the MGBv and absent from other higher-order auditory thalamic regions, thereby providing a specific model for studying MGBv function.

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Poster

PSTR135: Auditory Circuits, Anatomical Organization, and Plasticity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR135.17/Y11

Topic: E.05. Auditory and Vestibular Systems

Support: R01DC016599
Graduate Fellows Program at the Beckman Institute for Advanced Science and Technology
R01DC013073
R21DC021605

Title: A multimodal mapping approach reveals frequency-dependent molecular and connectional organization of the mouse auditory cortex

Authors: *S. SINGH[1,3], G. XIAO[4,3,5], M. RODE[6], D. LLANO[7,3,5,8,2];
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Abstract: Neocortical maps form the basis for sensory perception, plasticity, and flexible behavior. Currently, the field of auditory neuroscience lacks a precise understanding of the organization of auditory cortical (AC) subfields, limiting our ability to understand auditory processing. To resolve this dilemma, we propose multiscale mapping of AC using multiple

modalities in a single mouse to understand the structure-function relationship of auditory cortical subfields. In this study, we will characterize the microstructural composition and top-down projections of AC subfields. First-generation hybrids derived from crosses between cross-bred albino (CBA/CaJ) and mice with genetically encoded calcium indicators (GCaMP6s) were imaged transcranially using intrinsic and calcium imaging methods to map AC subdivisions in response to pure tones. Brains were extracted, sectioned, and stained for various microstructures such as myelin using the Gallyas silver method, while parvalbumin-expressing inhibitory neurons (PV), and SMI-32, which labels a subset of excitatory pyramidal projection neurons, were stained via immunohistochemistry. Imaging and histological data were coregistered to assess differences in neuronal microstructures across functional subdivisions of AC. We observed that primary AC subfields have higher concentrations of PV, SMI-32, and myelin than non-primary subfields. Interestingly, tonotopically organized areas show a gradient in which high-frequency areas have greater densities of PV, SMI-32, and myelin than low-frequency areas. To further explore this finding, we sought to determine how this chemical/frequency organization may relate to top-down connectivity. Following calcium imaging, we injected anterograde tracers into high- and low-frequency areas of primary auditory cortex (A1), secondary auditory cortex (A2), and anterior auditory field (AAF). Our data demonstrate that A1 sends projections across all divisions of the medial geniculate body (MGBd), while AAF and A2 sends its projections to the ventral division of MGB (MGBv). AAF sends most of its projections to the ventral part of MGBv, while A2 sends most of its projections to the dorsal part of MGBv. Furthermore, projections from high- and low-frequency areas of each AC subfield do not overlap in the MGB. We also observed that AAF sends more projections to the inferior colliculus (IC) than A1 and A2. Projections from A1 to IC are around the shell. High-frequency AAF projections are densest in the lateral and medial IC, while low-frequency AAF sends dense projections to the dorsal IC. Projections from A2 to IC are located on the shell of the lateral IC and some on the dorsal IC.

Disclosures: S. Singh: None. **G. Xiao:** None. **M. Rode:** None. **D. Llano:** None.

Poster

PSTR136: Visual Cognition: Attention and Decision-Making

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR136.01/Y12

Topic: E.06. Vision

Support: NIH R01 MH118929

Title: Impact of reward on perceptual decisions and neuronal responses in visual cortex

Authors: *A. C. TANGEN[1], M. E. MCDONNELL[1], S. M. CHASE[1], M. A. SMITH[2];
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Abstract: As relative reward increases during a task, individuals tend to improve their performance. However, when the availability of a rare and large magnitude of reward ("jackpot") is signaled, subjects often experience a surprising drop in performance. This phenomenon, known colloquially as "choking under pressure," occurs in a variety of tasks. Recent work by our groups has shown that monkeys also exhibit this phenomenon in motor tasks with concomitant changes in motor cortex. Here, we investigated the impact of expected reward on behavioral performance and neuronal responses in visual cortex in a "choking under pressure" task paradigm. We trained rhesus macaques to perform a visual change detection task that required them to report the change in the stimulus with a saccade to a peripheral target cued at the stimulus onset. As we varied stimulus difficulty levels, we recorded neural activity from the primary visual cortex (V1) and a mid-level visual cortical area (V4) implicated in visual attention and other cognitive processes. We found that while monkeys' performance increased monotonically from small rewards to large rewards, their performance significantly decreased on jackpot trials, providing evidence that the animals "choked under pressure." Additionally, the neuronal response characteristics were different on jackpot trials compared to other reward conditions in both V1 and V4. Overall, our results demonstrate that changes in early sensory areas may contribute to performance deficits during choking under pressure.

Disclosures: A.C. Tangen: None. **M.E. McDonnell:** None. **S.M. Chase:** None. **M.A. Smith:** None.

Poster

PSTR136: Visual Cognition: Attention and Decision-Making

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR136.02/Y13

Topic: E.06. Vision

Support: Deutsche Forschungsgemeinschaft, DFG), SFB 1528 - Cognition of Interaction

Title: Social context modulates neuronal activity in areas MT and LIP during continuous perceptual decision-making in rhesus monkeys

Authors: *F. SCHNEIDER, A. NAZARI, A. CALAPAI, I. KAGAN, A. M. GAIL, S. TREUE; Cognitive Neurosci. Lab., German Primate Ctr., Göttingen, Germany

Abstract: Access to social information during perceptual decision-making changes the behavioral responses of humans. We seek to determine the neural correlates of this social information integration in the brain of behaving rhesus macaques. To that end, we developed a continuous perceptual report (CPR) task with peri-decision wagering to determine if and how direction-selective neurons in brain areas MT and LIP integrate sensory and social information about noisy random dot motion (RDM) stimuli. In humans, this task allows real-time assessment of perceptual accuracy and confidence in solo and social contexts (Schneider et al. 2024). Here, social context consisted of side-by-side monkey-human confederate dyads. Two human partners

with slightly different psychometric thresholds participated in the experiments. On a shared display, the stimulus and the continuous perceptual reports of both the monkey subject (n=2) and the partner were shown simultaneously. To deliver precisely controlled social information to the monkey, the human confederate followed an accurate computer agent in a subset of sessions. This artificial agent expressed graded levels of confidence, scaled with RDM coherence. Extracellular spiking activity was recorded using two 32-channel Plexon V-probes along the superior temporal and intraparietal sulci. Preliminary results reveal behavioral and neural differences between dyadic and solo conditions. Accuracy and confidence were on average higher in the dyadic condition while hit rates declined, indicating that the monkey attempted to exploit both social information and peri-decision wagering. In addition, a fraction of MT and LIP neurons significant altered their firing patterns in the dyadic condition, even though the sensory input remained unchanged. This modulation was not uniform and seemed to depend on the tuning properties of the neuron. Furthermore, the neuronal activity correlated with the upcoming behavioral report of the monkey, and this relationship was stronger in the dyadic condition. These results suggests that areas MT and LIP contribute to the integration of social cues with sensory evidence during perceptual decision-making. Schneider, Calapai, Mundry, Báez-Mendoza, Gail, Kagan, Treue (2025) Confidence over competence: Real-time integration of social information in human continuous perceptual decision-making. eLife https://doi.org/10.7554/eLife.101021.2. Funding information: This publication was supported by the German Research Foundation (Deutsche Forschungsgemeinschaft, DFG), SFB 1528 - Cognition of Interaction.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

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Topic: E.06. Vision

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RFIS外国学者研究项目：National Natural Science Foundation of China (Grant No. W2432019)

Title: Non-linear subspace transformation that maps object identities to action plans in the primate prefrontal cortex

Authors: *Z. LI[1], J. WU[1], G. OKAZAWA[2];
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Abstract: The primate brain recognizes a myriad of object categories and associates them with a limited number of appropriate actions. While existing frameworks of perceptual decision have largely been developed for binary stimulus categorization, it remains poorly understood how the brain performs the massive dimension reduction to transform object information into action plans. In the prefrontal cortex (PFC), studies have observed both low-dimensional population dynamics during decision formation and complex selectivity for visual stimuli, but frameworks linking these two representations have also been lacking. Here, we identify nonlinear gating as a key computation that maps high-dimensional object information onto low-dimensional action plans. We recorded from the PFC of monkeys performing a multi-identity face recognition task, in which multiple face identities were each associated with one of two choices. We found that population activity spanned two subspaces: a high-dimensional face identity subspace and a low-dimensional choice subspace, each characterized by different encoding geometries. The face subspace encoded individual identities along orthogonal axes and represented the morph continuum between two identities as a rotation between these axes. In contrast, the choice subspace exhibited ramp-like dynamics toward one of the two choices, whose buildup rates were modulated by morph strength, consistent with evidence accumulation. Critically, during decision formation, only the axis encoding the presented identity in the face subspace exhibited significant noise correlation with later activity in the choice subspace, indicating a selective information transfer from face to choice subspaces. This selective routing was reproducible only by models incorporating a nonlinear gating mechanism. A decision model based on this neurally informed nonlinear filtering mechanism predicted that choice accuracy and reaction time should be invariant to the number of alternative identities, which were confirmed by monkey behavior. Together, these results establish nonlinear gating as a computational principle that enables the brain to transform high-dimensional object representations into low-dimensional action plans, addressing a fundamental challenge of naturalistic decision making.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

Location: WCC Halls A-C

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Program #/Poster #: PSTR136.04/Y15

Topic: E.06. Vision

Support: R01HD105735

Title: A novel and efficient approach to assessing visuoconstructive impairments after stroke

Authors: *R. C. SPRANSY, K. STACK, R. HAU, A. SEYDELL-GREENWALD; Neurol., Georgetown Univ. Med. Ctr., Washington, DC

Abstract: Constructional apraxia (CA), characterized by difficulty with recreating figures or patterns from their components, is a prevalent visuospatial deficit following right-hemisphere

(RH) stroke. Commonly used assessments such as the Rey-Osterrieth Complex Figure (ROCF) task and WAIS Block Design subtest are sensitive to CA but are time-intensive and lack specificity, as their complexity also captures broader impairments in executive function. Here, we investigate whether CA can be detected effectively using a simple copying task that includes 6 figures from the Beery-Buktenica Developmental Test of Visuo-Motor Integration (Beery VMI). While items are traditionally scored all-or-nothing (0 or 1), we developed a new scoring system with 3 qualitative subscores (accuracy, placement, fragmentation) inspired by the Boston Qualitative Scoring System (BQSS) for the ROCF. Blinded raters independently scored the copies of 14 RH stroke survivors (RHSS), 14 left-hemisphere stroke survivors (LHSS), and 12 age-matched controls (CTRL). Consensus scores for the traditional scoring scheme were submitted to a one-way ANCOVA with age as a covariate due to its known effect on visuoconstructive abilities. As expected, we found a significant group effect ($F = 9.26$, $p<.001$), with RHSS scoring lowest ($M = 2.63$, $SE = 0.39$) and CTRL highest ($M = 5.09$, $SE = 0.42$). A MANCOVA run on our in-house scoring method revealed significant group differences in mean accuracy ($F = 3.58$, $p = 0.038$) and placement ($F = 7.70$, $p = 0.002$) but not fragmentation ($F = 0.006$, $p = 0.994$), with RHSS scoring lower on accuracy and placement than CTRL, while LHSS scored in between without differing significantly from either of the other groups. The traditional raw score and all 3 subscores were significantly correlated with the Benton Judgment of Line Orientation test, a widely used measure of visuospatial deficits. Taken together, these results suggest that our abbreviated version of the Beery VMI may offer a fast and simple screening tool for CA in stroke survivors and support the validity of our new scoring system, which may provide a more nuanced characterization of visuoconstructive deficits in RH stroke than current approaches alone.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

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Program #/Poster #: PSTR136.05/Y16

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Title: Eyes on the prize: a neural basis of perceptual choking under pressure

Authors: *M. E. MCDONNELL[1], A. CHANDRASEKARAN[5], C. KI[2], A. L. SMOULDER[6], H. MIYATA[3], B. M. YU[7], A. P. BATISTA[8], S. M. CHASE[2], M. A. SMITH[4]; [2]Neurosci. Inst., [1]Carnegie Mellon Univ., Pittsburgh, PA; [3]Carnegie Mellon Univ., PITTSBURGH, PA; [4]Biomed. Engin. and Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA; [5]Neurosci., Univ. of Pittsburgh Ctr. For Neurosci., Pittsburgh, PA; [6]Dept. of Biomed. Engin., Boston Univ., SOUTH BOSTON, MA; [7]CMU, Pittsburgh, PA; [8]Bioengineering, Univ. of Pittsburgh, Pittsburgh, PA

Abstract: Performance tends to improve when the offered reward is increased. However, a paradoxical decrease in performance can occur when rare and exceptionally large "jackpot" rewards are offered, known as "choking under pressure". Previous studies in an animal model of choking under pressure primarily focused on motor outcomes. In this work, we investigated the effects of jackpot rewards on visual perception. We trained rhesus monkeys to perform a challenging visual change detection task, where they reported a subtle color change on an oriented grating by making a precise joystick movement to a peripheral target (far from the visual stimulus). A symbol within the target indicated to the monkeys the reward that would be received if successful on that trial: on 95% of trials the reward was modestly sized (small, medium, or large), while on the remaining 5% of trials an exceptionally large jackpot reward was offered. We found that monkeys exhibited decreased perceptual performance when rare jackpot rewards were offered. That is, they choked under pressure on the perceptual component of the task. Here, we asked whether attention-related changes in neural population activity in visual cortex might explain the perceptual component of choking under pressure. To investigate a potential visual cortical basis for choking under pressure, we recorded the activity of populations of neurons in visual area V4 with 96-electrode "Utah" arrays. On jackpot trials, we found evidence supporting that the animals misallocated their attention to the peripheral target (which contained the reward information) rather than the visual stimulus, to the detriment of perceptual performance. We considered V4 population activity during two time periods in our task: the stimulus presentation period when the visual system should be prepared to detect an upcoming change, and the period just after the change when the visual system should signal the altered stimulus. We found that the visual stimulus signals in V4 during both periods of the task were compromised on jackpot trials, including increases in shared variability consistent with impaired attention to the visual stimulus. Furthermore, we found that the effect of the peripheral target on V4's activity was greatest on the jackpot trials, potentially indicating a distraction from the visual stimulus. Jointly, these results support that the perceptual component of choking under pressure in this task was mediated by inappropriate allocation of spatial attention.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

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Topic: E.06. Vision

Support: NIH P50MH132642
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Title: The effects of proximity and uncertainty in divided spatial attention

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Abstract: Spatial attention is defined as the enhancement of sensory processing at a specific location in space. As a fundamental mechanism for selecting relevant information from the environment, it is critical for navigating dynamic situations in the face of limited neural resources. By prioritizing behaviorally relevant stimuli, spatial attention optimizes performance and efficiency within cognitive networks. However, when behavioral relevance is uncertain or distributed across multiple spatial locations, cognitive demand increases and resources must be allocated differentially to support goal-directed behavior. Literature suggests that covert attention can be divided between multiple, non-contiguous locations. However, few experiments have been devised that differentiate multiple foci of attention from the zoom lens hypothesis. Do humans simply expand or shrink their attentional window based on task demands or are there two distinct windows with no enhanced processing in between? We hypothesized that if attention can be allocated simultaneously to multiple spatial loci, performance should be organized around multiple local maxima rather than a single broad attentional gradient. Therefore, we developed a novel psychophysics paradigm involving divided attention and cognitive uncertainty. A probabilistic cue indicated the likely side of an upcoming contrast change, varying in uncertainty from fully informative to completely uninformative. Within each side of the array, contrast changes followed a fixed spatial distribution biased toward the central location creating an attentional locus in each field. Goal relevant stimuli are present both towards and away from the secondary locus. This design allowed us to investigate whether observers distribute attention according to the probabilistic structure of the environment and how uncertainty shaped the spatial profile of attentional allocation. Our results provide evidence that humans allocate attention in two separate foci. Specifically, we found attentional effects at each central locus that diminish with distance from the cued location. Notably, performance is not enhanced between the loci indicating near surround suppression at the edges of the two attentional windows. These spatial patterns were further modulated by cue certainty, as greater uncertainty significantly predicted poorer task performance. Taken together, these findings support models in which visuospatial attention can be distributed across multiple behaviorally relevant locations while remaining sensitive to probabilistic uncertainty.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR136.07/Y18

Topic: E.06. Vision

Support: NIH R01 HD105735

Title: A computerized line bisection task to investigate perceptual and motor neglect after stroke

Authors: *M. BOLDEN[1], A. SEYDELL-GREENWALD[2];
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Abstract: Spatial neglect, a unilateral attentional disorder not attributable to primary sensory deficits, affects roughly 20% of chronic right hemisphere stroke survivors (RHSS) and is linked to greater mobility issues, pain, anxiety, and depression compared to left hemisphere stroke survivors (LHSS). Previous studies use the paper line bisection task to disentangle two components of spatial neglect: perceptual-attentional ("where") bias and motor-intentional ("aiming") bias. Using a computerized version of this task, we compared these biases in 38 RHSS, 20 LHSS, and 17 healthy age-matched controls. Participants dragged a mouse cursor from the top left and top right portions of the screen to the midpoint of a 12 cm horizontal line in a pseudorandomized paradigm. Cursor mapping was congruent during the first 12 trials and incongruent (i.e., if the mouse moved left, the cursor moved right and vice versa) during the second 12 trials, with separate blocks of the mouse starting at body midline (center) and ipsilesional (non-center) positions. Deviation from the midpoint on all trials was decomposed into errors attributable to “where” and “aiming” bias. Repeated measures ANOVAs investigated the effects of stroke diagnosis on average deviation from the midpoint, “where” bias, and “aiming” bias, accounting for congruent and incongruent cursor-mapping conditions and center and non-center mouse placement. There is a significant effect of group on average deviation from the midpoint ($p=0.002$), such that RHSS show a leftward deviation while LHSS and controls show a rightward deviation. There is also a significant effect of group on “where” bias ($p= 0.002$), such that RHSS show a “where” bias to the left while LHSS and controls show a “where” bias to the right. Group also has a significant effect on “aiming” bias ($p=0.046$), such that RHSS and controls bias leftward while LHSS bias rightward. Based on prior literature, we expected controls to consistently deviate to the left of the midpoint, a phenomenon known as pseudoneglect. We furthermore predicted LHSS to make leftward errors and RHSS patients to make rightward errors. However, across most conditions, participants consistently deviated from the midpoint in the opposite directions evidenced by prior literature. This suggests that different visuomotor and spatial mapping mechanisms may be at work during the computerized paradigm compared to the paper line bisection task. Future work should validate aspects of the computerized line task and explore underlying neural mechanisms at play within the visual and motor attention networks.

Disclosures: M. Bolden: None. **A. Seydell-Greenwald:** None.

Poster

PSTR136: Visual Cognition: Attention and Decision-Making

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR136.08/Y19

Topic: E.06. Vision

Support: NIH Grant U19NS118246

Title: Causal inference during dynamic navigation: monkey behavior and large-scale cortical recordings

Authors: *V. VENCATO[1], W. CHOI[2], E. FERNANDEZ SANTORO[3], Y. GUO[1], N. J. MAJAJ[2], J. A. MOVSHON[2], D. E. ANGELAKI[4];
[2]Ctr. for Neural Sci., [1]New York Univ., New York, NY; [3]New York Univ., New York,, NY; [4]Dept of Neurosci., Baylor Col. of Med., Houston, TX

Abstract: To navigate a dynamic environment, the brain must infer whether visual motion is caused by self-motion, object motion, or both. Behavioral studies suggest that this problem is solved through causal inference, but the neural mechanisms supporting these computations remain poorly understood. We trained two rhesus macaques to perform a virtual-reality steering task in which a briefly presented target was stationary or moving while animals experienced either no self-motion or simulated yaw rotation. After target disappearance, monkeys navigated with a joystick to the estimated target location. Under yaw, retinal motion no longer uniquely accounts for target motion because self-motion contributes to the target's apparent movement, creating an explicit causal-inference problem. Behavior varied systematically with target velocity and self-motion condition. Relative to no-yaw trials, simulated self-motion biased target-velocity estimates toward stationarity, consistent with a normative causal-inference model in which retinal motion is only partially attributed to self-motion. Human observers performing the same task exhibited similar biases. To investigate the neural basis of these computations, we acquired simultaneous Neuropixels recordings across MSTd, area 7a, area 8Ar, and dorsolateral prefrontal cortex while animals performed the task. Neural populations exhibited robust modulation across observation, navigation, and reward epochs, with activity varying systematically across self-motion and target-motion conditions. Together, these results suggest that cortical populations represent latent beliefs about the causes of retinal motion, distinguishing whether visual motion is attributed to self-motion, object motion, or both during dynamic navigation.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

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Program #/Poster #: PSTR136.09/Y20

Topic: E.06. Vision

Support: HHMI
The Grossman Center for the Statistics of Mind

Title: Single-trial coordination of choice-related activity across lateral intraparietal area and superior colliculus revealed by simultaneous Neuropixels recordings

Authors: *Y. XIE[1], G. VISHNE[2], G. YU[4], B. MADEIRA[3], T. ZHU[1], M. N. SHADLEN[5]; [1]Zuckerman Mind Brain Behavior Inst., [2]Data Sci. Inst. & Zuckerman Mind Brain Behavior Inst., [3]Columbia Univ., New York, NY; [4]Lab. of Sensorimotor Res., HHMI, Columbia Univ., New York, NY; [5]Columbia University/HHMI, NEW YORK, NY

Abstract: Perceptual decisions are thought to arise through the accumulation of sensory evidence to a decision variable that ultimately drives action. In the random-dot motion task, lateral intraparietal area (LIP) activity has long been associated with this accumulation, yet the process involves a broader visuomotor circuit that includes the superior colliculus (SC). Recent recordings suggest that LIP and SC have distinct roles, with SC contributing primarily to decision termination (Stine et al., 2023). For SC to terminate a decision, however, it must have access to - or itself represent - the accumulating decision variable. This predicts that drift-diffusion signatures should be detectable in SC, a prediction that previous lower-density V-probe recordings may have been underpowered to test. Using simultaneous high-density Neuropixels recordings from both regions, we asked whether drift-diffusion signatures are present in both LIP and SC, and how their choice-related activity is coordinated on individual trials. We recorded from LIP and SC simultaneously in one macaque performing a random-dot motion discrimination task. After motion viewing, the animal maintained fixation through a variable delay before reporting its choice with a saccade. We identified choice-related population activity using linear discriminant analysis with 5-fold cross-validation, and transformed decoder filters into activation patterns (Haufe et al., 2014) for interpretability. Choice information was dynamically encoded in both LIP and SC throughout delayed motion decisions. Drift-diffusion signatures were present in both regions during motion viewing (decoding accuracy at 400-500 ms, mean ± SEM across 10 sessions: LIP: 65.7 ± 1.3%; SC: 70.4 ± 2.7%). Projecting single-trial activity onto the choice axis revealed rich temporal structure consistent with evidence accumulation in both regions, extending to SC what had previously been characterized in LIP (Steinemann et al., 2024). Cross-temporal correlations between single-trial projections using the pre-transformed decoding weights revealed temporally structured shared fluctuations across the two areas, with SC activity leading LIP activity in the choice-related subspace. This SC-leading relationship challenges a simple feedforward view in which SC merely executes a decision formed in LIP, and raises the possibility that SC contributes active signals during the accumulation phase itself. Ongoing work aims to compare accumulation and termination signatures across LIP, SC, and pulvinar to characterize the functional architecture of this circuit.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

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Topic: E.06. Vision

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Title: DOI-Induced Infra-Slow Oscillations Modulate Cortical State Dynamics During Sensory Discrimination Task Performance

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Abstract: Infra-slow oscillations (ISO; <.1Hz) represent a fundamental temporal organization of neural activity observed across diverse vertebrate species and throughout multiple levels of the nervous system, from cellular excitability to large-scale cortical networks. Emerging evidence suggests that ISO regulates the excitability landscape in which neural computations occur by coordinating activity across distributed neuronal populations and modulating interactions between local and large-scale networks (Vanhatalo et al., 2004; Hiltunen et al., 2014). Effective sensory perception and decision-making require neural circuits to dynamically balance responsiveness to relevant stimuli with suppression of competing activity. Ongoing fluctuations in cortical state alter neuronal responsiveness, sensory representations, and behavioral performance, suggesting that perception depends on both external sensory input and internal network dynamics (McGinley et al., 2015; Jacobs et al., 2020). Because ISOs occur on a timescale compatible with transitions between functional brain states, they may organize cortical networks into states that optimize sensory processing. Consistent with this idea, ISO can modulate faster neural dynamics within sensory systems, suggesting that ISO phase may influence the computational state of neural circuits and their ability to process incoming information (Orlowska-Feuer et al., 2021). Beyond sensory processing, ISO dynamics may contribute to neural plasticity by regulating the timing and coordination of distributed neuronal ensembles. Recently, our laboratory identified a pharmacological approach to reliably induce ISO in awake behaving mice through the administration of 2,5-Dimethoxy-4-iodoamphetamine (DOI). In this study, mice perform a Go/No-go sensory discrimination task under DOI while simultaneously monitoring calcium imaging, behavioral state, and ISO through pupil dilations. Our results demonstrate that performance is modulated strongly by ISO phase and the phase of the oscillation ‘gates’ sensory decision-making by shaping cortical activity patterns associated with successful perception.

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Poster

PSTR136: Visual Cognition: Attention and Decision-Making

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR136.11/Y22

Topic: E.06. Vision

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Title: Intermittent pre-task light enhances cognitive control and visual strategy

Authors: *D. MAHFOUD[1], R. P. NAJJAR[1,2];
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Abstract: Light modulates cognition through intrinsically photosensitive retinal ganglion cells (ipRGCs), which project to circadian, limbic, and prefrontal networks. Although bright light can acutely improve alertness and mood, it remains unclear whether brief exposure before cognitive testing can influence subsequent performance, and whether these effects are reflected in visual strategy beyond performance metrics. We tested whether intermittent pre-task full-spectrum light enhances cognitive function and task-related oculomotor behavior in healthy young adults. Twenty-four healthy males (28.2 ± 4.4 years) completed a randomized, counterbalanced, within-subject crossover protocol. Afternoon visits were scheduled relative to each participant's actigraphy-derived mid-sleep phase. Participants received two 15-min exposures to either full-spectrum light (FL; 1200 lux; 1100 melanopic equivalent daylight illuminance [mEDI]) or standard indoor light (SL; 380 lux; 230 mEDI), separated by a 10-min interval during which alternate Montreal Cognitive Assessment (MoCA) versions were administered. After exposure, participants completed the Digit Symbol Substitution Task (DSST), Balloon Analogue Risk Task (BART), auditory Psychomotor Vigilance Task (PVT), and auditory Oddball under dim light, with concurrent eye tracking. Mood, wellbeing, and sleepiness were assessed at baseline, immediately post-exposure, and 30 min post-exposure. Outcomes were compared using paired t tests and repeated-measures ANOVA with Bonferroni-corrected post hoc tests. FL selectively enhanced higher-order cognitive outcomes. Compared with SL, FL increased MoCA executive subscores ($p < 0.01$) and DSST accuracy (+1.6 ± 3.7%; $p < 0.05$). Eye tracking during DSST revealed greater digit dwell time (+4.1 ± 9.4%; $p = 0.04$) and more digit fixations (+3.8 ± 8.6%; $p = 0.04$), suggesting increased use of task-relevant visual information. Mood declined 30 min after SL (−0.6 ± 0.7; $p < 0.001$) but was preserved after FL. FL also reduced reward-seeking behavior during BART, indexed by fewer voluntary trials (−4.8 ± 0.2; $p = 0.02$). These effects were not accompanied by changes in PVT reaction time, oddball performance, MoCA attention, or subjective sleepiness (all $p > 0.05$). Brief intermittent full-spectrum light exposure before cognitive testing enhanced executive performance, stabilized mood, and shifted visual attention toward task-relevant information without evidence of generalized arousal effects. These findings suggest that spectrally enriched bright light may prime higher-order cognitive networks before demanding tasks and support more efficient information gathering.

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Poster

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Topic: E.06. Vision

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Title: Neural Dynamics of Cognitive Flexibility Sculpted by Arousal and Behavior

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Abstract: Successful dynamic behavior requires context-dependent flexibility. A particular stimulus may drive a behavior necessary for survival in one context, while that same stimulus may be irrelevant to behavior in another context. In order to achieve such behavioral flexibility, the supporting brain activity must also be flexible and responsive, possessing the ability to adapt on a moment-to-moment time-scale depending on the environment, context, internal states (arousal, attention, etc.) and external states (movement/behavioral state). Sensory-driven behavior is supported by the transformation of sensory representations into motor outputs. This transformation is guided by the current context and is impacted by the neural landscape, shaped by internal and external states. Recently, it has been demonstrated that broad cortical engagement occurs during decision-making task performance (Goard et al. 2016; Allen et al. 2017; Kyriakatos et al. 2017; Wekselblatt et al. 2016; Makino et al. 2017) and arousal and behavioral state strongly impact widespread brain dynamics and sensory responses (McGinley et al. 2015; Drew et al. 2018; Musall et al. 2019; Stringer et al. 2019). Recently, our lab has shown that neuromodulatory activity in cortex, specifically acetylcholine and norepinephrine, is tightly coupled to arousal and behavioral state changes (Collins et al. 2023). Here we utilize various mesoscale calcium imaging techniques with simultaneous monitoring of arousal and behavioral states in mice, while they perform context-dependent sensory discrimination tasks. Using this approach, we identify the widespread cortical interactions that support such cognitive flexibility, addressing how sensory and motor signals are represented and propagated across different contexts, as well as how fluctuations in arousal and behavioral state influence context-dependent task performance and related cortical activity. We also demonstrate how fluctuations in arousal and behavioral state, are accompanied by a remodeling of the cholinergic tone in cortex, which can facilitate or hinder optimal sensory-guided decision-making.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Support: NIH Grant 1RF1NS131984-01
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Title: Movement signaling by locus coeruleus neurons along dorsal-ventral gradient

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Abstract: Arousal and movement are intimately related to activity of the locus coeruleus (LC) norepinephrine system, but relationships between specific features of movement and LC neuron activity remain largely unclear. Recent work demonstrates a dorsal-ventral gradient of LC organization and function, with distinct physiological and genetic properties associated with dorsal neurons projecting to the forebrain and ventral neurons projecting to the hindbrain (Su et al, bioRxiv 2026.04.10.717727). Here, we investigated how LC activity along the dorsoventral axis relates to different aspects of movement, including the overall transition from quiescence to active movement and specific kinematic features.Here, we recorded the single-unit spiking activity of optogenetically identified LC norepinephrine-releasing (LC-NE) neurons in mice performing a “sequence licking” task (n = 152 neurons across both hemispheres). During the task, an auditory cue prompted mice to transition from rest (non-licking) to a task-performing state, directing a sequence of licks to drive a lick port through either a left-to-right or a right-to-left standard sequence. In a subset of trials (25%), mice encountered an unexpected “missed lick,” indicating they had to switch rapidly from the ongoing standard sequence to an alternative sequence, reversing directions from one lick to the next.LC-NE neurons responded robustly to the sequence-initiating auditory cue that changed the body state from quiescent to active movement, and to the rewarded licks that marked sequence termination. In contrast, LC-NE neurons showed mostly weak responses to the mid-sequence omission cue, despite the fact that it required an abrupt switch in the ongoing motor program and, presumably, served as a strong attentional cue or salient event. LC-NE activity therefore bookended periods of active motor engagement. These engagement-linked responses were more prominent among dorsal LC-NE neurons. Activity of LC-NE neurons also showed trial-by-trial correlations with the magnitude of tongue/jaw kinematic parameters, the direction of licking sequence progression, and sequence-start reaction times. These correlations with features of ongoing movement were more prominent among ventral LC-NE neurons.Our data show that LC neurons signal varied and specific aspects of movement—engagement-linked responses that bookend periods of movement and kinematics-

linked responses that report features of ongoing self-motion—and that these signaling properties are segregated along the dorsal-ventral axis. Together these observations imply that LC routes distinct movement signals to forebrain and hindbrain targets.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Topic: F.04. Voluntary Movements

Support: R01NS134968

Title: OROFACIAL MOTOR CORTEX PREFERENTIALLY ENCODES TONGUE POSTURE

Authors: *L. CAMARA[1], S. D. MARTIN[2], N. SENTHIL[3], C. F. ROSS[4], N. G. HATSOPOULOS[1];
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Abstract: Precise control of tongue and hyoid musculature is critical for fundamental behaviors such as feeding and speech production, yet the neural mechanisms underlying control of soft-bodied effectors remain poorly understood. Previous research suggests cortical motor neurons encode movement velocity during reaching arm movements but preferentially encode joint posture over hand movement dynamics during grasping tasks. Given the tongue's role in object interaction and manipulation during feeding, analogous to the hand during grasping, we hypothesized that orofacial motor cortex would preferentially encode tongue postural features over movement dynamics. Here we investigated cortical motor encoding of the tongue by simultaneously recording multicellular neural activity in orofacial primary motor cortex and three-dimensional tongue kinematics using X-ray Reconstruction of Moving Morphology (XROMM) during naturalistic feeding in rhesus macaques. Using regularized Poisson generalized linear models, we found results consistent with our hypothesis that orofacial motor neurons preferentially encoded tongue posture over velocity (Wilcoxon signed-rank test, $p < 0.0001$), replicating across both subjects. Nested model comparisons revealed that detailed kinematic features explained substantially more neural variance than parameters related to gape cycle and magnitude alone, suggesting that neural encoding reflects active control of tongue morphology beyond the rhythmic structure of feeding. These findings indicate that postural encoding is a shared computational principle across cortical motor regions controlling manipulatory movements, whether of the hand or tongue, despite fundamentally different effector biomechanics. Understanding these principles provides insights for developing brain-

computer interfaces for speech restoration and clinical interventions for hyolingual motor dysfunction.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Topic: F.04. Voluntary Movements

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Title: Dynamically coupled control of motor sequencing in a polychronous premotor network

Authors: *J. C. GORMAN[1], L. M. OSTROWSKI[3], E. M. ARNEODO[4], P. TOSTADO MARCOS[2], L. STANWICKS[5], T. GENTNER[6];
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Abstract: Continuous motor behaviors require precise yet flexible coordination between premotor and motor circuits, yet the nature of this coordination across motor networks remains poorly understood. The zebra finch (*Taeniopygia guttata*) song system provides a powerful model to study this coordination in the context of a learned, natural vocal behavior. One long-standing assumption is that song is produced via the premotor region HVC driving activity in its downstream target, the motor region RA, in a strictly feedforward manner. To test this assumption, we recorded simultaneously from large populations of single neurons in HVC and RA during singing (n=3 birds), then used a biophysical network model to understand the empirical HVC-RA dynamics. Canonical correlation analysis (CCA) shows that coordinated activity between the two populations transiently fluctuates with vocal behavior, and is more strongly elevated during song motifs compared to introductory notes and inter-motif gaps (Δ = 0.29, $p < 0.0001$). Decomposing HVC activity into RA-potent (the CCA-aligned subspace) and RA-null (orthogonal) components shows that HVC rotates into the RA-potent subspace during preparatory activity, then progressively rotates out between motifs and across the bout (Mann-Whitney U=1774, p=3.5e-07), indicating multiple regimes of coordination rather than a single feedforward organization. In addition, in a signature of coupled dynamics, canonical HVC-RA correlations peak at zero lag rather than at the positive lag predicted by feedforward drive (CC1 = 0.99 at 0ms lag in all 159 bouts; $p < 10^{-35}$).

We then constructed a biophysical HVC-RA network model that allowed us to compare two possible HVC architectures, polychronous chains (Izhikevich 2006) and synfire chains (Abeles 1991), and to assess the contribution of RA-to-HVC feedback. Only a polychronous HVC architecture with feedback reproduced both the zero-lag CCA peak and the motif-locked elevation of HVC-RA coupling.
Together, these findings argue that song production emerges from a dynamically coupled network spanning HVC and RA, rather than a unidirectional sequence relay, and that polychronous HVC architectures with RA feedback parsimoniously explain how this coupling is implemented at the circuit level.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Topic: F.04. Voluntary Movements

Support: NIH RO1 NS108424
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Title: Imprinting neural sequences into the zebra finch premotor circuit using two-photon optogenetic holography

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Abstract: Neural sequences of activity underlie the precise production of learned motor behaviors. This can be seen prominently in the zebra finch premotor region HVC, which operates with millisecond precision to ensure the stereotypy of adult song. HVC contains two principal classes of projection neurons, intratelencephalic neurons (IT) projecting to a pallial motor 'cortex', and corticostriatal neurons (CST) innervating the basal ganglia. Both populations of neurons produce sparse stereotyped activity during song. However, the underlying circuit architecture of these neuronal groups and their unique contributions to song production remain unclear. Previous circuit models propose that song-generation in HVC relies exclusively on IT neurons, which are hypothesized to be organized in feed-forward excitatory chains. However, we recently found that CST neurons make abundant monosynaptic connections with IT neurons and that both classes of neurons are essential for the progression of song sequences. To better understand the functional network architecture in HVC, we used two-photon optogenetic holography (2pOH) to imprint artificial ensembles of neuronal sequences into IT or CST neuron populations in offline states and examined how these manipulations impacted neuronal network

activity and song production. We found that while both neuronal types displayed an increase in both spontaneous and ensemble member-evoked activity after 2pOH, IT and CST neurons differed in how they responded to tests of pattern completion. IT sequences responded to pattern completion prompts by strengthening responses in the forward direction, whereas CST sequences were more ambiguous in their directionality of responses. This indicates that IT and CST neurons, although interconnected, might differ in their circuit organization motifs. We also found that 2pOH of either group changed the timing of song produced by the birds. Interestingly, we find that CST 2pOH also induces a change in the acoustic properties of song. These changes are not simply reflected in any specific acoustic variable, such as pitch or amplitude, but instead may involve a complex combination of acoustic variables, suggesting the role of HVC in informing higher-order acoustic gestures. These results are coherent with previous studies, which suggest that HVC sequences can encode song timing or acoustic song gestures in their sparse firing during song. Our work shows that this unique application of cellular-resolution, sub-type specific optogenetic holography can be used to understand how neural sequences can uniquely contribute to the production of skilled motor behaviors.

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Poster

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Topic: F.04. Voluntary Movements

Support: NIH/NIDCD R01DC022610

Title: Premotor control of preparatory activity in the gustatory cortex

Authors: *E. BROZOST[1,2], J. CHEN[2], A. BERENJI KALKHORAN[1,2], A. MAFFEI[1,2], A. FONTANINI[1,2];
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Abstract: The gustatory cortex (GC) is involved in processing cognitive signals related to a gustatory experience. In mice engaged in a delayed-response task, where specific tastants guide directional licking, GC's activity progresses from taste coding into preparatory coding predicting lick decisions. While this preparatory and decision-related activity is consistently observed in GC, mechanisms by which GC comes to exhibit this activity remain unclear. A probable candidate in coordinating this activity is the anterior-lateral motor cortex (ALM), given its involvement in the planning and execution of goal-directed licking. In this study, we investigate ALM as a potential modulator of GC preparatory activity in a taste-guided two-alternative choice (2AC) task. We first anatomically identified direct ALM inputs in GC using AAV-based tracing approaches. The synaptic connectivity of this projection was confirmed through patch clamp experiments in brain slices, together establishing functional connectivity of ALM inputs to GC.

We then performed simultaneous electrophysiological recordings to understand the coordination between GC and ALM during 2AC task performance. Results show that ALM neurons exhibit earlier preparatory activity than GC and have higher selectivity for lick direction during the delay period. To determine the impact of ALM preparatory signals on GC activity, we performed transient optogenetic inhibition of ALM during the delay period while recording GC activity. Inactivation of ALM cell bodies, as well as local inhibition of ALM axons in GC, showed reduced preparatory activity and direction selectivity in GC. These results support a role for ALM as a direct source of preparatory signals to GC. Our findings demonstrate that frontal premotor inputs significantly contribute to GC preparatory activity during taste-guided decision making.

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Poster

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Fondation Leducq (22CVD0)
St. Jude Children's Research Hospital

Title: Functional organization of the mouse motor cortices

Authors: *C. L. FREEMAN[1], W. XU[2], A. BISHT[1], L. XU[1], W. LI[1], E. M. C. HILLMAN[1]; [1]Imaging Sci., St. Jude Children's Res. Hosp., Memphis, TN; [2]Columbia Univ., New York, NY

Abstract: Decoding the functional relevance of anatomical brain maps is key to gaining a holistic understanding of neuromotor systems in health and disease. Although mapping of mouse primary sensory cortex (S1) is relatively straightforward, primary motor (M1) and secondary motor (M2) regions are more challenging to map, with most atlases defining coarse regions that lack body-part specificity.
In a recent study, we demonstrated that both sensory and motor subregions can be delineated using in vivo wide-field optical mapping of cortex-wide neuronal calcium in behaving mice performing spontaneous voluntary locomotion. We identified body-part-specific subregions of M2 by recognizing unexpected correlations in neuronal fluctuations between S1 and M2 sub-regions, which were most prominent during resting periods (defined as minimal movement). This 'resting state functional connectivity' was closely matched by physical connectivity between S1 and M2 regions revealed by anterograde cortical viral tracing. Although this work identified

hindpaw and forepaw M1 regions using retrograde viral injections targeting corticospinal neurons, it raised important questions about the body-part topography and interconnectivity of other M1 regions, particularly those associated with facial regions such as the whiskers, nose and mouth.
Here, we extend this study to explore discontinuities in functional connectivity across the cortex, revealing a foundational distinction in sensory and motor maps between the spinal regions (spanning tail, trunk, hindpaws, and forepaws) and the cranial / orofacial regions (including whisker, nose, and mouth). We find that separations between these two cortical strips in S1 are mirrored in M2. Moreover, although our previous study confirmed that forepaw and hindpaw M1 regions are closely adjacent and medial to hindpaw and forepaw S1 regions, our new results suggest an alternative (yet synergistic) organizational relationship between S1, M1 and M2 regions for cranial / orofacial regions. We validate this new organizational structure using functional imaging, and demonstrate the ability to predict spontaneous behavior from cortical recordings spanning S1-M1 and M2. We further explore how these functional and behavioral mappings are impacted in altered physiological and disease states as a step towards understanding how movement disorders are represented across the neuromotor system. Finally, we present an open-source interactive tool that permits high-fidelity analysis of state-dependent functional connectivity relationships across the cortex.

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Poster

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Support: NIH GRANT R01NS129576

Title: A thalamocortical communication subspace for skilled locomotion

Authors: *K. CAI, E. KIRK, B. SAUERBREI;
Case Western Reserve Univ., Cleveland, OH

Abstract: To control locomotion over complex terrain, motor cortex must transform inputs conveying information about the environment and the state of the body into descending commands which modify muscle activity. While prior studies have reported firing patterns in thalamic and cortical regions during locomotion, the population-level signals transmitted from thalamus to the cortex remain unclear. To address this question, we used Neuropixels 2.0 probes to record from ensembles of thalamic and motor cortical neurons in freely-moving mice trained to step over an obstacle while trotting on a treadmill. Thalamic units were recorded in the ventral anterior lateral complex (VAL), which receives cerebellar and basal ganglia input and projects

strongly to the motor cortex, and the posterior complex (PO), a higher-order nucleus involved in sensorimotor processing. Unit locations were verified by registering histological sections to the Allen Mouse Brain Common Coordinate Framework. Data were segmented into sequences of seven steps, where the fourth traversed the obstacle. Sequences were then grouped based on whether the first limb to cross the barrier was contralateral (lead condition) or ipsilateral (trail condition) to the probe. At the single neuron level, activity in VAL and PO was strongly modulated by locomotor phase (87% and 85%) and by the interaction between step number and lead / trail condition (79% and 82%). Because firing patterns in VAL and PO were highly similar, units were pooled for subsequent analysis. At the population level, the dominant factors identified with principal component (PC) analysis were near-sinusoidal (PCs 1-2, 20% and 14% of variance), and were followed by smaller, transient signals synchronized with obstacle proximity (PCs 3-4, 13% and 11%). To determine what signals are transmitted from the thalamic population to cortex, we modeled the relationship between these areas using reduced rank regression, which extracts a low-dimensional channel, or communication subspace, through which thalamocortical signals flow. The largest signals in this subspace did not resemble the largest, oscillatory PCs in thalamus, but were instead brief transients occurring immediately before or throughout obstacle traversal. Correspondingly, the thalamic factors which communicated the highest variance to cortex were not the large, sinusoidal PCs (1-2), but the smaller, transient PCs (3-4). In conclusion, these results identify a communication subspace which amplifies transient thalamic signals as the animal approaches an obstacle, and which conveys this salient information to motor cortex, enabling it to generate appropriate corticospinal commands.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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F31 NS147704-02

Title: Pontine Integration of Cortical Inputs Relates to Movement Dynamics

Authors: *R. B. SHUGG[1], A. J. KHALIL[2], V. MENON[4], S. SPIJKER[3], H. D. MANSVELDER[2], J. D. COHEN[5], S. M. LEMKE[6], J. GUO[1], L. WITTER[7], A. W. HANTMAN[5]; [1]Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [3]Ctr. for Neurogenomics and Cognitive Res., [2]Vrije Univ. Amsterdam, Amsterdam, Netherlands; [4]Neurol., Columbia Univ., New York,

NY; [5]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [6]Univ. of North Carolina, Chapel Hill, NC; [7]Univ. Med. Ctr. Utrecht, Utrecht, Netherlands

Abstract: The cortico-cerebellar pathway is essential for the precise execution of skilled movements. Cortical signals reach the cerebellum primarily through the basilar pontine nuclei (bPN), making the bPN central to understanding how motor-related cortical activity is processed before cerebellar computation. As a major anatomical bottleneck, the bPN has often been viewed as a relay, in part because its inputs from different cortical regions are organized into distinct terminal zones. However, we found anatomical evidence that suggests that some bPN neurons may integrate across these zones, as their dendritic arbors extend beyond the boundaries of individual cortical terminal zones. These observations raise the possibility that the bPN not only relays segregated cortical inputs, but also combines and transforms them before they reach the cerebellum. Here we test whether individual bPN neurons integrate inputs across cortical sites, and whether this integration shapes skilled-movement dynamics.
To address this, we trained mice to perform a dexterous reach-to-grab task wherein mice reach for a food pellet upon presentation of an auditory cue. After mice achieved high performance, we made large-scale electrophysiological recordings in the ipsilateral bPN during task execution. During the same recordings, we used single- and dual-fiber optogenetic stimulation of distinct somatomotor cortical areas in Slc17a7-IRES2-Cre; Ai32 mice to test how pontine neurons integrate cortical inputs.
We found that a subset of bPN neurons received input from more than one cortical stimulation site. This convergence was reflected in the timing of movement-related neural dynamics. Highly convergent neurons were recruited earlier in the movement sequence than less convergent neurons. To determine how these inputs are combined, we examined neuron responses to dual-site cortical stimulation. Rather than summing linearly, coincident activation of cortical inputs typically produced sublinear responses, indicating suppressive integration within the bPN. Additionally, the more cortical sites a neuron responded to, the stronger the suppression. Together, these findings support a model in which inhibition within the bPN transforms convergent cortical inputs, shaping pontine dynamics before cerebellar processing.

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Poster

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Topic: F.04. Voluntary Movements

Support: Multidisciplinary Frontier Brain and Neuroscience Discoveries (JP24wm0625315)

Title: Parietal-dominant contralateral bias in cervical-projecting cortical neurons in macaques

Authors: *M. SUZUKI[1], K. KOBAYASHI[2], Y. NISHIMURA[3];
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Abstract: The corticospinal tract is a major pathway for voluntary limb control in primates, with cortical origins distributed across frontal and parietal areas. However, the regional composition and hemispheric asymmetry of cervical-projecting cortical neurons have not been fully quantified across these cortical sources. To address this issue, we examined cortical neurons retrogradely labeled after unilateral injection of the viral vector AAV2retro into the cervical spinal cord (C7-C8) in six macaque monkeys. Labeled neurons were counted bilaterally across frontal motor-related and parietal somatosensory/association areas. Regional composition was calculated as the proportion of all labeled neurons across both hemispheres, and hemispheric asymmetry was quantified using a laterality index, defined as (contralateral − ipsilateral)/(contralateral + ipsilateral). Labeling was strongly biased toward the hemisphere contralateral to the injection side: 90.8 ± 2.5% (mean ± sem) of labeled neurons located contralaterally, and the overall laterality index was 0.82 ± 0.05. The labeled population was dominated by contralateral M1, which accounted for 53.1 ± 2.1% of all labeled neurons. Contralateral S1 and area 5 also contributed to the labeled population, accounting for 19.3 ± 2.1% and 5.6 ± 1.2%, respectively. Ipsilateral labeling was substantially smaller and was dominated by M1 (7.3 ± 2.2%), whereas ipsilateral S1 (0.4 ± 0.1%) and area 5 (0.1 ± 0.1%) contributed minimally. The degree of hemispheric asymmetry differed between frontal and parietal areas. Parietal areas showed consistently strong contralateral bias, with laterality indices of 0.96 ± 0.01 in S1, 0.96 ± 0.01 in area 5, and 0.98 ± 0.02 in area 7. In contrast, frontal motor-related areas showed weaker and more variable laterality, including M1 (0.76 ± 0.06), PMd (0.73 ± 0.15), PMv (0.88 ± 0.05), SMA (0.79 ± 0.11), and CMA (0.71 ± 0.11). Area-wise comparison confirmed greater contralateral bias in parietal than frontal areas (mean difference, 0.194 ± 0.060; two-sided sign-flip permutation test, p = 0.031).These findings demonstrate that hemispheric asymmetry of cervical-projecting cortical neurons with parietal regions exhibiting stronger contralateral dominance than frontal motor-related regions.

Disclosures: M. Suzuki: None. **K. Kobayashi:** None. **Y. Nishimura:** None.

Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Program #/Poster #: PSTR137.10/Z1

Topic: F.04. Voluntary Movements

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the National Institute of Neurological Disorders and Stroke (NIH R01 NS134634 and NIH UF1NS126485, A.L.O.)

Title: Condition-invariant signals in frontal motor cortices are shared between the reaching and the saccade tasks

Authors: *T. OUCHI[1], R. CANFIELD[2], L. R. SCHOLL[1], A. L. ORSBORN[1];
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Abstract: Neural control of reaching has distinct stages: preparation, movement initiation (trigger), and execution (Churchland 2024). Neural population activity in the premotor (PMd) and primary motor cortex (M1) consistently rise just prior to reach onset, regardless of the upcoming reach direction (Kaufman 2016). These condition-invariant signals (CIS) are thought to reflect a trigger signal that serves to transition neural states from movement preparation to execution. Yet, behaviorally, hand and eye movements are tightly coordinated during reaching: saccades typically initiate just before reach onset, and saccade and reach reaction times (RTs) are highly correlated (Dean 2011). Despite these tight behavioral links, CIS have largely been studied in the context of the reach system. To better understand the role of CIS, we investigated how CIS relate to both reach and saccade initiation. We trained one male monkey to perform two tasks on the same day: a reaching task with uncontrolled eye locations and a saccade task with controlled hand locations. The reaching task required arm movements to one of 8 peripheral targets from a central starting location without any fixation requirement. The saccade task required a saccade to one of 3 eye targets from one of 3 starting eye locations, with hand position controlled across trials. We recorded neural activity using a Neuropixels probe in PMd and M1, separately (PMd: N=82, M1: N=132). We then applied demixed principal component analysis to identify dPCs of CIS for each task. In the reaching task, saccade and reach RTs were correlated, consistent with Dean (2011). Next, we examined whether dPC1 could predict reach and saccade RTs in both tasks. Threshold-crossing time (CT) was defined as the time when normalized dPC1 exceeded a threshold. In the reaching task, CT in dPC1 was correlated with both reach and saccade RTs. In the saccade task, where no reach was required, the CT also predicted saccade RTs. We asked whether the CIS was similar across tasks and brain regions (PMd vs. M1) using canonical correlation analysis (CCA; Gallego 2017). We compared across-task CCA (CCA between different tasks) with within-task CCA (CCA between non-overlapping trials from the same tasks). We applied a similar analysis to compare across- and within- brain region CCA. We found that across-task CCA was comparable to within-task CCA. Across-region CCA was also nearly as high as within-region CCA. Together, these results suggest CIS may reflect a shared internal trigger across multiple frontal cortical areas regardless of the movement effector. Our findings provide new insights into how CIS in PMd and M1 contribute to movement initiation across effectors.

Disclosures: T. Ouchi: None. **R. Canfield:** None. **L.R. Scholl:** None. **A.L. Orsborn:** F. Consulting Fees (e.g., advisory boards); Meta Reality Labs, EpiaNeuro.

Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Program #/Poster #: PSTR137.11/Z2

Topic: F.04. Voluntary Movements

Support: NIH Grant R01NS129576-03

Title: Cortical sculpting of a rhythmic motor program

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Abstract: The standard model of motor cortex maintains that muscle activity is a function of cortical firing rates. This model has successfully explained the control of voluntary movements such as reaching, but fails when cortex must interact with a spinally-generated rhythm. During locomotion, the basic motor rhythm is produced by spinal networks, and cortex acts to further change muscle activity in response to environmental challenges, like when stepping over an obstacle. Here, we show that motor cortex is necessary for performing this task: cortical lesions selectively disrupt kinematics in the contralateral forelimb when the animal attempts to step over an obstacle while trotting on a treadmill. In this task, information about obstacle proximity and the locomotor phase must be transformed into descending commands that alter motor output. To determine how the brain implements this computation, we recorded activity in mouse forelimb motor cortex using chronically-implanted Neuropixels 2.0 probes. Neurons in motor cortex display rhythmic activity locked to stepping, transients near the obstacle, or complex mixtures of these patterns. At the population level, activity is dominated by a preparatory factor synchronized with obstacle proximity, independently of which limb crosses the obstacle first. This factor is robust to removal of whisker or visual information, suggesting it reflects motor preparation, instead of sensory input. Next, we identify rhythmic factors synchronized with the locomotor pattern. Comparison of activity during active locomotion with passive cycling suggests these factors are driven mainly by an efference copy from the spinal rhythm generator, rather than sensory feedback. Readout factors representing voluntary changes in muscle activity account for a small fraction of the total firing rate variance. Finally, we propose a simple model which transforms rhythmic input conveying locomotor phase and transient input signaling obstacle proximity into descending commands. These commands are integrated with central pattern generator signals at the spinal level to produce the final motor output in the task.

Disclosures: E. Kirk: None. **K. Cai:** None. **B. Sauerbrei:** None.

Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR137.12/Z3

Topic: F.04. Voluntary Movements

Support: Ciencia Básica A1-S-8686 (GR-P)
UNAM-DGAPA PAPIIT IN201121 (GR-P)
UNAM-DGAPA-PAPIME PE205821 (RO-M)

Title: From Single Cells to Population Dynamics: Intrinsic and Extracellular Characterization of Corticospinal and Corticorubral Neurons

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Abstract: *Introduction.* The specific roles of distinct subtypes of pyramidal tract neurons (PTNs) in movement control within the sensorimotor cortex remain largely unknown. In this study, we examined the electrophysiological properties of two classes of PTNs: corticospinal (CS) neurons, which project to the spinal cord, and corticorubral (CR) neurons, which project to the red nucleus, aiming to characterize their distinct extracellular and intrinsic properties.*Methods.* To evaluate extracellular electrophysiological properties, we performed *in vivo* phototagging experiments targeting CS or CR neurons in the primary motor cortex of anesthetized rats. We analyzed the differential features (including spontaneous and evoked activity, firing rates, and response latencies) of all photoidentified units. Additionally, to assess intrinsic membrane properties and firing dynamics, we conducted whole-cell patch-clamp recordings in acute brain slices targeting CS and CR neurons retrogradely labeled with retrobeads. *Results.* At the single-cell level, we observed significant differences in their individual biophysical properties. Specifically, corticorubral (CR) neurons exhibited a significantly higher membrane resistance and a lower current threshold for first action potential generation compared to corticospinal (CS) neurons, indicating a state of higher intrinsic excitability. Furthermore, our network-level analysis revealed that population dynamics widely diverged between the two pathways. Together, this combinatorial approach reveals a clear divergence in both cellular and population-level features between these two major motor outputs.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

Location: WCC Halls A-C

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Topic: F.04. Voluntary Movements

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ASAP Grant ASAP-020572
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Title: Emergence of Task-Related Motor Cortical Dysfunction in Mice with Progressive Parkinsonism

Authors: *H. CHEHADE[1], D. BEREZHNOI[2], S. SOMAVARAPU[2], Z. WANG[4], J. JIANG[4], L. CHEN[2], B. RISK[4], T. WICHMANN[5], H.-Y. CHU[3];
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Abstract: There are substantial functional changes in the primary motor cortex (M1) in Parkinson's disease (PD). However, the temporal relationship between midbrain dopaminergic (DA) neurodegeneration, M1 circuit dysfunction, and Parkinsonian motor symptoms remains poorly understood. Using a genetic mouse model of progressive nigrostriatal DA degeneration ("MitoPark" mice), we determine the time course of M1 cellular dysfunction and skilled movement impairment as the midbrain DA neurons gradually degenerate. M1 pyramidal neuronal subtypes were identified using AAV-mediated retrograde labeling. During progressive DA loss, MitoPark mice developed gradually impaired performance in a reach-to-grasp single-food-pellet task. These impairments were detectable at a moderate motor stage of Parkinsonism. In vivo GCaMP6f imaging revealed that impaired skilled movement was associated with reduced cellular activity and movement responsiveness of M1 pyramidal neurons at a moderate motor stage of Parkinsonism. While both the corticospinal (CSp) and intratelencephalic (IT) neurons send glutamatergic inputs to the striatum, only the CSp neurons showed a selective and significant reduction in cellular activity and movement responsiveness during reaches. At the population level, we found that M1 pyramidal neurons include heterogeneous functional clusters with distinct temporal profiles in response to skilled movement. While movement encoding by different functional clusters is longitudinally stable in control mice, it degrades and diverges significantly in MitoPark mice. The impaired stability is further supported by a longitudinal analysis of individual neuronal activity related to movements. Together, these results provide novel insights into the emergence of M1 circuit pathophysiology at cellular and neural population levels during progressive Parkinsonism.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR137.14/Z5

Topic: F.04. Voluntary Movements

Support: R01NS134968

Title: Bilateral coordination of orofacial motor cortex during naturalistic feeding in the macaque

Authors: *S. D. MARTIN[1], L. CAMARA[1], N. G. HATSOPOULOS[2], C. F. ROSS[2];
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Abstract: Cortical control of jointed limbs has been characterized in extensive detail, but cortical control of the tongue remains poorly understood despite its central role in feeding, swallowing, and speech. The tongue poses a problem with no clear analog in the limb literature: as a midline effector, its movement is represented in orofacial motor cortex (M1o) of both hemispheres, and neurons in each M1o project to both sides of the hypoglossal nucleus, requiring integration of control signals across hemispheres. How motor control is distributed between the two M1o hemispheres, and how their activity is functionally coordinated, remains unresolved. Existing evidence is conflicting: anatomical tracing and TMS studies indicate a contralateral bias, and unilateral lesions produce lateralized lingual deficits, yet fMRI shows bilateral activation and whole-tongue shape can be decoded with high accuracy from unilateral M1o activity. To address this directly, we simultaneously record neural activity from bilateral M1o, together with bilateral lingual EMG and 3D tongue kinematics (via X-ray Reconstruction of Moving Morphology, XROMM), in rhesus macaques during an untrained, naturalistic feeding task. This combined preparation lets us ask two questions that have not previously been accessible at single-unit resolution. First, how is information about tongue movement and muscle activity distributed across the two hemispheres? We hypothesize that each hemisphere carries information about the entire tongue, with a contralateral bias that is most pronounced in the muscle-activity domain and during swallowing. Second, how is activity in the two hemispheres coordinated across the feeding sequence? We hypothesize that interhemispheric coordination is behaviorally modulated, strengthening during the rhythmic phases of mastication and swallowing, where bilateral coordination is essential, relative to non-rhythmic phases dominated by lateralized voluntary movement. This work aims to provide the first direct account of how bilateral motor cortex coordinates control of a midline effector, extending the cortical motor control framework beyond the jointed-limb model into the orofacial domain.

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Poster

PSTR137: Cortical Planning and Execution: Animal (Behavior/Physiology/Imaging) II

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Program #/Poster #: PSTR137.15/Z6

Topic: F.04. Voluntary Movements

Support: NIH R01 NS133403
NIH R01 NS131466
NIH T32 HD057850

Title: Inactivation of Premotor Cortex Disrupts Recovery-Associated Reorganization of Spared Sensorimotor Populations After Stroke

Authors: *M. NISHIMOTO[1], S. GHOLITABAR[2], P. B. NELSON[5], H. M. HUDSON[3], A. G. ROUSE[4], D. J. GUGGENMOS[3];
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Abstract: Stroke impacts over 800,000 people in the United States annually, leaving many survivors with lifelong motor impairments that can severely diminish quality of life. Strokes affecting the primary motor cortex (M1) can disrupt corticospinal pathways necessary for the execution of skilled movement, often manifesting in hemiparesis and other sensorimotor deficits. Interestingly, spontaneous motor recovery can still occur despite the loss of M1. Although extensive post-stroke reorganization within spared premotor cortex (PM) supports a PM-driven hypothesis of recovery, it is unclear how population-wide changes in PM activity relate to recovery of sensorimotor function. To determine the role of PM in post-stroke motor recovery, we performed a longitudinal study in Long-Evans rats using an ischemic stroke model to unilaterally damage M1. Rats were trained on an automated, skilled pellet retrieval task for the assessment of behavioral performance and task-alignment of neural activity. Rats were chronically implanted with microwire arrays in ipsilesional PM and primary somatosensory (S1) cortices prior to injury. Following stroke induction, PM was temporarily inactivated in a subgroup of animals for three weeks via continuous infusion of muscimol (1 mg/mL @ 1 μL/hr), a GABAA receptor agonist that suppresses local neural activity. Behavioral and neural recordings were collected pre-injury and biweekly for two months following stroke induction. Task-related population activity within the spared PM-S1 network was characterized by neural trajectory analyses. Dimensionality reduction techniques were used to better capture recovery-associated changes in within- and between-area population structure. M1 stroke alone induced significant behavioral deficits in the pellet retrieval task. M1 injury coupled with PM inactivation increased impairment on task-initiation and motor performance, resulting in delayed motor recovery relative to non-muscimol controls, with recovery aligned with the cessation of muscimol infusion. Although global grasp-aligned population activity was broadly preserved across sessions, preliminary neural trajectory analyses revealed recovery-dependent changes in PM-S1 population structure. Specifically, we observed an increase in neural dimensionality during recovery, which was attenuated by temporary PM inactivation. Collectively, these results emphasize PM's critical role in post-stroke behavioral recovery and the recovery-associated reorganization of task-related activity within spared PM-S1 populations.

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Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

Location: WCC Halls A-C

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Program #/Poster #: PSTR138.01/Z7

Topic: F.05. Brain-Machine Interface

Support: NIH R01NS094396
NIH R01NS115707
NIH R01NS129632
NIH R01NS105691
NIH F31NS145596
NIH F31NS125982
NSF CAREER CBET 1943906

Title: Implanting microelectrodes near but avoiding descending arterioles reduces blood-brain barrier damage and improves chronic recording performance

Authors: *A. M. FORREST, K. C. STIEGER, G. ZHANG, H. CHO, K. CHEN, S. M. WELLMAN, J. R. ELES, T. D. KOZAI;
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Abstract: Brain-computer interfaces (BCIs) often use implanted microelectrodes to record neural activity. Decoding performance of this activity can decline over time due to silencing or death of nearby neurons. Neurons near the electrode may be negatively impacted by blood-brain barrier (BBB) damage resulting from the implantation injury. Here, we asked how electrode implantation strategies that vary the degree of vascular injury impact chronic tissue health and device performance. Mice were implanted in visual cortex by either inserting through a penetrating arteriole (targeted), near but avoiding a penetrating arteriole (avoided), or into a capillary bed without large vessels (capillary). Visually evoked electrophysiology recordings were collected for 20 wk, followed by post-mortem histology on a subgroup of animals. A second cohort perfused at 24 h after implantation was also analyzed. Average single unit yield in the targeted group was significantly lower than the avoided group from 7 - 20 wk (targeted: 14.3% ± 10.1%, capillary: 37.3% ± 14.0%, avoided: 50.0% ± 20.5%, N = 5 per group; ANOVA: $p = 0.012$, Tukey HSD: avoided vs targeted, $p = 0.009$; capillary vs targeted, $p = 0.088$; avoided vs capillary, $p = 0.422$). Insertion strategy was a significant predictor of background-normalized IgG intensity at 24 h (LME, $p<0.001$). Within 50 μm of the electrode, the capillary group exhibited the highest average IgG intensity (targeted: 4.14 ± 1.21, capillary: 6.38 ± 3.74, avoided: 2.40 ± 0.43, N = 4 per group). However, this result was not statistically significant (ANOVA: $p = 0.097$) likely due to low sample size and high variability in the capillary group. Insertion strategy also significantly predicted background-normalized IgG intensity at 20 wk (LME, $p=0.004$) with the capillary group having the highest mean IgG intensity. We observed reduced normalized neuronal density within 50 μm of the electrode at 20 wk (targeted: 62.7% ± 12.4%, N = 3; capillary: 63.3% ± 25.8%, N = 4; avoided: 67.6% ± 30.4%, N = 4). Distance from the electrode had a significant effect on neuronal density (LME: $p = 0.006$), however, insertion

strategy had no effect (p = 0.885) and no significant interaction with distance (p = 0.961). These results suggest that implanting near but avoiding penetrating arterioles may help mitigate declines in signal detection and reduce disruption to the BBB compared to implanting through arterioles. Given that insertion strategy had no significant impact on neuronal density, recording performance differences are consistent with silencing of these neurons rather than cell death. Identifying methods to minimize BBB disruption may reduce silencing and improve chronic device performance.

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Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR138.02/Z8

Topic: F.05. Brain-Machine Interface

Support: 5R01NS105691-07
5R01NS129632-03

Title: Vibrational insertion of intracortical microelectrode does not yield significant differences in microglial response and recording performance.

Authors: *V. SINGH[1,2], T. THAI[1,2], N. AIZEZI[1], J. GREASER[3], G. ZHANG[1], R. BAGWELL[3], M. L. MULVIHILL[3], T. D. KOZAI[1,2];
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Abstract: Microelectrodes are used as both therapeutic and experimental tools in neuroscience research. The insertion of microelectrode arrays causes tissue damage and glial scarring, which can degrade electrode signal quality. Electrode-tissue friction during insertion imposes structural strain contributing to the overall injury, motivating the use of high-frequency vibrational insertion. Vibration may limit insertion-related damage by reducing tissue displacement caused by the friction. To investigate this, we compared vibrational insertion (20 kHz, ~5 μm axial displacement, 0.05 mm/s insertion velocity) against direct insertion using a 4-shank, 16-channel Michigan-style array implanted at a 30° angle from the cortical surface into the left visual cortex with dura removed. Cx3cr1-GFP/Thy1-jRGECO1a mice (n = 6 vibration, n = 7 control) were used to enable simultaneous imaging of microglial dynamics and neuronal calcium activity. Two-photon imaging, electrophysiological, and impedance recordings were acquired on days 0, 1, 2, 3, 7, 14, 21, and 28 post-implantation and compared using a mixed-effects model with Holm-Sidak correction for multiple comparisons. Microglial probe coverage was calculated at each time point to quantify the evolution of glial scarring, and transitional and directionality

indices were used to track the polarization of microglial processes toward the electrode over time. Electrophysiological recording quality was assessed via single-unit site yield, noise floor, and impedance. Vibrational insertion produced no measurable difference in tissue response or recording quality relative to direct insertion across the 28-day period. Across all time points, microglial probe coverage ($p = 0.233$), transitional index ($p = 0.070$), directionality index ($p = 0.097$), single-unit yield ($p = 0.368$), noise floor ($p = 0.490$), and impedance ($p = 0.437$) were not significantly different between groups. On day 28, microglial probe coverage was $37.5 \pm 3.72\%$ vs. $31.1 \pm 1.80\%$ ($p = 0.176$), transitional index was 0.948 ± 0.017 vs. 0.996 ± 0.036 ($p = 0.289$), and directionality index was 0.961 ± 0.030 vs. 0.972 ± 0.044 ($p = 0.843$). Single-unit site yield ($75.0\% \pm 7.66\%$ vs. $66.9\% \pm 3.06\%$, $p = 0.120$), noise floor ($4.654\mu V \pm 0.362\mu V$ vs. $4.577\mu V \pm 0.260\mu V$, $p = 0.867$), and impedance ($0.738M\Omega \pm 0.087M\Omega$ vs. $0.629M\Omega \pm 0.100M\Omega$, $p = 0.633$) were also not significantly different. These results demonstrate that vibrational insertion at these parameters introduces no detectable detriment to tissue response or recording performance, supporting its continued use in flexible electrode deployment and other implantation contexts where its mechanical advantages are desired.

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Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR138.03/Z9

Topic: F.05. Brain-Machine Interface

Support: NIH NINDS
NSF NCS
Simons Foundation
NIH MSTP T32

Title: Uncoupled learning across motor cortical areas

Authors: *N. FREEDMAN[1], S. SNYDER[3], E. R. OBY[5], A. P. BATISTA[4], B. M. YU[6], S. M. CHASE[2];
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Abstract: The brain is endowed with a remarkable ability to learn. Changes in neural activity which support learning are often wide-spread throughout the cortex and depend on interactions between functionally related areas. However, it remains unclear whether learning-related

changes in activity are always coupled between interacting cortical areas that support the learned behavior. One possibility is that activity may be coupled, changing in tandem regardless of an area's direct influence on behavior. Alternatively, area-specific (i.e., uncoupled) changes may arise to support learning in accordance with their direct behavioral relevance. We pursued this question in dorsal premotor cortex (PMd) and primary motor cortex (M1), two regions which interact throughout motor behavior and learning. It is challenging to distinguish between the two possibilities in natural movement paradigms because the precise relationship between PMd/M1 neurons and natural movement is typically unknown. Without knowledge of the behavioral relevance of PMd/M1 neural activity, it is difficult to determine if uncoupled changes in neural activity within each area support learning. To overcome this hurdle, we used a brain-computer interface (BCI) paradigm in which we can define a causal relationship between recorded neural activity and BCI cursor movements. Monkeys controlled a BCI using only M1 activity while PMd activity was simultaneously and passively recorded. Following practice with an intuitive BCI mapping, animals were challenged to learn a novel M1 BCI mapping which required changes to M1 activity for proficient control. No explicit demands were placed on PMd activity throughout the experiment and we observed how neural activity changed in both areas as animals learned the novel M1 BCI mapping. First, we asked if PMd neural activity changed while the animal learned, despite those changes not being required for task success. Activity changed in both PMd and M1 as behavior improved through the novel mapping. We next tested if changes in PMd and M1 were coupled by estimating the interaction structure between the areas before learning and then assessing if changes in one area could be explained by the other after learning. Each area exhibited changes that were not reflected in the other area. Finally, we asked whether the uncoupled changes in M1 were behaviorally relevant and found that changes in M1 activity which were not coupled with PMd were important for learning. Together, our results demonstrate that some learning-related changes in M1 neural activity may be uncoupled from PMd and suggest that interacting cortical regions may undergo area-specific changes to solve learning problems.

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Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

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Topic: F.05. Brain-Machine Interface

Support: NIH Grant 1U01NS126052-01
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Title: Optimized Spacing of Ultra-Microelectrodes for Sensory Discrimination

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Abstract: Intracortical microstimulation (ICMS) involves directly activating neural tissue to modulate or produce experiences, which can restore sensory function when implanted in the visual or somatosensory cortices. However, current microelectrode technology used to interface with the brain is limited by the foreign body response (FBR). The FBR encapsulates the device in glial scarring, leading to reduced quality of recorded signals and other failure modes. Literature has established electrodes with subcellular dimensions, or ultra-microelectrodes, can reduce the severity of the FBR (Luan et al, 2017). This work aims to establish amplitude-dependent optimized spacing between ultra-microelectrodes to reduce overlapping neuronal activation of ICMS and achieve sensory discrimination. Ultra-microelectrode devices were custom designed alongside NeuroNexus Inc., with 24 planar gold contacts of 5 or 10 μm diameters coated in sputtered iridium oxide film (SIROF). The electrodes were implanted to a depth of 1750 μm in the somatosensory cortex of 6 Sprague-Dawley rats. Stimuli were delivered to electrode sites at 200 Hz using 650 ms pulse trains with 0.2 ms phase duration and 0.04 ms interpulse intervals. Amplitude varied between trials to test amplitude effects on spatial thresholds, but the total charge injected per electrode site was kept below the maximum charge density to avoid tissue or electrode damage. Spatial thresholds were determined through a modified conditioned avoidance behavioral paradigm (Kunigk et al, 2022). In short, water-deprived rats were trained to stop licking a spout when they detected a difference in spatial distance to avoid a mild cutaneous shock. An adaptive algorithm adjusted this difference based on animal performance until a threshold was reached. Safe and warning trials were pseudo-randomly dispersed to monitor licking patterns. Behavioral responses to neural stimulation through ultra-microelectrodes were observed over 5 months. Increasing amplitude led to increased spatial thresholds on all contact sizes, which aligns with literature on the spatial volume of activation increasing with amplitude (Kumaravelu et al, 2022). These results highlight the feasibility of ultra-microelectrodes to elicit functional behavior in rodents with extremely low currents and high spatial resolution over chronic time periods.

Disclosures: E.T. Su: None. **E. Papez:** None. **B. Stettler:** None. **E. Muntean:** None. **K.J. Otto:** None.

Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR138.05/Z11

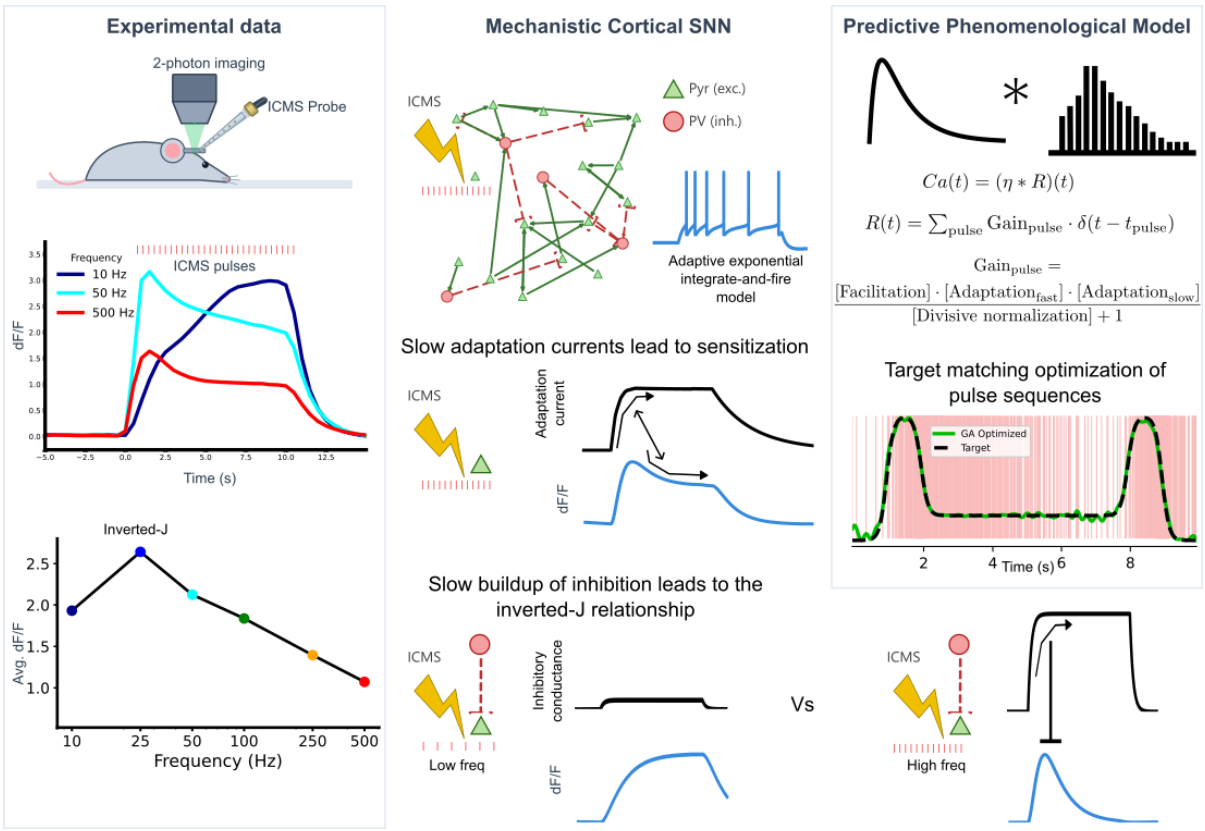
Topic: F.05. Brain-Machine Interface

Support: Pitt Momentum Funds
Pittsburgh Integrated Translational Neuroscience Institute (PIT-NI) funding

Title: Mechanistic and predictive modeling of cortical adaptation during prolonged intracortical microstimulation

Authors: *A. KUMAR[1], A. VAZQUEZ[2], B. M. HOOKS[3], O. A. GHARBAWIE[3], R. A. GAUNT[4], T. D. KOZAI[5], C. HUANG[6,7];
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Abstract: Intracortical Microstimulation (ICMS) is a vital technique for providing artificial sensory feedback in Brain-Machine Interfaces (BMIs) and sensory restoration paradigms. However, the precise network mechanisms underlying ICMS remain poorly understood, particularly regarding the phenomenon of perceptual fading during prolonged stimulation. To decode and predict evoked network dynamics, we developed biologically inspired spiking neural network (SNN) and predictive models of the cortical microcircuitry. These models were constrained using in-vivo calcium fluorescence data recorded from pyramidal neurons in the visual cortex of awake, head-fixed mice across a wide range of stimulation frequencies (10 Hz to 500 Hz). Our SNN models demonstrate that a slow adaptation process, coupled with a temporal buildup of synaptic inhibition, accounts for both the observed population-level adaptation and the characteristic inverted-J relationship between neural response and ICMS frequency. Interestingly, the optimal ICMS frequency was dependent on the relative recruitment of excitatory versus inhibitory neural populations. Concurrently, our predictive phenomenological model achieved a high goodness of fit ($R^2 = 0.98$) to the population-averaged calcium responses. Virtual ablation of distinct model components demonstrated how these components underlie different aspects of the neural response: removing facilitation eliminated the slow sensitization observed at low frequencies; omitting resource-dependent adaptation parameters abolished the rapid initial increase and subsequent desensitization; and removing divisive normalization resulted in a loss of cross-trial adaptation. These findings offer a quantitative and mechanistic framework to overcome adaptation-induced perceptual fading, paving the way for dynamically optimized stimulation protocols and more robust, reliable BMI applications.



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Poster

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Topic: F.05. Brain-Machine Interface

Support: Blackrock Neurotech
NIH BRAIN Initiative UG3NS107688

Title: Improved Reactive Accelerated Aging Station with Electrochemical Closed Loop Control

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Abstract: *Introduction:* Implanted brain-computer interfaces (BCIs) record and stimulate neurological sensory and motor signals to treat neural disorders. Maintaining long-term (>5 year) performance of implanted microelectrode technologies continues to be a challenge partly due to electrode degradation. Thermally accelerated aging does not adequately model in vivo degradation. Reactive accelerated aging (RAA) adds hydrogen peroxide (H_2O_2) to represent the oxidative species from the tissue response, but closed loop peroxide concentration control for >1 month has proven difficult. We aim to develop and validate a stable, scalable RAA platform and use it to test polyimide-base electrodes. *Methods:* A glass 5-neck flask with electric heating mantle was used to maintain an H_2O_2 concentration of 15mM in phosphate buffered saline at temperatures of 67 or 87 °C. Calibration, validation, and stability of peroxide sensing using chronoamperometry with a platinum 25 µm microdisk electrode was performed using Ag|AgCl reference and large platinum counter electrode. Periodic ground-truth chemical titration measurements were made to validate measurement accuracy. A cohort of 8 thin film polyimide implantable electrodes were immersed for 1 month at 67 °C. Each electrode was characterized with optical microscopy, FT-IR, electrochemical impedance spectroscopy (EIS), cyclic voltammetry (CV), and voltage transient measurements (VT) before, during, and after the RAA protocol. *Results:* New physical and electrochemical cleaning protocols were developed to maintain peroxide measurements at 15 ± 2 mM over a 1-month test. Measurement accuracy was validated using rigorous chemical titration measurements of peroxide. The initial mean cathodic charge storage capacity (CSCc) was = 25.7 ± 1.4 mC/cm^2, and a mean impedance at 1 kHz of 26 ± 1 MΩ. Infrared spectroscopy of the polyimide material peak wavelengths and intensities of 2900-3100 cm^{-1} C-H stretch and 1770-1780 cm^{-1} C=O indicated fully polymerized material (Yao et al. 2017). Device characterizations were made at 1 week and 1 month. *Conclusion:* Improved RAA test station and measurement methods were developed with robust closed loop control of peroxide concentration at elevated temperature. Ground-truth chemical titration validated sensor accuracy and stability over 1-month with protocol improvements. EIS spectra indicated a decrease shift in impedance at higher frequences, while the CV waveform shows more pronounced peaks at cathodic potentials. Characterization data was used to generate an updated accelerated aging factor of temperature and H_2O_2 and extrapolate encapsulation lifetimes.

Disclosures: T.M. Stump: B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Blackrock Neurotech. **H. Finklea:** None. **H. Henderson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Blackrock Neurotech. **J. Vankirk:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Blackrock Neurotech. **P. Candland:** None. **S. Negi:** A. Employment/Salary (full or part-time):; Blackrock Neurotech. **L. Rieth:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and

pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; Blackrock Neurotech.

Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR138.07/Z13

Topic: F.05. Brain-Machine Interface

Title: Neuropixels mapping of corticostriatal neuronal firing patterns under subthalamic nucleus deep brain stimulation

Authors: *H. LIU[1,2], A. WOLTERS[3], S. HESCHAM[4];
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Abstract: Neuropixels mapping of corticostriatal neuronal firing patterns under subthalamic nucleus deep brain stimulation
Hengjian Liu[1,2], Anouk Wolters[1,2], Hans Clusmann[3], Yasin Temel[1,2,4], Sarah Hescham[1,2,3]1. Department of Neurosurgery, Maastricht University Medical Centre, Maastricht, the Netherlands2. European Graduate School of Neuroscience (EURON), Maastricht University, Maastricht, the Netherlands3. Department of Neurosurgery, RWTH Aachen University Hospital, Aachen, Germany4. Istanbul Atlas University, Istanbul, Turkey
AbstractDeep brain stimulation of the subthalamic nucleus (STN-DBS) is an effective neuromodulation therapy that primarily acts through the modulation of basal ganglia-motor circuits. However, stimulation-related side effects may involve the unintended recruitment of limbic-associated circuits. Therefore, identifying the brain regions and neuronal firing patterns affected by different DBS frequencies is important for understanding the circuit-level effects of STN-DBS. In this study, Neuropixels recordings were performed in rats to monitor single-unit activity in the M1/M2 motor cortex, prelimbic/infralimbic cortex (PrL/IL), and nucleus accumbens (NAc) during low-frequency stimulation (LFS) and high-frequency stimulation (HFS) of the STN.Although full analyses are ongoing, preliminary findings indicate that neuronal modulation is both region- and frequency-dependent. In the PrL/ILregion, neuronal responses were observed under both stimulation conditions, with predominantly excitatory modulation. In M1/M2, high-frequency stimulation induced more pronounced neuronal modulation compared with low-frequency stimulation, with a mix of excitatory and inhibitory responses. In contrast, NAc activity appeared more strongly modulated during low-frequency stimulation, with comparatively limited responses during high-frequency stimulation.These preliminary findings suggest that STN-DBS may shape neuronal firing activity in a frequency-dependent and region-specific manner. This regional variability may help explain how different DBS parameters engage distinct motor and limbic-related circuits and may provide insight into the neural basis of stimulation-related effects.

Disclosures: H. Liu: None. **A. Wolters:** None. **S. Hescham:** None.

Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

Location: WCC Halls A-C

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Program #/Poster #: PSTR138.08/Z14

Topic: F.05. Brain-Machine Interface

Support: Research Ireland 12/RC/2289_P2
Research Ireland 22/FFP-A/10954

Title: A Computational Model of Utah Array Microelectrode Recordings from Layer V Pyramidal Neurons

Authors: *P. SAIKIA[1], J. ORLOWSKI[1], C. BYRNE[2], M. LOWERY[1];
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Abstract: Penetrating microelectrode arrays, such as the Utah array, enable single-neuron recordings for high-performance brain-computer interface (BCI) applications. However, their long-term reliability is limited by changes in the neuron-electrode configuration and the electrode-tissue interface (ETI), including variations in impedance, immune responses, and glial encapsulation, altering extracellular recording sensitivity and spatial selectivity. We present a computational model quantifying the impact of ETI properties and neuron location on recorded extracellular voltages in Utah-array-like geometries. A 3D finite element (FE) model of a 5×5 Utah electrode array is developed and located at the depth of cortical layer V. The FE model is coupled to a morphologically and biophysically detailed, conductance-based model of a layer V pyramidal neuron, including the soma, apical and basal dendrites, and an axon with axon initial segment, hillock, and 30 nodes and internodes [1, 2]. The effect of neuron-electrode distance on extracellular action potential (EAP) amplitude was examined in simulation by varying the neuron position relative to the recording electrode contact. The root mean square (RMS) amplitude of the EAP decreased as the soma-electrode distance increased. Beyond 200 μm in the transverse direction and 300 μm in the longitudinal direction from the contact, the RMS amplitude fell below 10% of that at 10 μm. EAPs were simulated under four different ETI conditions: no encapsulation, conductive peri-electrode space, resistive encapsulation around each electrode shank, and full array encapsulation. Full array encapsulation increased the EAP amplitude more than individual shank encapsulation. In contrast, the conductive peri-electrode space suppressed the EAP amplitude compared to no encapsulation. Across a population of 100 neurons randomly distributed around the electrode, repeated-measures ANOVA with Tukey's post hoc test confirmed a significant effect of conductive peri-electrode space ($p = 0.015$) and full array encapsulation ($p < 0.001$) on EAP RMS amplitude. The simulations illustrate the effect of neuron locations and volume conductor electrical and geometrical properties on single-neuron

recordings from microelectrode arrays. [1]. Hay et. al, PLoS Comput. Biol., 2011. [2]. Mainen et.al, Nature, 1996.

Disclosures: P. Saikia: None. **J. Orlowski:** None. **C. Byrne:** None. **M. Lowery:** None.

Poster

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Program #/Poster #: PSTR138.09/Z15

Topic: F.05. Brain-Machine Interface

Support: Paul g. Allen Foundation

Title: Inhibitory neuron plasticity during brain-computer interface learning in motor cortex

Authors: *C. WANG[1,5], M. ROZSA[2], K. AITKEN[3], M. D. GOLUB[6], S. MIHALAS[4], K. SVOBODA[2], K. DAIE[2];
[2]Allen Inst. for Neural Dynamics, [1]Allen Inst., Seattle, WA; [3]Mindscope, Allen Inst., SEATTLE, WA; [4]Studio D3, Allen Inst., Seattle, WA; [5]Grad. Program in Neurosci., [6]Computer Sci. & Engin., Univ. of Washington, Seattle, WA

Abstract: Brain-computer interfaces (BCIs) provide a powerful paradigm for studying the neural basis of learning. Prior work has shown that rapid BCI learning in the motor cortex is associated with sparse activity changes and local causal connectivity reorganization in excitatory circuits. However, whether inhibitory circuits undergo learning-related plasticity and what learning rules govern these changes remain unknown.
We performed two-photon calcium imaging in the primary motor cortex of head-restrained mice during a BCI task, in which mice learned to modulate the activity of a single excitatory conditioned neuron to control the position of a motorized reward port. RiboL1-jGCaMP8s was expressed pan-neuronally to record excitatory and putative inhibitory neurons across sessions. ChRmine was selectively expressed in GABAergic neurons to map local causal connectivity via single-cell photostimulation before and after BCI learning.
Inhibitory neuron plasticity was better described by a two-factor learning rule. GABAergic neurons with high pre-trial activity on trials where performance improved showed a non-specific increase in inhibitory output. The magnitude of this change depended on reward prediction error (RPE), quantified as the difference between current and previous reward rates. This inhibitory learning rule contrasts with excitatory neuron plasticity, which was found to follow a three-factor rule, with synaptic weight changes correlated with both Hebbian co-activity and RPE.
These results suggest that inhibitory and excitatory neurons in the motor cortex implement distinct plasticity rules during BCI learning. Excitatory plasticity selectively updates synapses associated with rewarded pre- and postsynaptic coactivity, whereas inhibitory plasticity depends

on presynaptic inhibitory activity and RPE and broadly strengthens outputs across postsynaptic targets.

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Poster

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Location: WCC Halls A-C

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Program #/Poster #: PSTR138.10/Z16

Topic: F.05. Brain-Machine Interface

Support: ONR N62909-24-1-2015

Title: Automated Closed-Loop Intracranial Stimulation Maps Reward-Competent Brain Regions and Enables Behavioral Conditioning in Teleost Fish

Authors: *D. ZLOTNIKOV[1,2], A. LAZAROVICH[2], R. SEGEV[3], O. BEN-SHAHAR[4]; [1]Ben-Gurion Univ. of the Negev, Petah Tikva, Israel; [2]Ben-Gurion Univ. of the Negev, Beer Sheva, Israel; [3]Ben Gurion Univ. of the Negev, Beer Sheva, Israel; [4]Ben Gurion Univ. of the Negev, Beer-Sheva, Israel

Abstract: Identifying neural substrates capable of mediating reward is fundamental to understanding vertebrate reinforcement learning. While mammalian reward processing is strongly associated with dopaminergic mesostriatal circuits, homologous systems in teleost fish remain incompletely characterized. Reliable intracranial reinforcement is also a prerequisite for developing fully virtual conditioning paradigms in which behavior can be shaped without natural rewards. Toward that end, we developed a fully automated closed-loop platform for depth-resolved intracranial reward mapping and semi-virtual operant conditioning in adult teleost fish. A chronic stimulating electrode was advanced in 50 μm increments through the posterior tuberculum, a region proposed to contain homologs of mammalian reward circuitry. At each depth, fish underwent automated conditioning sessions in which a compound visual-auditory cue signaled an opportunity for reward following a predefined behavioral response. Responses were detected in real time using computer vision, and successful trials triggered biphasic intracranial stimulation whose magnitude decayed with response latency, preferentially reinforcing rapid reactions. Electrode positioning, stimulation delivery, behavioral monitoring, and reward assignment were performed automatically without experimenter intervention. Systematic mapping identified a focal region within the posterior tuberculum that consistently supported reward-seeking behavior. Stimulation at this site produced above-chance response rates and progressive improvements across trials, consistent with acquisition of a learned cue-reward association rather than a fixed sensorimotor reflex. In contrast, control animals exposed to identical sensory cues without intracranial reward showed no comparable improvement. These

findings identify a candidate reward-competent region in the teleost brain and demonstrate that stimulation of this site can serve as an effective reinforcement signal capable of supporting operant learning. More broadly, this work establishes a framework for automated mapping of reinforcement circuitry and a first step toward fully virtual conditioning paradigms driven by artificial neural reward signals.

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Poster

PSTR138: BMI Neurophysiology: Implanted Electrodes and Other Direct Interactions With Neurons

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Program #/Poster #: PSTR138.11/Z17

Topic: F.05. Brain-Machine Interface

Support: Carney Innovation Award

Title: Subdural electrical stimulation of the spinal cord using a network of microimplants

Authors: *G. PORTO MACHADO[1], R. ZHAO[2], M. VU[2], A. V. NURMIKKO[2], D. A. BORTON[1];
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Abstract: Epidural electrical stimulation (EES) has been widely used for the treatment of neuropathic pain and restoration of motor function after spinal cord injury (Nahm 2020, Wagner et al. 2018). However, in the lumbar spine, epidural electrodes are typically separated from their neural targets by ~1.5-2.5 mm, limiting spatial selectivity and resulting in higher activation thresholds (Kaydu et al. 2021; Hong et. al 2011). Subdural stimulation, with electrodes placed closer to the spinal cord, lowers the stimulation amplitude needed to reach tissue activation thresholds and improves spatial selectivity. However, chronic subdural systems are limited by the need for transdural cabling, which introduces risks associated with cerebrospinal fluid shunts, including infection (Arts et al. 2021). These challenges motivate a wireless subdural stimulator that avoids transdural leads. We have previously developed a wireless network of silicon microimplants capable of delivering patterned biphasic stimulation with programmable current amplitudes (up to 120 μApp) and pulse durations through wireless power and data communication, and demonstrated successful neuromodulation of the motor and sensory cortices in freely behaving rats (Lee et al. 2024). To support subdural spinal cord stimulation, we redesigned the microchips for higher current capacity (3 mApp) and supply voltage (12 V), and used low impedance metal oxides such as ruthenium oxide (RuOx) electrodes, whose charge injection capacity is >10× higher than reported values for conventional bare metal electrodes (Chakraborty et al. 2021; Cogan 2008). To evaluate implant geometry and target muscle groups, cadaveric porcine dissections were performed to characterize spinal anatomy and implant

dimensions. Terminal surgeries were performed to assess device functionality in vivo, initially using a wired setup, in which the new microchip is programmed by a field-programmable gate array (FPGA) and drives a custom-fabricated RuOx electrode pair packaged on a flexible PCB. Future versions of the device will be a network of microchips distributed across the subdural space and receive radio frequency power from an external transducer. These findings and ongoing research aim toward establishing a new model for targeted subdural neuromodulation, opening paths to treat neuropathic pain, and function restoration after spinal cord injury with improved muscle specificity.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: NIH 5R21EB037322-02

Title: Solvent-Cast Liquid Crystal Polymer as a New Material for Flexible Thin-Film Neural Interfaces

Authors: *J. W. JUDY[1], L. JIRACEK[2], R. WILKERSON[2];
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Abstract: Thin-film flexible neural interfaces can achieve high channel counts and densities, but material-delamination failure mechanisms continue to limit their long-term reliability in chronic implants. Polyimide is the most common dielectric for these devices because it is biocompatible, readily spin-processed, and compatible with the fabrication of multilayer thin-film structures made of polymer and metal. However, reactive accelerated aging (RAA) soak tests that consist of saline and reactive oxygen species, such as those generated during the foreign body tissue response, can rapidly compromise the polyimide-to-polyimide bond and thus the chronic reliability of bioelectronic implants. Liquid crystal polymer (LCP) is a promising alternative due to its thermoplastic nature, ultra-low moisture absorption, and high chemical robustness. Because LCP layers can fuse and intertwine at the molecular level when heated near their melting point, multilayer LCP devices may eliminate the polymer-polymer interfaces that delaminate. However, most LCP bioelectronics are fabricated from two commercial sheets that are >25 μm thick, making the devices too thick (50 μm) and stiff to minimize tissue response.Here we evaluate a solvent-processable spin-on LCP (SO-LCP) as a microfabrication-compatible dielectric and encapsulant for flexible neural interfaces. SO-LCP films were spin-cast on silicon carrier wafers, processed with soft-bake and hard-bake cures, integrated with a thin layer of

patterned metal, etched by an oxygen-plasma to reveal electrodes and define the geometry of the implants, and released using an electrochemical sacrificial-aluminum release process. Initial process development produced continuous LCP films less than 5 µm thick and high-resolution metal interconnects, electrodes, and pads. Independent commercial cytotoxicity testing (ISO 10993-5) of the SO-LCP showed no detectable cytotoxic response. Electrical-impedance, channel-isolation, and water-ingress behavior are being evaluated using a variety of test structures (e.g., open and buried electrodes, interdigitated electrodes, metal witness structures, etc.) and saline-based accelerated-aging (AA) and RAA soak tests.The results to date support SO-LCP as a promising platform technology broadly for flexible bioelectronics and specifically for neural-interface encapsulation. Ongoing work will quantify the chronic reliability of the SO-LCP-to-SO-LCP bond and SO-LCP-to-metal bond for bioelectronic implants.

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Program #/Poster #: PSTR138.13/Z19

Topic: F.05. Brain-Machine Interface

Title: A soft electrocorticography platform enables high-fidelity cortical recording and clinical brain mapping across epilepsy, auditory, and somatosensory applications

Authors: *N. GNINENKO[1], A. DIOP[1], K. JANIKOWSKA[1], A. TROUILLET[2], F. FALLEGGER[2], N. TANDON[3], S. P. LACOUR[2], L. SEREX[1], N. VACHICOURAS[1]; [1]Neurosoft Bioelectronics, Geneva, Switzerland; [2]Swiss Federal Inst. of Technol., Lausanne, Switzerland; [3]McGovern Med. Sch. at UT Hlth., Houston, TX

Abstract: Conventional electrocorticography (ECoG) grids are mechanically rigid, constraining electrode-to-cortex contact in anatomically folded regions and limiting signal fidelity at high frequencies. We present a bench-to-bedside translational validation of a soft, conformable, thin-film ECoG array (Neurosoft Bioelectronics) spanning in-vitro biophysical characterization, large-animal preclinical implantation, and first-in-human intraoperative recordings in patients with drug-resistant focal epilepsy.In-vitro electrochemical impedance spectroscopy revealed a flat impedance magnitude spectrum and a near-zero phase angle across the recording bandwidth, indicating that resistive components dominate the overall impedance, in contrast to the predominantly capacitive spectrum of conventional platinum-silicone grids. Despite a higher impedance magnitude at 1 kHz, in-vivo signal-to-noise ratio (SNR) in a Göttingen minipig model (N = 6) was equivalent to that of a co-implanted commercial reference array, directly challenging the prevailing assumption that impedance magnitude, rather than the character of the electrode-tissue interface, governs signal quality.In patients undergoing craniotomy for drug-resistant focal epilepsy (N = 9) at two neurosurgical centers (Utrecht, NL, EU and Houston, TX,

USA), the soft array achieved significantly greater electrode-to-cortex contact than a co-implanted commercial reference array, including within post-resection surgical cavities inaccessible to conventional rigid devices. Broadband SNR was significantly higher across all recorded channels, with the advantage most pronounced at high frequencies, consistent with the resistive impedance model. The improved high-frequency signal fidelity enabled robust intraoperative detection of high-frequency oscillations (HFOs, 80-500 Hz) and interictal epileptiform discharges, which are common biomarkers for seizure onset zone delineation and guiding the extent of surgical resection.In two cases, proof-of-concept recordings demonstrated broadband gamma activation over the auditory cortex during speech stimulation, as well as somatosensory evoked potentials during motor mapping, confirming versatility for intraoperative functional brain mapping beyond epilepsy. These results link electrode biophysical properties to measurable benefits for clinical use, establishing a translational evidence base that positions the soft ECoG platform as a high-fidelity tool for epilepsy monitoring, functional cortical mapping, and cortical brain-computer interfaces.

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Poster

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Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR138.14/Z20

Topic: F.05. Brain-Machine Interface

Support: ERC PoC Grant 101189526

Title: Development of a multiple electrode array for regenerative peripheral nerve interfaces to enable bidirectional communication

Authors: *Z. BAILEY[1], R. GREEN[2];
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Abstract: Regenerative peripheral nerve interfaces (RPNIs) are known to prevent neuromas and reduce phantom limb pain in patients with amputations. However, they also provide an attractive target tissue for bioelectronic interfacing, enabling bidirectional neuroprosthetic communication. This study assessed whether an open-mesh 12-channel electrode array implanted during RPNI construction preserves graft viability and reinnervation while obtaining multichannel electromyographic (EMG) recordings and evoking afferent neural responses.A soft, mesh multielectrode array was designed to meet requirements for graft viability and tissue conformability. Adult Lewis rats underwent RPNI construction using a muscle graft with an embedded transected common peroneal nerve. Terminal studies compared RPNI alone with RPNI plus array at 8 weeks (n=6) and included microCT, EMG recording from the RPNI, and RPNI stimulation while recording afferent compound nerve action potentials (CNAPs). Independent component analysis was used to quantify localized myofibril activation within the RPNI.RPNIs showed no gross necrosis or dislodgment, and microCT demonstrated angiogenesis through the array mesh. Array implantation did not reduce graft viability or function versus controls with no electrodes (weight: −18.7±10.3% vs −14.8±5.9%; maximal compound muscle action potential: 4.27±0.97 mV vs 4.48±1.32 mV). The array of electrodes captured multiple local field potentials (LFPs) across the RPNI. While there was some overlap in LFPs across electrodes (mean |r|=0.526±0.056), there were 3.24±0.36 independent components identified in the evoked EMG of the RPNI. Freely moving pilot recordings showed lower correlation (mean |r|=0.339±0.157) and 6.14±0.62 independent components. RPNI stimulation evoked sciatic CNAPs with an average conduction velocity of 48.2±5.31 m/s, consistent with Aβ-range afferent recruitment. CNAP magnitude increased with stimulation amplitude and pulse width, and subfascicular activation of the peroneal nerve was observed.
Implantation of an open-mesh 12-channel RPNI array preserved early graft survival and reinnervation, while enabling multichannel recording and evoked responses in rats. These results demonstrate the advantage of higher-channel peripheral nerve interfaces for RPNIs.

Disclosures: Z. Bailey: A. Employment/Salary (full or part-time):; US Government. **R. Green:** None.

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.01/Z21

Topic: F.05. Brain-Machine Interface

Support: NS Card: A.P. Giannini Postdoctoral Fellowship, Burroughs Wellcome Fund Career Awards at the Scientific Interface
M Wairagkar: Paradromics, Inc.
T Singer-Clark: NeuralStorm NRT Award #2152260, ARCS Foundation Scholar Award, F31 from NIDCD (1F31DC023776-01)
LR Hochberg: NIH-NIDCD (U01DC017844), VA RR&D (A2295-R)
SD Stavisky: DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055), DOD CDMRP ALS Pilot Clinical Trial Award (AL220043), Searle Scholars Program, Career Award at the Scientific Interface from the Burroughs Wellcome Fund
DM Brandman: ALS Association Assistive Technology Grant (24-AT-732)

Title: Sustained daily communication via a code-word intracortical speech BCI in a functionally locked-in ALS participant

Authors: *X. HOU[1,2], H. PERACHA[2], N. CARD[2], C. IACOBACCI[2], T. BRAILOW[2], M. WAIRAGKAR[2], T. SINGER-CLARK[2], L. R. HOCHBERG[3], S. D. STAVISKY[2], D. BRANDMAN[2];
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Abstract: Individuals with amyotrophic lateral sclerosis (ALS) whose disease progresses such that they are unable to use commercial augmentative and alternative communication (AAC) devices, including eye trackers, currently lack an effective communication channel. Recent intracortical speech BCIs have achieved near-conversational throughput in participants with ALS and retained orofacial articulation [Willett et al., 2023; Card et al., 2024, 2026]. But in ALS patients past this regime, reduced speech-related neural tuning and ventilator-coupled articulation timing may not support reliable phoneme-level decoding [Jude et al. 2026a]. While typing-based intracortical BCIs from the hand motor cortex have recently been demonstrated in functionally locked-in ALS [Jude et al. 2026b], whether attempted-speech decoding can provide robust independent communication in this regime remains unresolved.
A 41-year-old man ('T19') with locked-in ALS, ventilator-dependent, was enrolled in the BrainGate2 clinical trial. Four 64-microelectrode arrays were placed in the left precentral gyrus. We trained a Transformer neural network to classify neural activity into one of 30 classes (26 NATO code-words for the alphabet, "Undo", "Space", "Do nothing", and "Right hand squeeze" imagery) within an 8-s decoding window synchronized to the peak of ventilation cycles. This window duration matched the participant's preferred articulation rate, which was entrained to the ventilator cycle. In conversation mode, decoded code-word sequences were passed to a language model for real-time sentence prediction; sentences were terminated by a decoded "Right hand squeeze" imagery and synthesized through a personalized text-to-speech model trained on T19's pre-ALS voice.
On a cued single-code-word copy task, decoding accuracy was 94.5% ± 4.8% (mean ± SD). In conversation mode, T19 produced 5 characters/min (8 s decoding window + 4 s inter-word interval). Over 11 months of near-daily home use, T19 has accumulated 719 hours of system use, 4225 sentences, and 28576 code-words. Across this period, his remaining behavioral communication channels degraded: eye-tracker control became unreliable and was discontinued;

eyebrow-raise yes/no responses were lost; horizontal eye saccades supported only slow, low-reliability binary signaling. BCI decoding performance remained stable throughout this trajectory, and the system became T19's primary communication device. These results demonstrate that an attempted speech code-word intracortical BCI is a viable option to sustain daily communication in a functionally locked-in ALS participant for whom no behavioral AAC remains viable.

Disclosures: X. Hou: None. **H. Peracha:** None. **N. Card:** A. Employment/Salary (full or part-time):; worked as a visiting neuroengineer for Neuralink from September 2025 to February 2026. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventors on intellectual property assigned to the University of California related to brain-computer interfaces. **C. Iacobacci:** None. **T. Brailow:** None. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UC Davis IP related to intracortical BCIs. **T. Singer-Clark:** None. **L.R. Hochberg:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro, for which LRH provides consultative input. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. Other; Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC). **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S.D.S is an inventor on intellectual property assigned to Stanford University and the University of California related to brain-computer interfaces. F. Consulting Fees (e.g., advisory boards); S.D.S is an advisor to Subsense and was a consultant to Neuralink. **D. Brandman:** F. Consulting Fees (e.g., advisory boards); D.M.B. was a surgical consultant to Paradromics Inc., and is currently an advisor to Globus Medical.

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.02/Z22

Topic: F.05. Brain-Machine Interface

Support: NIH-NIDCD (U01DC017844)
VA RR&D (A2295-R)
DP2 from the NIH Office of the Director and managed by NIDCD (1DP2DC021055)
DOD CDMRP ALS Pilot Clinical Trial Award (AL220043)

Searle Scholars Program
Career Award at the Scientific Interface from the Burroughs Wellcome Fund

Title: Abstract lexical information is available in speech motor cortex during conversational speech

Authors: *J. YEATON[1], Z. FOGG[2], N. CARD[2], C. IACOBACCI[2], T. BRAILOW[2], L. R. HOCHBERG[3], D. M. BRANDMAN[2], S. D. STAVISKY[2];
[2]Neurolog. Surgery, [1]Univ. of California, Davis, Davis, CA; [3]Neurol. / Engin., Brown University, VA Providence Healthcare System, Massachusetts Gen. Hospital, and Harvard Med. Sch., Boston, MA

Abstract: Speech motor cortex has traditionally been understood as a substrate for the sensorimotor planning and execution of articulation. Yet its potential role in encoding higher-level linguistic structure remains poorly characterized. Brain-computer interface (BCI) systems that record from this region offer a rare opportunity to examine action potential-resolution neural representations of language during naturalistic behavior. Here we ask whether part of speech (POS) information is decodable in speech motor cortex, and whether such representations are stable across distinct speech contexts.We analyzed chronic intracranial recordings from four microelectrode arrays implanted in the precentral gyrus of a man with ALS (Participant T15). Neural data were collected during two speech conditions: unconstrained conversational speech (34,430 utterances) and cued sentence production (7,849 utterances). For each word, we extracted spike-band power in 20ms bins and trained a recurrent neural network (RNN) to decode POS {noun, verb, adjective, adverb, proper noun} every 80ms. Estimated phoneme-related neural encoding was regressed out prior to analyses. Decoding performance was evaluated using cross-validated accuracy and compared across the two speech contexts. An RNN trained on neural data from -2000ms to 500ms about word onset decoded POS correctly for 54.8% of in-vocabulary tokens (chance = 20%), and 49.5% for out-of-vocabulary tokens. This performance dropped to 36.2% when tested on cued production. Verbs had the highest decoding accuracy, followed by nouns. Peak decoding accuracy was ~1500ms before word onset. POS category representations were relatively stable from -2500ms until word onset. We found decoding accuracy was substantially higher during conversational speech than during cued sentence production for lexical-syntactic decoding, despite equivalent low-level motor demands (and similar phoneme decoding accuracy) across conditions. This asymmetry was consistent across part-of-speech classes. These findings demonstrate that human speech motor cortex carries decodable higher-order lexical information beyond articulation, and that the structure of these representations is not fixed but rather may scale with the demands of the speech context. We interpret the advantage for conversational speech as reflecting richer top-down linguistic context during spontaneous language use, which may stabilize or sharpen lexical representations. These results challenge a strictly motor view of the precentral gyrus and suggest that speech motor cortex participates in broader language processing in a context-dependent manner.

Disclosures: J. Yeaton: None. **Z. Fogg:** None. **N. Card:** 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.; Neuralink. **C. Iacobacci:** None. **T. Brailow:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach

Neuro, for which LRH provides consultative input.. Other; Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC);, charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **D.M. Brandman:** 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.; Paradromics, Inc. F. Consulting Fees (e.g., advisory boards); Globus Medical, Inc. **S.D. Stavisky:** F. Consulting Fees (e.g., advisory boards); Subsense, Neuralink.

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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NIH NINDS (U01NS123101, T32NS100663)
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CAUTION: Investigational Device. Limited by Federal Law to Investigational Use

Title: Stable contrastive latent representations for neural decoding in human intracortical brain-computer interfaces

Authors: *Z. DU[1,2], R. LI[2,3], H. LEVI-AHARONI[5], J. J. JUDE[5], T. HOSMAN[2,6,3], A. ACOSTA[5], B. E. LACAYO[5], L. A. PANAGOS[5], A. KAPITONAVA[5], C. E. VARGAS-IRWIN[4,6,3], L. R. HOCHBERG[2,5,7,6,3], J. D. SIMERAL[2,6,3];
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Abstract: Reliable day-to-day movement intent decoding remains a central challenge for intracortical brain-computer interfaces (iBCIs). Contrastive representation learning projects neural activity into a low-dimensional space that preserves task-relevant structure while reducing nuisance variability. We asked whether a sequence-based supervised contrastive latent representation can improve discrete gesture decoding from human intracortical recordings. We compared two decoders: a direct Gaussian Naive Bayes (GNB) decoder that averages neural

features over each trial, and a contrastive latent decoder that uses a gated recurrent unit to embed trial sequences with supervised contrastive and classification losses before fitting the same GNB classifier in latent space. We analyzed three gesture tasks from two BrainGate participants with tetraplegia: a 13-class gesture sweep (T18, 5 sessions), a 30-class finger sweep (T18, 2 sessions), and a ten-finger piano task (T11, 7 sessions). Within-session performance was measured by stratified fivefold cross-validation within each recording day and summarized across sessions. *Across-session* performance was measured by training on earlier sessions, calibrating with the first N=0-4 blocks from a held-out final session, and computing accuracy on the remaining held-out blocks. The latest training and held-out sessions were separated by 91 days for T18 gesture, 399 days for T18 finger, and 2 days for T11 piano. Within-session accuracy improved with contrastive latent decoding: T18 gesture improved from 91.1+/-1.2% with direct GNB to 93.1+/-0.9%; T18 finger from 92.5+/-0.8% to 95.7+/-0.7%; and T11 piano from 71.5+/-4.5% to 91.3+/-4.3%. In across-session training with 3 (T11) or 4 (T18) calibration blocks, contrastive latent decoding again exceeded direct GNB on held-out trials: T18 gesture reached 93.4% versus 88.5%; T18 finger reached 85.7% versus 75.4%; and T11 piano reached 88.1% versus 62.9%. With no target-session calibration (N=0), contrastive accuracy remained high for T18 gesture (91.0%) and T11 piano (86.6%) but was poor for T18 finger (13.0%), likely because the 399-day gap and only one prior 30-class reference session left the uncalibrated latent space poorly matched to the held-out day; performance recovered with target-day calibration. These results show that sequence-based supervised contrastive latent spaces improve offline intracortical decoding across discrete gesture datasets and support inter-day recalibration using limited target-session data. This approach provides a foundation for improved closed-loop multi-gesture iBCI decoding and future latent-space alignment studies.

Disclosures: Z. Du: None. **R. Li:** None. **H. Levi-Aharoni:** None. **J.J. Jude:** None. **T. Hosman:** None. **A. Acosta:** None. **B.E. Lacayo:** None. **L.A. Panagos:** None. **A. Kapitonava:** None. **C.E. Vargas-Irwin:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement (CRSA) with Ability Neurotech, Analog Devices, Axoft, Medtronic, Neuralink, Neurobionics, Paradromics, Precision Neuro, Reach Neuro, and Synchron, for which LRH provides consultative input. Mass General Brigham (MGB) convenes the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC); charitable gift agreements to MGB, including those received to date from Axoft, Blackrock Neurotech, Neuralink, Paradromics, Precision Neuro, and Synchron, support the iBCI-CC, for which LRH provides effort. **J.D. Simeral:** None.

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.04/Z24

Topic: F.05. Brain-Machine Interface

Support: United States Department of Defense, Office of the Secretary of Defense (AL220043, S.D.S.)

NIH Office of the Director (1DP2DC021055, S.D.S.)
Office of Research and Development, Department of Veterans Affairs (A2295-R, L.R.H.)
Searle Scholars Program (S.D.S.)
Burroughs Wellcome Fund Career Awards at the Scientific Interface (N.S.C. and S.D.S.)
A. P. Giannini Foundation Postdoctoral Fellowship and Leadership Award (N.S.C.)

Title: Accurate closed-loop semantic intent decoding from intracortical neural activity

Authors: *Z. FOGG[1], N. CARD[2], J. YEATON[1], C. IACOBACCI[3], T. BRAILOW[1], L. R. HOCHBERG[4], D. BRANDMAN[5], S. D. STAVISKY[6];
[1]Univ. of California, Davis, Davis, CA; [2]Bioengineering, Univ. of California, Davis, SACRAMENTO, CA; [3]Univ. of California, Davis, Pacifica, CA; [4]Neurol. / Engin., Brown University, VA Providence Healthcare System, Massachusetts Gen. Hospital, and Harvard Med. Sch., Boston, MA; [5]Neurolog. Surgery, UC Davis Hlth., Sacramento, CA; [6]Neurolog. Surgery, Univ. of California Davis, Davis, CA

Abstract: Neurological injury and disease, including ALS and stroke, can cause loss of communication abilities, either by paralyzing the vocal tract or by damaging cortical regions that support speech and language. Speech brain-computer interfaces (BCIs) that decode phonemes from neural activity during attempted speech have restored communication in patients with paralysis. However, a much larger population cannot communicate due to aphasia which prevents them from forming a speech-motor plan, meaning they cannot benefit from current speech BCIs. Rather than decoding motoric units such as phonemes, an alternative approach is to decode upstream, higher-level representations of intended communication, which could provide a means of communication via a language BCI for this population.
We prototyped a language BCI in T15, a BrainGate2 speech BCI clinical trial participant who is a 48-year-old man with ALS and has 256 microelectrodes implanted in his left precentral gyrus. T15 is dysarthric due to ALS but has no impairment of language comprehension or production. We trained a neural semantic encoder that maps language-related intracortical neural recordings during attempted speech to a large language model (LLM) semantic latent space. Because the resulting neural embeddings lie in the same latent space the LLM operates in, they can be decoded into text using a variety of existing techniques. On held-out data, the neural semantic encoder produced neural embeddings whose mean cosine similarity to the target LLM embeddings of the corresponding sentences was 0.898 (95% CI [0.897, 0.900]; shuffled-pairing chance: 0.425, 95% CI [0.423, 0.426]). In closed-loop sessions with the participant, our algorithm classified attempted speech among six semantic categories of everyday communication—including categories as closely related as room comfort ("Can you turn on the light?") and technology ("Can you turn on my computer?")—with 82.5% accuracy (95% CI [74.7%, 88.3%], n = 120 trials; chance: 16.7%). In the same session, neural embeddings were also decoded into full sentences via nearest-neighbor lookup against a large text corpus, recovering sentences semantically close to those intended (mean cosine similarity 0.779, 95% CI [0.745, 0.811], n = 78 trials; permuted chance: 0.238 [0.214, 0.266]). These results establish the feasibility of decoding semantic intent from intracortical neural recordings and represent a promising step toward a language BCI for the millions living with language disorders.

Disclosures: Z. Fogg: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Z.M.F. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces. **N. Card:** A. Employment/Salary (full or part-time):; N.S.C. worked as a visiting neuroengineer for Neuralink from September 2025 to February 2026.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); N.S.C. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces.. **J. Yeaton:** None. **C. Iacobacci:** None. **T. Brailow:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement (CRSA) with Ability Neurotech, Analog Devices, Axoft, Medtronic, Neuralink, Neurobionics, Paradromics, Precision Neuro,, Reach Neuro, and Synchron, for which LRH provides consultative input. Mass General Brigham (MGB) convenes the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC);, charitable gift agreements to MGB, including those received to date from Axoft, Blackrock Neurotech, Neuralink, Paradromics, Precision Neuro, and Synchron, support the iBCI-CC, for which LRH provides, effort. **D. Brandman:** 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.; D.M.B. is the site-PI for the Connect-One Early Feasibility Study with Paradromics Inc., and is currently an advisor to Globus Medical.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); D.M.B. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S.D.S. is an inventor on intellectual property assigned to Stanford University and also the University of California related to brain-computer interfaces. F. Consulting Fees (e.g., advisory boards); S.D.S is an advisor to Subsense and was a consultant to Neuralink..

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: F.05. Brain-Machine Interface

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Burroughs Wellcome Fund Career Awards at the Scientific Interface (N.S.C. and S.D.S.)
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United States Department of Defense, Office of the Secretary of Defense

(AL220043, S.D.S.)
Office of Research and Development, Department of Veterans Affairs (A2295-R, L.R.H.)

Title: An intracortical speech neuroprosthesis that generalizes across users

Authors: ***N. S. CARD**[1], Z. M. FOGG[1], M. WAIRAGKAR[2], A. SRINIVASAN[1], T. SINGER-CLARK[1], X. HOU[1], E. OKOROKOVA[3], H. PERACHA[1], C. IACOBACCI[1], T. BRAILOW[1], J. JUDE[4], H. LEVI-AHARONI[5], T. LE[7], D. MIFSUD[7], P. I. DEEVI[7], S. R. NASON-TOMASZEWSKI[8], B. RICHARDS[7], A. PRITCHARD[9], Y. ZHANG[10], P. H. BECHEFSKY[7], L. R. HOCHBERG[11], Z. WILLIAMS[12], N. AU YONG[7], D. B. RUBIN[6], C. PANDARINATH[13], D. M. BRANDMAN[14], S. D. STAVISKY[3];
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Abstract: Intracortical brain-computer interfaces (BCIs) can restore communication to people with vocal tract paralysis by decoding cortical activity during attempted speech into text in real time. State-of-the-art systems that pair neural-to-phoneme encoders with phoneme-to-word language models have achieved online word error rates (WERs) as low as 1% with a 125,000-word vocabulary, but only after collecting thousands of sentences of pretraining data from the user. For people who have lost the ability to speak, shortening their individual data collection process would meaningfully reduce the time from device implant to high-accuracy communication. Cross-user generalizability offers a theoretically-appealing potential solution, but prior brain-to-text demonstrations have largely been limited to single participants. Here we introduce a Transformer-based phoneme encoder trained jointly across six participants in the BrainGate2 clinical trial. For every participant — regardless of sex, etiology of disease, or attempted speaking strategy — a multi-user model decoded speech more accurately (mean of 52.0% lower relative word error rate) than single-user models trained on each individual users' data. These offline accuracy gains transferred to closed-loop sessions, where the multi-user decoder again outperformed single-user baselines (mean of 50.4% lower relative word error rate). Notably, the multi-user model could be fine-tuned on as few as 90 sentences from a held-out ("new") user to achieve a WER below 12%, drastically reducing the amount of training data required to achieve practically-usable speech decoding compared to previous single-user start-from-scratch approaches. Together, these results show that pooling intracortical speech data across people yields a more accurate, more generalizable, and more rapidly-deployable decoder than individually trained models — a practical path toward clinical speech BCIs that work for new users with minimal calibration requirements.

Disclosures: N.S. Card: A. Employment/Salary (full or part-time):; N.S.C. worked as a visiting neuroengineer for Neuralink from September 2025 to February 2026.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding

diversified mutual funds); N.S.C. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces. **Z.M. Fogg:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Z.F. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces. **M. Wairagkar:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); M.W. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces.. **A. Srinivasan:** None. **T. Singer-Clark:** None. **X. Hou:** None. **E. Okorokova:** None. **H. Peracha:** None. **C. Iacobacci:** None. **T. Brailow:** None. **J. Jude:** None. **T. Le:** None. **D. Mifsud:** None. **P.I. Deevi:** None. **S.R. Nason-Tomaszewski:** None. **B. Richards:** None. **P.H. Bechefsky:** None. **L.R. Hochberg:** F. Consulting Fees (e.g., advisory boards); The MGH Translational Research Center has a clinical research support agreement with Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro, for which LRH provides consultative input., The Implantable Brain-Computer Interface Collaborative Community (iBCI-CC), for which LRH provides effort, has received charitable gift agreements from various neurotech companies.. **Z. Williams:** None. **N. Au Yong:** None. **D.B. Rubin:** None. **C. Pandarinath:** F. Consulting Fees (e.g., advisory boards); C.P. is a consultant for Meta (Reality Labs). **D.M. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); D.M.B. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces.. F. Consulting Fees (e.g., advisory boards); D.M.B. was a surgical consultant to Paradromics Inc., and is currently an advisor to Globus Medical. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); S.D.S. is an inventor on intellectual property assigned to the University of California related to brain-computer interfaces., S.D.S. is an inventor on intellectual property assigned to Stanford University related to brain-computer interfaces.. F. Consulting Fees (e.g., advisory boards); He is an advisor to Sonera and Subsense and was a consultant to Neuralink..

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.06/AA2

Topic: F.05. Brain-Machine Interface

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Title: Differential encoding across the bilateral precentral gyri during bimanual iBCI cursor control in a person with tetraplegia.

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Abstract: Most tasks of daily living require bimanual coordination, yet intracortical brain-computer interfaces (iBCIs) studies have mostly reproduced unimanual upper limb behavior. As restoring upper limb functionality has been rated a top priority to improve life satisfaction by people with tetraplegia, it is critical to develop bimanual iBCIs. Understanding how the neural processes in the bilateral motor cortices coordinate bimanual behavior is essential to restore bimanual behavior. Here, through simultaneous neural control of two cursors, we demonstrate how neurons in the bilateral precentral gyri encode bimanual information in one iBCI participant. We recorded neural data from a single human participant (T18) enrolled in the ongoing BrainGate pilot clinical trial (www.ClinicalTrials.gov; Identifier: NCT00912041). T18 is a 48 y/o male with tetraplegia from a cervical spinal cord injury (C4 ASIA A). T18 has four 64-channel intracortical microelectrode arrays placed in the hand knob area of the left precentral gyrus and two in the right precentral gyrus. Using a rapid-calibration paradigm, T18 was able to gain bimanual control of two cursors on the first session day. A kalman filter trained on multiple blocks reached a success rate of 88% ± 16% across sessions, and >98% for the last five blocks. We then selectively provided lateralized neural features to the iBCI to evaluate the contribution of each hemisphere to bimanual cursor control, and observed significant differences in control. Ensemble activity exclusively from T18's right (non-dominant) hemisphere enabled bimanual control, whereas the left (hand dominant) hemisphere did not. We then characterized the observed differences from a single electrode, latent space and computational similarity perspective. We observe that T18's right (non-dominant) hemisphere contains unique effector-specific encoding on a single electrode level that arises after cue onset in an instructed-delay task. Spatially-agnostic computational analysis uniquely clustered electrodes in the two right hemispheric arrays. The results suggest asymmetric roles for T18's precentral gyri during bimanual control and motivate further investigations of the non-dominant hemisphere for bimanual iBCIs.

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Foundation). Mass, General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC); charitable gift agreements to MGB, including those received to date from Paradromics, Sy, nchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort..

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

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Title: A mix of distinct skills and compositional reuse in speech motor cortex

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Abstract: To what extent can we view a skilled compound movement's underlying neural activity as the modular combination of basic movements as opposed to its own new neural computation? This question has been studied extensively for upper limb movements, but can also be asked of the less-studied motor neuroscience of speech, which involves skilled coordination and sequencing of articulator movements. Does the brain utilize the same neural patterns to produce a basic articulator movement (e.g., pressing lips together) as it does to produce speech sounds that contain that same movement (e.g., the phoneme /m/ as in "me")? Reuse of neural patterns across different compositional unit levels of speech could also have implications for the design of flexible and generalizable speech brain-computer interfaces (BCIs). We collected action potential resolution neural recordings from up to 384 microelectrodes implanted in the

ventral precentral gyri of two BrainGate2 clinical trial participants (T15, T21) with ALS while they performed an instructed-delay task involving lips, tongue, and larynx. Each prompt belonged to one of the following unit levels: (A) a word to speak, such as “mall”, (B) a phoneme to speak, such as /m/, or (C) a basic movement to perform, such as [press lips together]. Conditions at all levels were highly decodable (classification accuracy [chance] = basic movements: 0.91 [0.21], phonemes: 0.81 [0.20], words: 0.81 [0.11]), despite many conditions being chosen for similarity instead of differentiation. Neural dimensions associated with specific movements were volitionally controllable in a closed-loop virtual face control task. Basic movement and speech neural activity overlapped moderately (subspace-alignment index=0.33-0.51). The largest-variance neural dimensions separated conditions by unit level, i.e., words clustered separately from basic movements. However, some smaller-variance neural dimensions preserved kinematic structure across unit levels, i.e., “mall”, “me”, and [press lips together] clustered together. Neural decoders trained on basic movements and applied to sliding windows over speech trials yielded outputs consistent with articulatory phonetics, e.g., the [press lips together] classifier activated for words with /m/, such as “mall” and “me”. These results suggest speech motor cortical activity contains a skill-agnostic kinematic encoding but it resides in small-variance neural dimensions, while large-variance neural dimensions primarily separate skill categories such as speech vs. basic movements. The extent to which the skill-agnostic kinematic encoding can be leveraged to improve speech BCIs is an open question.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

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Title: High-Accuracy Codeword Spelling for Signal-Limited Intracortical Speech BCIs

Authors: *A. ATALAY[1], S. YOON[2], C. K. VO[2], A. SINGH[2], D. T. AVANSINO[2], L. R. HOCHBERG[4,5,6], D. R. DEO[2], J. M. HENDERSON[2,3], F. R. WILLETT[2,3];
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Abstract: Intracortical speech brain-computer interfaces have shown great promise for restoring rapid and accurate communication with large vocabularies, although variability in performance across participants still remains. Optimal presurgical targeting is an unsolved problem, leading to variability in the brain areas and networks that are implanted. Blood vessels, the slant of the cortical surface, or the inaccessibility of optimal regions within sulci can preclude implantation in the most informative locations. Beyond targeting, array yield (the proportion of electrodes that record spiking activity) can vary across participants and may decline over time. Although we are optimistic that these issues will ultimately be solved, they currently limit the ability to achieve highly accurate, rapid, and large-vocabulary speech decoding in some participants. Prior work using ECoG grids has suggested that a spelling strategy based on speaking NATO codewords may enable robust communication from limited signals, but this strategy has not yet been evaluated with intracortical microelectrode arrays.
Here, we tested a NATO codeword spelling strategy in a participant with ALS, T20, enrolled in the BrainGate2 pilot clinical trial. T20 had two arrays placed in the ventral precentral gyrus, but these arrays did not have sufficient signals to support high accuracy for large-vocabulary direct decoding. We trained a recurrent neural network (RNN) to decode NATO codewords directly using the connectionist temporal classification loss function. To train the RNNs, the participant attempted self-paced spelling of short phrases from the Switchboard corpus using the NATO codewords corresponding to each letter of the English alphabet, such as "alpha" for "a." The participant indicated spaces between words by attempting to say "space." After training on ~1350 spelled words, averaging 4.1 characters each, the RNN achieved a mean offline character error rate (CER) of 4% with neural data alone at a speed of 39 characters per minute. When augmented with a 5-gram language model with a 120,000-word vocabulary, the RNN achieved a mean CER of 0.5% and a word error rate (WER) of 1.3%. These results represent a substantial

improvement in decoding capability over prior demonstrations of the NATO codeword spelling approach (WER of 1.3% vs. 10.5%), with a larger vocabulary and faster, self-paced spelling. This successful replication suggests that codeword spelling may be a viable high-accuracy communication alternative for individuals whose implants are not suitable for large-vocabulary speech decoding.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

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Searle Scholars Program
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Title: Neural decoding of speech using deep neural ensembles

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Abstract: Speech brain-computer interfaces (BCIs) can restore rapid communication for people with paralysis. However, accuracy can vary across users and hardware, and decoding errors still limit performance. In recent offline brain-to-text decoding competitions, deep ensemble methods, which combine predictions from multiple independently trained decoders, have delivered striking accuracy improvements and account for the largest gains over baseline approaches. However, these methods have not previously been tested in real-time, require substantial computational resources, and their performance under various clinically relevant constraints remains poorly understood. Here, we address this gap with the first comprehensive evidence supporting deep ensembles as a practical strategy for clinically viable speech BCIs. In a BrainGate2 clinical trial participant with microelectrode arrays placed in bilateral precentral gyri, we show that a real-time, deep ensemble BCI enabled by cloud resources can significantly reduce word error rate (WER) from 33.7% to 26.0% on a large vocabulary, relative to the single-decoder baseline. This improvement approaches a range considered minimally useful for functional communication, demonstrating that the substantial offline benefits of deep ensembles can translate into real-time use. With an offline multi-participant dataset spanning 67.7 hours, 3 participants, and 4 array configurations, we further show that these benefits may generalize to a wide range of data quality regimes and brain areas (average 29.2% WER reduction).Furthermore, we address the central challenge of implementing deep ensembles under practical computational constraints. We find several design principles for minimizing inference latency and balancing resource-accuracy tradeoffs. In addition, for environments where cloud access is limited, we propose a novel “pseudoensembling” technique that improves accuracy gains across participants offline while using only a single decoder, bypassing the computational bottleneck of traditional ensembles (average 13.5% WER reduction).Together, these results show that the benefits of deep ensembling can be realized in real time and under practical resource constraints, bringing speech BCIs closer to broader clinical adoption.

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Poster

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Title: Riding the Drift: Flow Matching Stabilizes Human Intracortical Brain-Machine Interfaces

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Abstract: Intracortical brain-computer interfaces (iBCIs) decode intended movements from neural activities, enabling paralyzed individuals to communicate and control assistive devices. A persistent bottleneck is neural nonstationarity: electrode recordings drift over time due to neuronal turnover, inflammation, and recording instability, causing the underlying neural manifold to shift between sessions. This cross-session instability degrades decoder performance and necessitates frequent recalibration, restricting long-term device practicality. Existing approaches include periodic retraining, subspace alignment via Canonical Correlation Analysis (CCA), and manifold stabilization methods such as NoMAD. CCA assumes linear inter-session relationships, and most approaches require labeled calibration data from each new session, which is a practical burden in clinical deployment. NoMAD is an unsupervised method yet it requires significant time for model calibration. We applied continuous flow matching (FM) to align neural population activity distributions across iBCI recording sessions separated by 13 months in a paralyzed human participant (BrainGate2; 31 individuated finger gestures, 541 shared neural features across cortical microelectrode arrays). Within-session average classification accuracy via Gaussian Naïve Bayes reached 93.5% and 95.2% for the reference and target sessions; direct cross-session decoding collapsed to 22.4%, confirming severe nonstationarity. We applied FM, a generative transport framework training a deep neural network to learn a continuous velocity field progressively warping one probability distribution into another, to align trial-averaged neural activity from the target session into the reference session coordinate frame. After FM transport, nearest centroid classification accuracy recovered to 98.4% , a 76-percentage-point recovery which matched within-session performance, with reverse transport achieving 97.7%. Per-gesture velocity coherence under the learned field was 0.78 ± 0.05, far exceeding the shuffled-label null (0.32 ± 0.05), confirming class-structured rather than arbitrary transport. The inter-to-intra class distance ratio peaked at 1.48 during FM transport, above the linear-interpolation baseline. CCA required 181 latent dimensions to approach comparable accuracy, whereas FM operated directly in the full 541-dimensional feature space. These findings establish flow matching as a high-capacity, nonlinear framework for cross-session neural alignment in iBCIs, pointing toward decoders that remain stable over months of clinical use without repeated recalibration.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.11/AA7

Topic: F.05. Brain-Machine Interface

Support: Postdoc.Mobility, Swiss National Science Foundation - Alessandro Marin Vargas
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Wu Tsai Neurosciences Institute at Stanford - Jaimie Henderson
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NIH NINDS/OD DP2 NS127291 - Chethan Pandarinath

Title: Representations spanning phonemes to syntax during speech production at single-neuron resolution

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Abstract: Prior fMRI and ECoG/sEEG studies have linked distinct cortical regions to different levels of the linguistic hierarchy, but how these features are represented at single-neuron resolution remains poorly understood. Here, using intracortical recordings obtained from people with paralysis in the BrainGate2 pilot clinical trial, we asked how motoric and linguistic features are represented during speech planning and production at single-neuron scale. Consistent with

prior work, we first identified a clear anatomical dissociation: arrays in ventral precentral gyrus (area 6v) were preferentially explained by phonemic and motor-related features, whereas arrays in language-related frontal sites in middle frontal gyrus and inferior frontal gyrus showed stronger tuning to abstract linguistic features. We then used encoding models to determine which levels of linguistic structure best explained activity in language-related regions. Using a large sentence-repetition dataset (131k words), we fit encoding models based on lexical, syntactic, semantic and LLM-derived contextual representations and quantified how well each feature space explained neural activity. We found relatively weak tuning to word-level lexical and semantic features, but substantially stronger tuning to syntactic and LLM-derived contextual representations, suggesting that frontal populations may preferentially encode sentence-level syntactic and contextual structure. A similar pattern was observed during an image question-answering task, suggesting that this tuning is not specific to sentence repetition alone. Notably, one array in middle frontal gyrus showed substantial overlap between motoric/phonemic and higher-level linguistic tuning, highlighting that very different levels of the speech hierarchy can overlap spatially within the same local neural population. These findings clarify the linguistic content of intracortical neural populations and identify sentence-level syntactic and contextual representations as promising targets for future neuroprosthetic decoding.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

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Program #/Poster #: PSTR139.12/AA8

Topic: F.05. Brain-Machine Interface

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NIH-NIDCD (U01DC017844)
VA RR&D (A2295-R)

Title: Intracortical brain-computer interface for highly intelligible voice synthesis and singing

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Abstract: Intracortical brain-computer interfaces (BCIs) that directly decode the intended speech of people with paralysis into voice (brain-to-voice) have the potential to restore real-time, naturalistic, and expressive speech. In our previous work (Wairagkar et al. 2025), we synthesized voice instantaneously and also captured intended intonation and pitch in closed loop with one participant, 'T15', who has amyotrophic lateral sclerosis (ALS) and severe dysarthria and enrolled in the BrainGate2 clinical trial. Despite state-of-the-art performance, the primary barrier to real-world adoption of brain-to-voice BCIs remains the insufficient intelligibility of synthesized voice.

Here, we designed a new decoding algorithm, 'Brain2Voice 2.0', focused on improving synthesis intelligibility using the same neural data from T15. Brain2Voice 2.0 is a multimodal Transformer-based neural decoder that translates intracortical neural activity into intelligible voice in real time. It is trained on multiple complementary speech targets providing continuous and custom-tokenized acoustic target features time-aligned with the participant's intended speech and phonemes. We used self-supervised and adversarial training objectives to further enhance synthesized voice quality. At every 10 ms timestep, the model causally outputs continuous and tokenized acoustic features alongside time-aligned phoneme predictions (raw phoneme error rate: 7%). We evaluated intelligibility by asking human listeners to transcribe BCI-synthesized voice—they achieved a word error rate of 5.24% (open-vocabulary transcription), an eightfold improvement over our prior results (43.75%).

People with speech loss also consistently report missing the ability to be expressive and to sing. We investigated whether rich prosodic encoding exists in single-neuron population activity. We decoded multiple classes of intonation and pitch from intracortical neural data from two BrainGate2 participants with ALS, T15 and T21. For intonation decoding, we classified 6 intonation profiles (statement, emphasis, question, happy, sad, angry) with over 80% accuracy in both participants. We further decoded 8 distinct pitch levels and applied this to a closed-loop BCI enabling T21 to sing a full major scale with audio feedback—a novel demonstration of an

expressive speech BCI.
This study demonstrates voice synthesis intelligibility crossing the threshold required for practical use (offline so far) and enhances closed-loop BCI-enabled singing—bringing expressive brain-to-voice neuroprostheses closer to clinical viability.

Disclosures: M. Wairagkar: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UC Davis IP related to intracortical BCIs. **A. Srinivasan:** None. **T. Singer-Clark:** None. **N. Card:** A. Employment/Salary (full or part-time):; worked as a Visiting Neuroengineer at Neuralink from September 2025 to February 2026. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UC Davis IP related to intracortical BCIs. **X. Hou:** None. **C. Iacobacci:** None. **T. Brailow:** None. **L.M. Miller:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UC Davis IP related to intracortical BCIs. **L.R. Hochberg:** Other; Research agreements through MGH Translational Research Center: Neuralink, Synchron, Axoft, Precision Neuro, and Reach Neuro for which LRH provides consultative input., Mass General Brigham (MGB) is convening the Implantable Brain-Computer Interface Collaborative Community (iBCI-CC); charitable gift agreements to MGB, including those received to date from Paradromics, Synchron, Precision Neuro, Neuralink, and Blackrock Neurotech, support the iBCI-CC, for which LRH provides effort. **D.M. Brandman:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UC Davis IP related to intracortical BCIs. F. Consulting Fees (e.g., advisory boards); Consultant at Globus Medical Inc. Other; Principal investigator for Connect-One clinical trial with Paradromics Inc. **S.D. Stavisky:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); UC Davis IP related to intracortical BCIs. F. Consulting Fees (e.g., advisory boards); Advisor to Subsense and was a consultant to Neuralink..

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.13/AA9

Topic: F.05. Brain-Machine Interface

Support: Robert and Janice McNair Foundation (NPS)
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Title: Towards Brain-Robot Shared Autonomy for Independent Feeding

Authors: *S. TAO[1], K. RAO[3], D. AVANSINO[5], A. SINGH[6], L. R. HOCHBERG[9], C. E. VARGAS-IRWIN[4], F. WILLETT[7], J. M. HENDERSON[8], N. R. PROVENZA[10], S. A. SHETH[10],

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Abstract: Intracortical Brain-Computer Interfaces (iBCIs) have demonstrated reliability in restoring communication for individuals with paralysis and promise for controlling robotic arms. However, translating these systems into functional activities of daily living (ADLs), such as self-feeding, remains a challenge. A major obstacle to a practical, home-deployable Brain-Robot Interface (BRI) for ADLs is the difficulty of accurately interpreting noisy neural signals during complex, real-world tasks, which demand precise coordination across multiple joints and continuous adaptation to varying object properties and interaction strategies. To address this gap, we present a context-driven BRI framework for self-feeding built on three core contributions. First, we implemented a Bayesian shared-autonomy algorithm that infers probable target locations from noisy decoded neural commands and fuses the neural command with a control policy for the target object, denoising the final control signal sent to the robotic arm. Second, we integrated a vision-language model (VLM) to identify expert control policy for each object. The VLM uses real-world knowledge to identify objects on the dining table and the most natural pose for grasping them. Third, we developed a custom end-effector designed for tool-based object manipulation, enabling realistic feeding behaviors such as scooping and twirling with a fork. To evaluate our framework, we defined a suite of benchmark tasks focused on self-feeding that account for real-world variations, including varying object properties (e.g., color, shape, texture), diverse interaction strategies (e.g., reach-and-grasp, tool use), and the use of different utensils (e.g., forks and spoons). Crucially, with noisy user input emulating raw control commands decoded from motor cortex neural activities, our framework significantly outperformed unassisted control on reach-and-grasp tasks, doubling the overall success rate and reducing the average trial duration by half. Our VLM-assisted BRI framework is more generalizable and efficient than traditional BCI paradigms. It aims to reduce reliance on the extensive, cognitively exhausting verbal or physical inputs often required by existing robot-assisted self-feeding pipelines, paving the way for a robust, home-deployable BRI for individuals with severe motor impairments.

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options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); JMH is a shareholder in Maplight Therapeutics and Enspire DBS, and is a co-founder and shareholder in Re-EmergeDBS., JMH is an inventor on intellectual property licensed by Stanford University to Blackrock Neurotech and Neuralink.. F. Consulting Fees (e.g., advisory boards); JMH is a consultant for Paradromics. **N.R. Provenza:** None. **S.A. Sheth:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); SAS is cofounder of Motif Neurotech.. F. Consulting Fees (e.g., advisory boards); SAS has received consultant fees or research support from Abbott Laboratories, Boston Scientific, Zimmer Biomet, Koh Young, Neuropace, Varian Medical, Sensoria Therapeutics.. **N.P. Shah:** None.

Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.14/AA10

Topic: F.05. Brain-Machine Interface

Title: Fast and efficient brain-to-text decoding on mobile devices

Authors: J. MCCART[1], ***P. I. DEEVI**[2], M. AZABOU[1], N. H. KRISHNA[3], C. MCKINNEY[1], N. CARD[4], S. D. STAVISKY[4], C. PANDARINATH[2,1];
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Abstract: Recent advances in speech neuroprostheses have enabled new communication avenues for people who have lost the ability to speak due to neurological illness or injury. These systems can decode neural activity during attempted speech into text by relying on language priors to achieve high decoding accuracy. This performance currently comes at the cost of using a compute-intensive language modeling stack, presenting a major bottleneck for real-world use. Further, current language models incur highly variable and disruptive inference latencies, limiting communication throughput and preventing users from reliably participating in natural conversation. We introduce FETTUCCINE, an end-to-end brain-to-text framework that leverages the speed and portability of automatic speech recognition (ASR) models to address the aforementioned practical challenges, while achieving usable (<10%) word error rates (WER), efficient adaptation to neural non-stationarities, and reliable performance on mobile devices. We show that this framework generalizes across two different model families, providing evidence that FETTUCCINE can potentially be extended to adapt any ASR model to brain-to-text. This enables us to choose models ideal for our application based on accuracy, throughput, and memory considerations. When trained on publicly available data from an intracortical speech neuroprosthesis user (the Brain-to-text '25 competition dataset), FETTUCCINE Whisper model outperformed previous end-to-end methods, achieving as low as 4.39% WER on the public test

set. When prioritizing speed, FETTUCCINE Parakeet model (optimized for running on an NVIDIA A40 GPU) achieved an incredible throughput of up to ~1300x real-time. Most notably, we show the first demonstration of brain-to-text decoding on a commercially-available mobile device (iPhone 15 Pro), with throughput reaching up to 370x real-time. FETTUCCINE models could also be efficiently finetuned to extend usable performance to future days. Beyond performance, the end-to-end architecture enables us to map the neural features most relevant to attempted speech using a gradient-based salience analysis. This analysis allows us to trace the neural dynamics of each word during speech, at the resolution of individual electrodes. Taken together, our results show that FETTUCCINE overcomes core infrastructural and computational barriers, setting new standards for end-to-end decoding performance and enabling a new class of portable brain-to-text communication.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: F.05. Brain-Machine Interface

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Title: Lexical representations are sequenced through a micro-scale dynamic code in inferior frontal gyrus

Authors: *I. ERGIN[1], A. KAZEMIAN[2], E. ROJAS[3], N. HAHN[4], F. KAMDAR[5], C. VO[5], S. S. MADUGULA[6], R. Z. WANG[7], C. FAN[8], E. M. KUNZ[5], D. T. AVANSINO[5], E. WANG[9], Y. ZHANG[9], C. SHAIN[10], L. R. HOCHBERG[14], J. M. HENDERSON[11], F. R. WILLETT[12], L.

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Abstract: Naturalistic speech is transient and time ordered, creating a computational challenge for comprehension: the brain must preserve and integrate earlier input while new words continue to arrive. A proposed algorithmic solution is to maintain linguistic representations dynamically across changing neural populations over time. This implements a long lived dynamic neural code, which enables parallel processing of successive inputs without inference between neighbours, and keeps track of their order in the sequence.
While this phenomenon has been documented in large neural populations for lower-level representations, its implementation at the neuronal scale for higher level linguistic representations remains unclear. We analyzed micro-scale neural activity from Utah arrays placed in the inferior frontal gyrus (IFG) of two BrainGate2 clinical trial participants while they listened to stories. These data ultimately help inform the decoders that translate intended speech into text.
First, we tested whether the micro-scale patterns of activity encode higher level speech information. Logistic regression classifiers showed significant decoding of Part of Speech (PoS) categories in both subjects. Notably, decoding performance persisted above chance for over 2s after word onset, far exceeding the average word duration.
Second, we tested whether the encoding of PoS was supported by a dynamic code at this scale. Temporal generalization analysis revealed that neural patterns at one time step generalize poorly to later ones, indicating that the underlying neural activity patterns that encode PoS evolve over time.
Third, we examined the underlying neural implementation of this dynamic code. Peristimulus time histograms (PSTHs) locked to word and sentence onsets revealed a peak response latency range of ~−0.5 to 1.5s. This indicates that nearby neural populations respond to the same information at different times, suggesting successive populations carry forward linguistic representations as processing evolves.
Finally, PCA of population-level PSTH responses revealed that just two components explained over 80% of the variance in responses to words and sentences. When projecting the PSTHs onto these two axes, responses traced a smooth state-space trajectory.
Our findings provide the first characterization of the micro-scale dynamics in IFG that sequence lexical representations during natural listening. Nearby neural populations respond to word onsets and encode similar lexical information, but responses at different electrodes vary widely in latency. The consequence is a dynamic neural pattern that encodes both linguistic content and relative time.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

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Topic: F.05. Brain-Machine Interface

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Wu Tsai Neurosciences Institute at Stanford
Larry and Pamela Garlick
Marcus Foundation
Simons Foundation

Title: Intracortical recordings from inferior frontal gyrus reveal encoding of linguistic and nonlinguistic operations, not speech production

Authors: *E. M. KUNZ[1], S. MADUGULA[2], H. CUI[3], A. D. LEVIN[3], R. WANG[3], A. MARIN VARGAS[3], D. AVANSINO[4], F. KAMDAR[5], C. VO[6], A. SINGH[7], N. HAHN[8], E. WANG[3], Y. ZHANG[3], L. R. HOCHBERG[11], S. DRUCKMANN[3], C. SHAIN[3], F. WILLETT[9], J. M. HENDERSON[10];
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Abstract: Inferior frontal gyrus has long been implicated in speech and language production, but its precise role remains poorly understood. As part of a communication neuroprostheses study, we recorded single-neuron activity from intracortical arrays implanted in the inferior frontal gyrus of two BrainGate2 participants with severe dysarthria due to amyotrophic lateral sclerosis. Across arrays, we found little evidence that IFG neurons were tuned to phoneme production or single-word output. Instead, neural activity reflected higher-order linguistic and cognitive processes. In one participant, IFG activity was strongly modulated during sentence reading and

production. Most of the variance underlying the sentence-specific neural patterns could be accounted for by syntactic structure largely independent of semantic content, although not all of it. In both participants, neural activity in metalinguistic tasks such as analogy solving represented the operation being performed as opposed to the answer word itself. Further controlled studies revealed distinct and decodable IFG neural patterns for syntactic, semantic, and morphological operations, regardless of the content to which they were applied. Similar modulation was also present in some nonlinguistic tasks, including melody reversal, indicating sensitivity to abstract transformations that extend beyond language. Differences in large-scale network affiliation accounted for some, but not all, of the diversity of responses across arrays. Together, these findings argue for the existence of language-relevant regions of IFG that are not primarily organized around speech motor planning or response output, but instead support higher-order transformations that are important for language but are not limited to it. These results refine theories of Broca's area and may help guide the design of communication brain-computer interfaces.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.17/AA13

Topic: F.05. Brain-Machine Interface

Support: NIH-NIDCD U01 DC019430
Wu Tsai Neurosciences Institute at Stanford
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Title: Distinct temporal profiles in middle frontal gyrus (MFG) and inferior frontal gyrus (IFG) during naturalistic comprehension

Authors: *E. WANG[1], Y. ZHANG[1], S. MADUGULA[2], E. M. KUNZ[3], C. VO[3], D. AVANSINO[3], R. WANG[4], I. ERGIN[5], L. R. HOCHBERG[6,7,8,10,9], L. GWILLIAMS[5], J. M. HENDERSON[3], F. WILLETT[3], C. SHAIN[1];
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Abstract: Despite individual differences, the language network (LN), identified using functional localizers and connectivity, consistently includes spatially separated but functionally related sites in the inferior frontal gyrus (IFG) and middle frontal gyrus (MFG). Some functional magnetic resonance imaging (fMRI) evidence suggests that these sites are similarly tuned to a range of linguistic processing demands, including sublexical, lexical, syntactic, and semantic. However, the detailed temporal dynamics of computation and representation between these two nodes remain poorly understood, because the slow fMRI measures needed to parcellate the network are ill-suited to study them. Here we present a case study with both spatial and temporal precision, in which a BrainGate2 clinical trial patient with amyotrophic lateral sclerosis was surgically implanted with intracranial microelectrode arrays (MEAs) in LN areas of both MFG and IFG identified presurgically using fMRI. The patient then perceived ten short stories, once in a written and once in a spoken modality. We then characterized the function of the neural circuits under the IFG and MFG language arrays by decoding theory-driven word features from their spike-band power (250-5000 Hz) responses in consecutive 500ms time windows from 500ms before to 2000ms after the word onset. We found differences between LN arrays in both functional tuning and response latency. In particular, 1) word surprisal could be decoded earlier from the inferior MFG array than from the anterior IFG array; 2) word frequency registered more strongly in the inferior MFG array than in the other arrays; 3) superior MFG array tracked word position within a sentence, whereas inferior MFG tracked constituent boundary. Our results suggested that LN nodes in IFG and MFG may perform different computations in service of language comprehension, despite fMRI evidence of functional similarity between these areas. Moreover, LN areas in MFG show earlier encoding of a wider range of linguistic properties, suggesting that MFG may be upstream from IFG within the LN. These findings could inform future brain-computer interface approaches for restoring speech and language function in a wider range of populations.

Disclosures: E. Wang: None. **Y. Zhang:** None. **S. Madugula:** None. **E.M. Kunz:** None. **C. Vo:** None. **D. Avansino:** None. **R. Wang:** None. **I. Ergin:** None. **L.R. Hochberg:** 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.; Ability Neuotech, Analog Devices, Axoft, Medtronic, Neuralink, Neurobionics, Paradromics, Precision Neuro, Reach Neuro, Synchron, Blackrock Neurotech. **L. Gwilliams:** None. **J.M. Henderson:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding

diversified mutual funds); Maplight Therapeutics, Re-EmergeDBS, Blackrock Neurotech, Neuralink Corp. F. Consulting Fees (e.g., advisory boards); Medical Advisory Board of Enspire DBS. **F. Willett:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blackrock Neurotech, Neuralink Corp. **C. Shain:** None.

Poster

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Simons Foundation Col- laboration on the Global Brain K23- DC021297

Title: Dynamics of Syntactic Resolution in the Inferior Frontal Gyrus During Natural Speech Comprehension

Authors: *E. ROJAS[1,2,3], I. ERGIN[1,4,3], A. KAZEMIAN[5], N. V. HAHN[6], F. KAMDAR[6], C. K. VO[6], S. S. MADUGULA[6], R. Z. WANG[7], C. FAN[8], E. M. KUNZ[6], D. T. AVANSINO[6], E. WANG[9,10], Y. ZHANG[9,10], C. SHAIN[9,4,10], L. R. HOCHBERG[11], J. M. HENDERSON[6,4,10], F. R. WILLETT[6,4], L. GWILLIAMS[5,4,3];
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Abstract: Syntactic processing, the extraction and resolution of structural dependencies between words, is critical for speech comprehension as the same words placed in different syntactic relationships have different meanings. These dependencies often connect non-adjacent words in an unfolding sequence (The *dog*$^{(dependent)}$ that the cat chased *barks*$^{(head)}$), requiring information coordination over intervening material. Prior fMRI studies found increased inferior frontal gyrus (IFG) activity during syntactic tasks, implicating it in syntactic processing. Here we ask two questions: Do IFG neural populations distinguish different types of syntactic relationships? How are those relations resolved as the sequence unfolds? We analyzed neural activity from microelectrode "Utah arrays" in the IFG of one BrainGate2 clinical trial participant with ALS. This dataset was collected to better understand neural language representations and design brain-

to-text decoders to restore communication. The participant listened to 15 hours of spoken narratives, which we transcribed and annotated for dependency type and head offset (the number of intervening words between a dependent and its head). A multinomial logistic regression shows most dependency types are decodable above chance 200-800 ms after word onset (F1 scores 0.05-0.15). This is driven by dependency types eliciting distinct response peak timing, duration, magnitude, and polarity across array electrodes. This suggests the IFG encodes dependency relations in spatially and temporally distinct patterns of activity. For short-to-medium distance dependencies (±5), neural peak time correlates strongly and linearly with head offset ($p < 0.001$), with peaks 0-2000 ms relative to head word onset. The relation holds above the correlated factor of word position. Responses are earlier when the dependent occurs earlier relative to the head, and later when it occurs later. This peak timing may relate to the moment of syntactic resolution, when head and dependent can be composed into higher order phrasal structure. Together, our results inform how local IFG neural populations resolve syntactic dependencies, by encoding relation type and coordinating response dynamics to resolve non-adjacent temporal structure during natural speech processing.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

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Program #/Poster #: PSTR139.19/AA15

Topic: F.05. Brain-Machine Interface

Support: Research support from Meta Platforms, Inc.

Title: Human motor cortex encodes muscle-relevant features during hand control

Authors: *R. BHATT[1], A. ABDAL QADER[1], J. MCCART[1,2], P. I. DEEVI[1], P. H. BECHEFSKY[1], L. R. HOCHBERG[3,4,5,6], N. AU YONG[7,8], C. PANDARINATH[1,7];
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Providence Healthcare Syst., Providence, RI; [7]Dept. of Neurosurg., [8]Dept. of Cell Biol., Emory Univ., Atlanta, GA

Abstract: Understanding how human motor cortex transforms population activity into muscle activity during dexterous hand movements can inform the development of more versatile intracortical brain-computer interfaces (iBCIs). Recent work has shown that residual surface electromyography (sEMG) combined with intracortical signals can improve iBCI decoding of hand gestures, suggesting that muscle activity can provide additional information about intended movements (Hahn et al, SfN 2024). However, it remains unclear what aspects of muscle activity are represented in human motor cortex and whether cortical activity can predict muscle signals during attempted hand movements in people with paralysis. In this study, we simultaneously recorded intracortical activity using two microelectrode arrays in hand knob area and EMG activity using an sEMG wristband from BrainGate2 participant T16. T16 has tetraplegia due to a pontine stroke, resulting in limited functional hand use. We identified hand movements in an isometric setup that elicited reliable neural and sEMG responses, then designed a delayed force production task in which T16 attempted index, thumb, or index+thumb flexion at one of seven force levels. First, we found that both neural and sEMG activities contained condition-dependent structure at the single-trial level. Individual neural channels were heterogeneous with tuning to force, effector, or both. At the population level, neural activity projected into low-dimensional state-space formed condition-separable trajectories during preparation that became more distinct during execution. Additionally, despite T16's limited hand function, sEMG activity showed condition-dependent structure during execution, with amplitudes scaling with intended force and spatial recruitment patterns differing across effectors. Then, we asked whether neural population activity could predict single-trial sEMG. Using ridge regression, we found that neural activity reliably predicted sEMG across held-out force levels for each effector (mean R^2: 0.60, 0.61, 0.59 for index, thumb, and index+thumb, respectively) and generalized across held-out force x effector conditions when all 21 conditions were pooled (mean $R^2 \pm$ SD: 0.55 ± 0.03). Together, this work shows that human motor cortical activity contains information about both intended movement goals and downstream muscle recruitment for hand control. Future work will test whether coordinated multi-digit movements arise from compositional structure shared with component single-digit representations and whether this structure enables generalizable decoding across more complex hand behaviors.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

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Topic: F.05. Brain-Machine Interface

Support: Stanford Bio-X Postdoctoral Fellowship

Title: Intracortical evidence for functional dissociation from word encoding to meaning integration within the language network

Authors: *Y. ZHANG[1,6], E. WANG[2,6], S. MADUGULA[3], E. KUNZ[3], C. VO[3], D. AVANSINO[3], R. WANG[4], A. MARIN VARGAS[3], I. ERGIN[5,7,8], L. GWILLIAMS[5,7,8], L. R. HOCHBERG[9,10,11,13,12], J. M. HENDERSON[3,7,6], F. WILLETT[3,14], C. SHAIN[2];
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Abstract: Recent neuroimaging studies identify a distributed network selective for language (LN, Fedorenko et al., 2024). Its internal organization and dynamics remain less clear due to the limited spatiotemporal resolution of neuroimaging methods such as functional magnetic resonance imaging (fMRI). We fill this gap by studying neural activities recorded by intracortical Utah microelectrode arrays (MEAs, 3.2 x 3.2 mm2, 64 electrodes/array) placed in inferior (IFG) and middle (MFG) frontal gyri in the LN based on preoperative fMRI in a participant enrolled in BrainGate2 pilot clinical trial who suffered from severe dysarthria due to amyotrophic lateral sclerosis. As part of a communication neuroprostheses program, this study aims to advance the understanding of the neural basis of language to empower more efficient speech BCI. Based on two MEA experiments, we found evidence of a functional dissociation between MFG and IFG within LN, with MFG tracking individual word informativity and phrase boundaries while IFG tuning to meaning coherence and expectation violation. The first isolated lexical, syntactic, and combinatorial semantic processing demand by comparing real English word and jabberwocky phrases of varying lengths. Although both areas were more active to real-word over Jabberwocky conditions (suggesting distributed lexical sensitivity), MFG arrays showed increased activations for more informative words (e.g., content words). The IFG and MFG arrays diverged at phrase boundaries, with a dip in activation in MFG and a bump in activation in IFG, indicating different functional roles for these two LN nodes in contextual integration of linguistic structure. The second experiment isolated the effects of word predictability (how likely a word is given context) from contextual constraint (how strongly the context predicts a specific word). One IFG array

showed sharp activations for low-predictable words in high constraining contexts that indicate expectation violation (e.g., During rush hours in a city it is hard to ride a winter on the green lane.), which was absent from the other arrays. These findings suggest a preference of IFG in the LN to higher semantic and contextual levels of information and a preference of MFG in the LN to word- and phrase-level information.

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Poster

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Topic: F.05. Brain-Machine Interface

Title: Independent, continuous brain-computer interface-based communication by an individual with ALS in a completely locked-in state

Authors: *H. LEVI-AHARONI[1,2], Y. LI[4], A. J. ACOSTA[1], A. DEMPSEY[1], B. E. LACAYO[1], L. A. PANAGOS[1], J. J. JUDE[1,2], C. E. VARGAS-IRWIN[5], J. D. SIMERAL[7,4], L. R. HOCHBERG[7,4,1,3,6,2], D. B. RUBIN[1,2];
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Abstract: Amyotrophic lateral sclerosis (ALS) progression can lead to a completely locked-in state (CLIS), in which individuals lose all voluntary movement and communication. EEG-based brain-computer interface (BCI) systems have been shown to enable communication in ALS [e.g. Okahara et al. 2018], including a recent demonstration in CLIS [Liu et al. 2025]. Implantable BCIs (iBCIs) have restored daily communication in ALS [Card et al. 2024], including in the locked-in state [Vansteensel et al. 2024], and have demonstrated communication in CLIS [Chaudhary et al. 2022]. However, for both BCIs and iBCIs, the long-term viability of restoring independent daily communication for people with long-standing CLIS remains unproven.
Here, we report on the development, deployment, and one year of longitudinal use of an iBCI for communication by an individual with ALS and CLIS enrolled in the BrainGate2 clinical trial (ClinicalTrials.gov ID: NCT00912041). Through real-time decoding of attempted movements,

the participant was able to communicate independently through use of either a three way (Yes/No/No Response) communication system (with an average online decoding accuracy of 63.9 ± 20.1%, where chance is 33.3%) or a or a five-way gesture decoding system that enabled communication via a custom-built nested keyboard interface (with an average accuracy of 65.5 ± 16.1%, where chance is 20.0%).
Despite being in a near-completely locked-in state at trial onset, the participant typed two words on the second day of using the system with the four-choice interface. The yes-no communication system was deployed as a carepartner-operated system for independent, daily use. Over one year, the system was used for communication for an average of 483 ± 156 minutes per day, including 24 ± 16 minutes dedicated to calibration.
Although online performance fluctuated over time, intracortical recordings revealed that motor signals remained sufficiently robust throughout the year to support iBCI-enabled communication despite prolonged CLIS. These results demonstrate that iBCIs can sustain reliable communication in CLIS, offering a viable pathway for restoring autonomy even in the most severe stages of paralysis.

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Poster

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Title: Discrete gesture-based navigation for precise and stable iBCI control

Authors: *A. ABDAL QADER[1], Y. ALI[1], P. H. BECHEFSKY[1], B. RICHARDS[1], A. ACOSTA[2], B. E. LACAYO[2], Z. WILLIAMS[3], L. R. HOCHBERG[2,4,5], N. AU YONG[6,7], C. PANDARINATH[1,6];
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Abstract: Intracortical brain-computer interfaces (iBCIs) have enabled individuals with paralysis to control computer cursors by decoding the intended instantaneous cursor velocity from motor cortical neural activity. However, this continuous control paradigm remains limited in both precision and stability, particularly as neural activity drifts over time. Here, we present a hybrid control paradigm that augments continuous cursor control with discrete gesture-based navigation. Discrete gesture decoding offers a complementary control strategy in which neural activity is classified into attempted hand and wrist movements as distinct commands rather than continuously mapped to kinematics. In BrainGate2 participants T11 and T16, implanted with microelectrode arrays in the hand knob area, we decoded four directional gestures and two action gestures in real-time, enabling them to traverse a grid and acquire targets of variable sizes. In a head-to-head comparison, discrete control maintained 91-100% accuracy across target sizes, while continuous control fell to 20-33% on small targets, demonstrating a clear precision advantage for discrete control. Additionally, by dynamically switching between continuous and discrete modes, both participants were able to acquire targets on a dense 18x18 grid at a 95.4% accuracy compared to 40.0% when using continuous control alone. To evaluate if the stability limitations of continuous control are mitigated under the discrete gesture decoding paradigm, we cumulatively trained a gated recurrent unit network on cued gesture task data from participant T16 recorded over the span of six months and evaluated next-session zero-shot performance offline. Preliminary results show that zero-shot decoding approached within-session accuracy, suggesting that the learned gesture representations transfer across recording sessions even without recalibration. Our findings demonstrate that discrete navigation offers a precision advantage over point-and-click, that a hybrid paradigm combining both provides intuitive and practical control, and that the underlying gesture representations show promising stability across recording sessions.

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Poster

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Title: Intracortical semantic encoding during speech production

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Abstract: For people who are losing or have lost their ability to communicate due to brainstem stroke, ALS, and other neurologic conditions that cause paralysis, brain-computer interfaces have been developed to restore and maintain communication by decoding intended movement directly from the motor cortex.
Participant T22 is a 42 year-old right-handed woman with a history of brainstem stroke that occurred approximately three years prior to enrollment. She has anarthria and tetraparesis at baseline, and communicates through a combination of silent orofacial gestures and an eye-gaze tracking system. Following a task-based and resting-state fMRI localization procedure to identify relevant anatomical targets for sensor placement, she underwent implantation of six 64-channel Neuroport microelectrode arrays in the left hemisphere. Five arrays were placed in the precentral gyrus (with one targeting Brodmann area 6d, three targeting area 55b, and one targeting area 6v) and one array was placed in the inferior frontal gyrus (IFG).
We recorded intracortical neural activity while T22 spoke a series of semantically diverse sentences across several days. We show that sentence-level neural representations of these spoken sentences can be learned by a model, such that large-language model (LLM) semantic embeddings can be predicted with relatively high accuracy (0.75 cosine similarity on average). Furthermore, using a model trained on neural features, we were able to predict spoken word boundaries. These boundaries were then used to train the semantic decoder with multiple context-dependent target embeddings along the sentence, rather than with a single sentence-level embedding. The goal was to guide the model's semantic alignment throughout the sentence and capture the linguistic context at a finer temporal resolution. This approach improved the overall decoding accuracy (cosine similarity).
Future work will focus on such diverging activity in the high-level linguistic representation

which will be used to improve sentence-level decoding accuracy when combined with phoneme-level decoding using articulatory encoded areas of cortex. For each iteratively built up sub-sentence from the language model the beam-search through FST probabilities would be narrowed to fit the most likely sentence based on semantic neural encoding.
Taken together, our work leverages state-of-the-art articulatory speech decoding methods and newly discovered higher-level linguistic and semantic neural features operating at larger timescales in order to explore ways to effectively correct for common error-modes resulting from purely articulatory decoding.

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Poster

PSTR139: Neuroprosthetics: Control of Computer, Devices, and Body Parts II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR139.24/AA20

Topic: F.05. Brain-Machine Interface

Support: McNair foundation

Title: Neural representation of object identity along with motion gesture during tool-use actions in human cortex

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Abstract: Human interaction with the physical environment relies on adaptable, sophisticatedmovements, yet the neural mechanisms translating high-level and context-adjustedcognitive goals into motor execution remain largely unknown. We addressed thisgap in the context of tool use by investigating how object-specific movements areencoded in area 55b and the ventral primary motor cortex (vM1).We recorded intracortical neural activity from a man with amyotrophic lateral sclerosis(ALS) enrolled in the BrainGate2 clinical trial (Participant T19, 41-year-old man withanarthria and tetraplegia). Using microelectrode arrays implanted in the left vM1 and area55b, we analyzed neural responses during an instruction-delay task. The participant wascued to attempt two distinct movements (grasping or pinching) for five everyday objectsfrom two functional categories: cooking utensils (fork, knife, tongs) and carpentry tools(hammer, screwdriver).Our results revealed a clear functional dissociation between these cortical regions.Activity in vM1 was organized by movement type (grasping vs. pinching) but not objectidentity, consistent with the grasping network previously described in non-humanprimates. Conversely, neural signals in area 55b were organized primarily by object identity, independent of the intended movement. Although the cues contained both motiongesture and target object instruction, area 55b selectively represented only the targetobject, suggesting a dissociation from general language processing. Furthermore, neuralrepresentations of objects belonging to the same functional category were correlated,suggesting an organization of accordance for objects. Temporally, tool-specific signals inarea 55b emerged earlier than movement-specific signals in vM1, consistent with asequential unfolding of cognitive-to-motor processing.These findings expand the functional role of area 55b beyond language and speechprocessing, suggesting that its target object encoding could provide cognitive contextto guide subsequent tool-specific movements. Additionally, they pave the way for next-generation neuroprostheses that integrate high-level cognitive goals with low-level motorcommands for more intuitive brain-computer interfaces.The content is solely the responsibility of the authors and does not necessarily representthe official views of the National Institutes of Health, or the Department of Veterans Affairsor the United States Government.CAUTION: Investigational Device. Limited by Federal Law to Investigational Use.

Disclosures: Y. Li: None. **C. Iacobacci:** None. **N. Card:** None. **A. Singh:** None. **D. Avansino:** None. **L.R. Hochberg:** None. **N.R. Provenza:** None. **S.A. Sheth:** None. **J.M. Henderson:** None. **F. Willett:** None. **D. Brandman:** A. Employment/Salary (full or part-time):; Paradromics Inc.. F. Consulting Fees (e.g., advisory boards); Globus Medical Inc.. **S.D. Stavisky:** None. **N.P. Shah:** None.

Poster

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Topic: F.05. Brain-Machine Interface

Support: McNair Foundation

Title: Pre-stimulation neural activity explains variability in electrical stimulation evoked responses

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Abstract: High resolution stimulation of neural circuits is promising for translational applications that aim to modulate neural activity. However, the brain's state is always shifting: animals experience fluctuations inattention, hunger, arousal and so on. Is the neural response to external stimulation dependent on the brain state prior to the stimulation onset? We investigated this question in the mouse cortex.
First, we modeled the responses of individual neurons to electrical stimulation. We applied single-pulse stimulation across 10electrodes and3amplitudes per electrode(3-5μA),and measured activity in 110 neurons using calcium imaging. Each stimulation was repeated over 8 trials across 3sessions. For a given electrode-current combination, the pre-stimulation activity of a neuron predicted the variability in stimulation-evoked activity. Moreover,incorporating pre-stimulation activity across the recorded population improved the prediction of stimulation-evoked activity for individual neurons, reducing error by 39% on average over heldout trials.
Next, we tested the effect of pre-stimulation population activity on the behavioral response to electrical stimulation. A mouse was trained to turn a wheel in response to electrical stimulation of the somatosensory cortex. Behavioral threshold was defined as the closest current level at which the mouse detected the stimulation with 50% probability. At this threshold, the pre-stimulation population activity predicted the behavioral response with over 90% accuracy.
Overall, our results show that apparent variability in neuronal and behavioral responses to electrical stimulation can be partly explained by fluctuations in pre-stimulation activity, which are shared across the population. Traditionally, stimulus-response models have assumed electrical stimulation produces a similar post-stimulation state regardless of the pre-stimulation state. Our results challenge this notion by providing evidence that the stimulation effect varies significantly depending on the pre-stimulation state. Eventually, we hope these observations will help build accurate forward models of electrical stimulation and corresponding inverse methods for precise, cellular-resolution closed-loop electrical stimulation.

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Poster

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Title: Benefits of high-channel-count devices for brain-computer interfaces

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Abstract: Intracortical brain-computer interfaces (iBCIs) decode behavior from neural recordings to restore communication or movement control. Recording hardware has scaled from <100 channels to thousands in state-of-the-art devices. As this scaling continues, two design considerations become increasingly important. First, increasing channel count introduces substantial engineering challenges and surgical considerations, but it remains unclear (1) whether decoding performance improves or saturates as more channels are added and (2) how decoding performance depends on the spatial distribution of recording channels within or across brain areas. Here we systematically examine how channel count and spatial coverage influence motor decoding performance and stability across multiple intracortical monkey BCI datasets. Our analyses span several behavioral paradigms (reaching, cursor control, and force production tasks) across effectors with varying degrees of freedom (DoF), recordings from multiple neural interface technologies (Neuralink N1, Neuropixels, and Utah arrays), and multiple subjects. We trained linear decoders to predict behavioral variables from spiking activity and expressed performance as SNR defined by -10log10(1-R2) (Makin et al., JNE, 2018). We found that decoding performance scaled log-linearly with channel count across tasks, recording devices, and subjects (ranging from 0.6 to 1.7 dB increase per channel doubling), with no evidence of saturation at up to 256 channels - even for single-DoF tasks such as isometric force tracking. Within primary motor cortex (M1), decoder performance was largely insensitive to how much cortical area was spanned by electrodes when sampled at matched channel counts. For multi-area recordings, however, increasing the number of spike-sorted neurons sampled from M1 provided substantially greater performance gains compared to neurons from the dorsal premotor cortex (PMd) (1.05 +/- 0.20 dB per doubling in M1 vs. 0.80 +/- 0.10 dB per doubling in PMd). Finally,

we found that higher channel counts improved decoder stability offline, with decoders trained on more channels maintaining performance over longer periods without recalibration (43.1% increase in half-life per doubling of channels). These results demonstrate that increasing the number of recorded neural channels provides multiple benefits for iBCIs, including improved decoding accuracy and enhanced long-term stability.

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Poster

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Topic: F.05. Brain-Machine Interface

Support: UC Davis School of Medicine Cultivating Team Science Award
NIH/NCATS: UC Davis Clinical and Translational Science Center (CTSC UL1-TR001860)

Title: Towards human-calibrated automated intelligibility evaluation of brain-to-voice synthesis

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Abstract: Intracortical brain-to-voice neuroprostheses can continuously synthesize voice in real-time from the neural activity of a person with ALS [Wairagkar et al. 2025]. Unlike brain-to-text speech decoding, where performance is measured by comparing decoded text against ground truth using established metrics such as word error rate (WER), brain-to-voice has no ground truth acoustic signal. As a result, there are few established metrics to measure synthesis performance. To date, the only reliable method for assessing intelligibility of synthesized voice has been human transcription quantified as WER. However, human transcriptions are costly, tedious, inconsistent across studies, and difficult to scale. Automatic speech recognition (ASR) models

present an appealing alternative, but they are trained on large quantities of typical speech and optimized to minimize WER on that distribution, rather than to match human perception. Because brain-to-voice synthesis differs substantially from typical speech in speaking rate and acoustic quality, and because we want to estimate human intelligibility, these models may be unreliable neuroprosthesis intelligibility evaluators.
We first asked whether human transcription itself is a consistent enough signal to serve as a training target. We characterized inter-transcriber agreement using our brain-to-voice datasets, demonstrating strong cross-group correlations in mean WER ($r = 0.77$-0.83) across semi-professional transcribers and speech language pathologist students, establishing that human transcription produces consistent, reproducible intelligibility signals. We then evaluated whether Whisper, a state-of-the-art ASR model, could serve as a drop-in replacement. Despite moderate correlation with human transcribers ($r = 0.64$ and 0.78 across two brain-to-voice models), Whisper's reliability is inconsistent. For lower-quality synthesis, it exhibits substantially inflated WER relative to humans (43% vs. 38%), hallucinating under low acoustic confidence. For higher-quality synthesis, WER converges closer to human levels, but strong language model priors still substitute probable words for those actually present thereby measuring linguistic plausibility rather than true intelligibility. In both regimes, Whisper does not faithfully reflect what a human listener would perceive.
To address this, we fine-tune Whisper on our brain-to-voice dataset paired with human transcriptions to suppress hallucinations and better reflect human perceptual judgments, laying the groundwork for a scalable benchmarking tool to accelerate brain-to-voice neuroprosthetics development.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

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Program #/Poster #: PSTR140.01/AA24

Topic: F.09. Motor Neurons and Muscle

Support: K01 1K01DE033040-01A1

Title: Masseter sensory-motor dysfunction induces masticatory impairments in humans and animal models of SMA.

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Abstract: Spinal muscular atrophy (SMA) is a neurodegenerative disease affecting motor neurons (MN) and skeletal muscles, where axial and trunk muscles are particularly vulnerable. Patients living with SMA (pwSMA) experience bulbar dysfunction characterized by impairments in food intake and malnutrition. Reduction in milk intake and severe denervation of the masseter muscle (essential for feeding behavior) have been reported in SMA animal models. However, the specific orofacial sensory-motor mechanism resulting in masseter dysfunction in SMA remains unclear. Furthermore, it is not clear whether reduction in body weight in SMA is due to specific impairments in suckling and masticatory behaviors. We hypothesize that impaired masseter muscle activity is a key contributor to reduced food intake and, likely resulting in reduced body weight. In this project, we analyzed masseter sensory-motor circuit activation in animal models as well as pwSMA. Using the SMAΔ7 mouse model, we demonstrate a reduction in the number of proprioceptive synapses on MNs and loss of MNs innervating the masseter muscle at postnatal day 10 (P10), a late stage of disease. To identify potential deficits in the mastication sensory-motor circuit, we investigated the functional and behavioral characteristics in SMAΔ7 mice at P5. We found a reduction in feeding behavior, masseter MN numbers, and proprioceptive sensory synapses (similar to P10), indicating that feeding deficits begin at early stages of disease. Additionally, patch-clamp intracellular recordings from MNs reveal differences between SMAΔ7 and wild-type mice at both P5 and P10; suggesting that the remaining MNs do not compensate for the degeneration of MNs. Lastly, to correlate masticatory deficiencies in pwSMA, we performed electromyogram recordings of the masseter muscle in non-ambulatory (Type II) pwSMA (under treatment with an FDA approved therapy) while measuring maximal bite force. The results revealed alterations in masseter muscle activity compared with healthy

controls, confirming the findings observed in the animal models, namely, a reduction in masseter muscle activity. Our preliminary results in mice and humans support the hypothesis that the reduction in body weight is not solely due to intrinsic muscle atrophy but may be exacerbated by nutritional deficiencies specifically related to masseter muscle dysfunction. Importantly, masticatory deficiencies in pwSMA persist even after treatment with currently available treatments for SMA. Thus, masseter muscle represents a major therapeutic target to address malnutrition in pwSMA and highlight the need to optimize current treatment strategies.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

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Program #/Poster #: PSTR140.02/AA25

Topic: F.09. Motor Neurons and Muscle

Support: JPMJSP2179
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JP20H00549
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Takeda Science Foundation

Title: Investigation of brain regions and molecular mechanisms underlying motor function recovery after brain injury, focusing on AMPA receptors

Authors: *A. YAJIMA, W. OTA, W. NAKAJIMA, Y. KATSUNO, M. NAGATA, T. YAMANOUE, S. ICHIJO, H. ABE, T. TAKAHASHI;
Physiol., Yokohama City Univ. Sch. of Med., Yokohama, Japan

Abstract: When the brain is damaged and loses motor function, other brain regions can compensate for the lost motor function. Such regions are referred to as "**compensatory areas.**" Synaptic plasticity is thought to play a critical role in the formation of compensatory areas. We have focused on AMPA receptors (AMPARs), key mediators of synaptic plasticity, and demonstrated that AMPARs in compensatory areas are critical for functional recovery (Abe *et al., Science,* 2018). However, **the mechanisms underlying the formation of compensatory areas remain unclear.** Our laboratory developed a positron emission tomography (PET) probe ([^{11}C] K-2) that enables visualization of AMPARs in the living human brain (Miyazaki *et al., Nat. Med.*, 2020). Using [^{11}C] K-2 in a clinical study, we found that a higher density of AMPARs in the anterior cingulate cortex (ACC) was associated with greater motor functional recovery

(Abe *et al.,* unpublished data). These findings imply the ACC as a potential predictor of post-stroke functional recovery and a key region involved in neural circuit reorganization during the formation of compensatory areas. To test the role of the ACC in the formation of compensatory areas, we knocked down AMPARs in the ACC of 8-week-old male Long-Evans rats and assessed functional recovery following motor cortex cryoinjury. Notably, AMPAR knockdown in the ACC significantly impaired functional recovery despite rehabilitative training (n = 8-9/group). To elucidate the molecular mechanisms underlying AMPAR-dependent synaptic plasticity during the formation of compensatory areas, we performed single-nucleus RNA sequencing of the ACC following motor cortex cryoinjury. Among the genes identified, we focused on Gene X, which was selectively upregulated in the ACC following motor cortex cryoinjury compared with controls. To determine its functional significance, we knocked down Gene X in the ACC and evaluated functional recovery after motor cortex cryoinjury. Gene X knockdown significantly impaired rehabilitation-induced functional recovery (n = 12/group). Together, these findings suggest that **AMPAR-mediated synaptic plasticity and Gene X signaling in the ACC are critical for the formation of compensatory areas**.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.03/AA26

Topic: F.09. Motor Neurons and Muscle

Title: Dendritic pathology of lumbar motor neurons in ageing rats

Authors: *M. J. FOGARTY, S. CHEUNG;
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Abstract: Lumbar motor neurons (MNs) within the lateral motor column innervate the striated muscles of the lower/hindlimbs. Dysfunction of the control of limb muscles may underlie movement deficits in the elderly. In the human and Fischer 344 (F344) rat motor systems, age-related muscle weakness and behavioural dysfunctions are contemporaneous to MN death. In brainstem MNs, dendritic degenerations are a fundamental pathophysiological component preceding neuronal death. We aimed to determine if dendritic and dendritic spine pathology in lumbar MNs were present in old age and if they occurred prior to MN loss. We used Golgi-Cox and Nissl histology to evaluate dendritic morphology and MN survival in young (6-month), late-middle-aged (18-month) and old (24-month) female and male F344 rats (*n*=8 per age per experiment). Dendritic regression and dendritic spine loss occurred in late-middle-age and old

age, predominantly in larger lumbar MNs (assessing a minimum of 15 MNs per rat). By contrast, lumbar MN death did not occur until old age, and was predominantly observed in larger MNs. Our results are consistent with established age-related motor deficits and sarcopenia in F344 rats. Although more work is needed to determine if synaptic degeneration is causative for age-related neuromotor dysfunction, our results suggest that strategies to preserve dendrites may be of therapeutic utility.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

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Topic: F.09. Motor Neurons and Muscle

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DOD HT94252310374

Title: RNA aptamers targeting ionotropic glutamate receptors are effective in ameliorating motor dysfunction and motor neuron death in both familial and sporadic ALS model mice

Authors: *M. AKAMATSU, J. THOMAS, L. NIU;
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Abstract: Glutamate receptor-mediated excitotoxicity correlates to many neurodegenerative diseases such as amyotrophic lateral sclerosis (ALS). In motor neurons of sporadic ALS patients, abnormal expression of unedited GluA2Q, a subunit of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), causes Ca^{2+} influx, which results in neuronal cell death. Thus, developing potent, selective inhibitors targeting glutamate receptors is a promising therapeutic strategy for ALS treatment. Using an in vitro evolution approach, we have discovered a group of RNA aptamers targeting glutamate ion channels, including those for AMPARs. An aptamer is a single-stranded RNA molecule with a length of 50-100 nucleotides. Due to its flexible tertiary structure, an RNA aptamer can bind tightly to its target and therefore selectively regulate the target function. We previously reported that RNA aptamers targeting AMPARs can ameliorate ALS pathology in AR2 mice, a conditional adenosine deaminase acting on RNA 2 (ADAR2) knock-out mouse model mimicking sporadic ALS. In this study, we further extended our study of RNA aptamers in SOD1-G93A (SOD1) mice, which is the most widely used familial ALS model. We administered RNA aptamers intraventricularly and assessed their efficacy and safety in SOD1 mice, in addition to AR2 mice. FB9s-r, which inhibits AMPARs, and FN1040s, which inhibits both AMPA and kainate receptors, showed significant improvement in the motor function in AR2 mice. Similarly, both RNA aptamers improved the motor function in SOD1 mice as well. Notably, FB9s-r extended the survival time in SOD1 mice for around 2 weeks (median survival time (MST):173 days, confidence interval (CI) 95%, 156 to

180 days), compared to the vehicle control group (MST: 161 days, 95% CI, 148 to 166 days). It should be noted, however, that these RNA aptamers must be administered to SOD1 mice pre-symptomatically (i.e., 8 weeks old SOD1 mice) to be effective. The fact that these RNA aptamers were efficacious in AR2 mice with abnormal AMPARs showed that they worked as intended by inhibiting AMPARs. In SOD1 mice, these RNA aptamers were also efficacious. Our results suggested that AMPARs were involved in motor neuron death, even though there is no known downregulation of ADAR2 in SOD1 mice. Furthermore, our results show that blocking AMPAR-mediated excitotoxicity before symptom onset is critical in preserving motor neuron health. In conclusion, AMPAR selective RNA aptamers are potential therapeutic candidates for treatment of both sporadic and familial ALS.

Disclosures: M. Akamatsu: None. **J. Thomas:** None. **L. Niu:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.05/AA28

Topic: F.09. Motor Neurons and Muscle

Support: NIH R21NS131752
NIH R03NS130425
NIH R01AG083874

Title: Proteomic characterization of the impact of daily enhanced presynaptic calcium entry at the NMJ in the SOD1^{G93A} mouse model of amyotrophic lateral sclerosis

Authors: D. YANG[1], X. ZENG[2], A. GILSRUD[2], P. WIPF[3], T. KARIKARI[2], S. D. MERINEY[1], ***Y. BADAWI**[4,1];
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Abstract: Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease characterized by progressive motor neuron loss and eventual paralysis. Despite intense investigation and significant advances in our understanding of ALS, the mechanisms that initiate and drive disease progression remain unclear, and no curative treatments exist. There is evidence indicating that early synaptic dysfunction at the neuromuscular junction (NMJ) precedes denervation and motor neuron degeneration, making preservation of NMJ integrity and function a critical and underexplored therapeutic target. We have tested the effect of GV-58, a novel Cav2-specific voltage-gated calcium channel gating modifier that we have developed, on neuromuscular function in SOD1^{G93A} ALS model mice. Previously, we showed that chronic daily treatment with GV-58 in these mice increased transmitter release and maintained NMJ innervation. Here, we performed the first comprehensive proteomic analysis of the effects of daily GV-58 treatment in the SOD1^{G93A} ALS model. Male SOD1^{G93A} mice (n=25 across three

independent cohorts) were randomized within litter to GV-58 (150 mg/kg/day IP; n=12) or DMSO vehicle (n=13) for 20 days starting at postnatal day (P) 90. Quantitative LC-MS/MS of quadriceps muscle was performed in all cohorts at P110. Cohort-corrected linear modeling and Ingenuity Pathway Analysis (IPA) identified differentially expressed proteins and enriched pathways; cross-cohort replication required significance in ≥2 of 4 independent analyses without effect direction reversals in any of the analyses. Of 3,633 detected proteins, 89 showed significant changes after GV-58 treatment (24 up-regulated, 65 down-regulated); 28 were significantly changed in at least 2 cohorts, with no reversals of direction in any cohort. These proteins fall into several themes relevant to ALS pathophysiology, including immune and inflammatory responses, calcium binding and transport, metabolism and energy, RNA processing and nuclear biology, cytoskeletal and structural proteins, membrane trafficking and endocytosis, connective tissue and matrix biology, and membrane repair and dynamics. These findings support GV-58 as a positive allosteric calcium channel modulator that strengthens the NMJ, maintains innervation, and exerts multi-target downstream protein effects in ALS model mouse muscle.

Disclosures: D. Yang: None. **X. Zeng:** None. **A. Gilsrud:** None. **P. Wipf:** None. **T. Karikari:** None. **S.D. Meriney:** None. **Y. Badawi:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.06/AA29

Topic: F.09. Motor Neurons and Muscle

Support: R01, NS078375 (NINDS)
R01, AA027079 (NINDS)
Project ALS

Title: Upregulation of Chchd10 leads to pathogenic changes in vulnerable motor units in ALS mice

Authors: *J. WANG[1], J. PARK[1], N. DELESTRÉE[1], K. LING[3], P. JAFAR-NEJAD[4], N. A. SHNEIDER[1], G. Z. MENTIS[2];
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Abstract: ALS is a progressive fatal neurodegenerative disease affecting mostly spinal motor neurons (MNs). Its hallmarks include MN loss, muscle atrophy, paralysis, and death. The most prominent, clinically relevant (recapitulating symptoms in ALS patients) and utilized mouse model of ALS is SOD1-G93A. This mouse model displays sex differences in disease progression, which is of high translational importance. In our study, we employed a behavioral assay that measures the daily travel distances for mice. Postnatal day 50 (P50) was

phenotypically determined to be the onset of disease in male SOD1 mice. Laser capture microdissection and RNA-seq of P50 α-motor neurons that innervate the tibialis anterior muscle, a vulnerable muscle in both human and mouse ALS, identified several dysregulated genes at disease onset. One of them, Chchd10, a gene known to be associated with human familial ALS, was for the first time found to be implicated in the SOD1 ALS pathogenesis. Its upregulation was validated at both mRNA and protein levels. An antisense oligonucleotide (ASO) treatment, which downregulates Chchd10, revealed rescue of the number of motor units destined to be lost under SOD1-G93A conditions. Our findings suggest that Chchd10 is a promising target for ALS therapy.

Disclosures: J. Wang: None. **J. Park:** None. **N. Delestrée:** None. **K. Ling:** None. **P. Jafar-Nejad:** None. **N.A. Shneider:** None. **G.Z. Mentis:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.07/AA30

Topic: F.09. Motor Neurons and Muscle

Title: Scalable iPSC-derived ioMotor Neurons for High-Throughput Screening, disease modelling, and functional genomics in ALS

Authors: *T. HARRIS-BROWN[1], A. VETELEANU[1], L. FOULSER[1], H. GARNETT[1], S. MILDE[1], S. BARBARIA[2], V. YIANNI[1], M. R. COSTA[3], B. NEWMAN[1], G. MASTROGIOVANNI[1], O. DOVEY[1], A. WILCZYNSKA[1], S. SALIC-HAINZL[2], K. FIRTH[1], T. OOSTERVEEN[1], W. BERNARD[1], S. FIEDLER[1];
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Abstract: Lower motor neurons regulate essential neuromuscular activities and their disruption can cause fatal motor neuron diseases like amyotrophic lateral sclerosis (ALS). Conventional iPSC differentiation protocols are lengthy, variable, and unsuitable for high-throughput screening, bottlenecking therapeutic development due to a lack of scalable human in vitro models. To overcome this, bit.bio developed opti-ox™, a deterministic cell programming technology for the rapid and reproducible generation of highly pure human cells. Using this platform, we created ioMotor Neurons, which display classical lower motor neuron morphology and robust neurite outgrowth. By day 4 post-thaw, these cells establish a defined identity, rapidly downregulating pluripotency markers (NANOG) while expressing pan-neuronal (MAP2, TUBB3), cholinergic (ChAT, VAChT), and specific motor neuron (MNX1 & ISL1/2) markers with lot-to-lot consistency confirmed by bulk-RNA sequencing. To facilitate high-throughput phenotypic screening, ioMotor Neurons were adapted into an automated, high-content 384-well imaging format. At 8 days in vitro (DIV), these micro-cultures exhibit pronounced structural networks positive for TUJ1 and ChAT, providing an optimised automated framework for single-cell, AI-guided, visual biology analysis. A major pathological hallmark present in up to 97% of

ALS cases is the nuclear depletion of the RNA-binding protein TDP-43, leading to alternative mRNA splicing failures and cryptic exon inclusion. To model this mechanism, we systematically interrogated the molecular consequences of ALS disease-relevant mutation. Bulk RNA-sequencing of ioMotor Neurons carrying heterozygous or homozygous TARDBP M337V mutations revealed patient-relevant cryptic splicing. Longitudinal profiling up to 30 DIV identified cell-type-specific and shared alternative splicing signatures mapped to validated disease-associated targets (DPP6, SETD5, PRUNE2, and CALD1) matching post-mortem patient tissue.
To demonstrate conserved biomarker downregulation, an antisense oligonucleotide strategy was used to achieve a controlled 50% knockdown of nuclear TDP-43. This depletion comprehensively recapitulated human ALS biology, driving the consistent mis-splicing and significant transcript downregulation of essential targets STMN2 and UNC13A. In conclusion, opti-ox provides a scalable, lot-to-lot consistent, and translationally relevant human platform for generating iPSC-derived motor neurons, representing a powerful tool for advanced disease modelling.

Disclosures: T. Harris-Brown: A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **A. Veteleanu:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **L. Foulser:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **H. Garnett:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **S. Milde:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **S. Barbaria:** A. Employment/Salary (full or part-time):; bit.bio, Vienna. **V. Yianni:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **M.R. Costa:** A. Employment/Salary (full or part-time):; Federal University of Rio Grande do Norte. **B. Newman:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **G. Mastrogiovanni:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **O. Dovey:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **A. Wilczynska:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **S. Salic-Hainzl:** A. Employment/Salary (full or part-time):; bit.bio, Vienna. **K. Firth:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **T. Oosterveen:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **W. Bernard:** A. Employment/Salary (full or part-time):; bit.bio, Cambridge. **S. Fiedler:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.08/Web Only

Topic: F.09. Motor Neurons and Muscle

Support: NS055028

Title: Loss of Neuronal PP1β Impairs Neuromuscular Synaptic Transmission and Causes Progressive Motor Dysfunction

Authors: S. SINGH[1], C. MCKEE[3], Y. LIU[1], Q. YE[1], H. XIA[4], *W. LIN[2];
[1]Neurosci., [2]UT Southwestern Med. Ctr., Dallas, TX; [3]Neurosci., Univ. of Rochester Sch. of Med. and Dent., Rochester, NY; [4]Pharmacol. & Physiology, of Neurosci., Univ. of Rochester, Rochester, NY

Abstract: Reversible phosphorylation is a fundamental regulatory mechanism that governsdiverse cellular processes including synaptic transmission, synaptic plasticity, mitosis,and sperm motility, thereby contributing critically to cognition, motor control, and fertility.Among serine/threonine (Ser/Thr) phosphatases, protein phosphatase 1 (PP1) accountsfor more than 40% of cellular dephosphorylation events in mammalian cells. PP1functions as a holoenzyme, composed of one of three catalytic subunits (PP1α, PP1β,or PP1γ) and one of more than 200 regulatory subunits. While PP1α and PP1γ havebeen extensively studied in neurotransmission and brain function, the role of PP1βremains relatively unexplored, with recent studies implicating it in hippocampal AMPARphosphorylation and presynaptic glutamate release. However, the function of PP1signaling at the neuromuscular junction (NMJ) and in motor function has remainedunknown. Here, we deleted PP1β in neurons using neuron-specific Thy1-Cre^{ERT2} andPP1β floxed mice (Ppp1cb$^{fl/fl}$). We found that PP1β conditional knockout (Thy1-Cre^{ERT2};Ppp1cb$^{fl/fl}$) mice develop severe motor deficits including paw clasping, shallowbreathing, progressive hindlimb dysfunction, and eventual paralysis.Electrophysiological analyses revealed profound impairments in NMJneurotransmission, including reduced miniature endplate potential (mEPP) frequency,impaired neurotransmitter release and defective short-term synaptic plasticity.Additionally, PP1β deficiency altered NMJ transmission kinetics and induced musclephysiological adaptations, including reduced sensitivity to an adult skeletal musclesodium channel inhibitor, suggesting compensatory postsynaptic responses todiminished presynaptic activity. Morphological analyses further demonstrated deficits inmotor innervation and axonal swelling in PP1β KO mice. Collectively, these findingsidentify critical role played by neuronal PP1β in regulating synaptic transmission,synaptic integrity, and motor function in mice.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.09/AA31

Topic: F.09. Motor Neurons and Muscle

Support: NIH R01 CA268125

Title: Motoneuron Drive of Spontaneous Muscle Spasms in Acute Neuropathy

Authors: *K. BUI[1], P. NARDELLI[1], N. HOUSLEY[1], T. C. COPE[2];
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Abstract: Chemotherapy-induced peripheral neuropathy is a common, dose-limiting toxicity of platinum-based agents such as oxaliplatin (OX). Although typically considered a sensory disorder, acute OX neuropathy includes muscle spasms and cramping associated with motor unit fasciculations, implicating motoneuron (MN) involvement. The cellular origin and mechanisms of this early motor dysfunction remain unknown. Here, we provide direct evidence that acute OX exposure rapidly induces centrally generated spontaneous MN activity. Adult Fischer rats were studied one day after OX (30 mg/kg, i.p.). Spontaneous EMG activity occurred in 12/20 (60%) OX-treated rats but was absent in controls. Spike-triggered averaging of simultaneous ventral root (VR) recordings revealed that VR activity consistently preceded EMG spikes with latencies matching axonal conduction, demonstrating a central origin and excluding peripheral sources. EMG-triggered averaging of intracellular MN recordings (n = 2 motor units) localized the source of spontaneous firing to the MN spike initiation zone, identifying a specific subcellular locus of dysfunction. Moreover, spontaneous activity persisted in 11/11 OX-treated rats following extensive dorsal root section, ruling out peripheral sensory drive as the sole source and demonstrating that OX acts independently on central motor circuits. Despite unchanged rheobase and input resistance, intracellular recordings revealed steeper frequency-current relationships in OX-treated MNs, indicating enhanced intrinsic excitability without changes in passive membrane properties. Together, these findings demonstrate acute OX toxicity rapidly inducing increased intrinsic MN hyperexcitability within the spinal cord and driving spontaneous motor output, independent of peripheral sensory activity. Ongoing studies are testing how OX alters voltage-gated conductances using dynamic clamp to establish causal mechanisms and potential therapeutic targets.

Disclosures: K. Bui: None. **P. Nardelli:** None. **N. Housley:** None. **T.C. Cope:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.10/AA32

Topic: F.09. Motor Neurons and Muscle

Support: NIH R01 CA221363
NIH R01 CA268125

Title: Reversing Chronic Motoneuron Hypoexcitability

Authors: *P. NARDELLI[1], T. M. ROTTERMAN[2], K. BUI[1], T. C. COPE[1];
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Abstract: Motoneuron firing becomes unsustainable and erratic in rats following treatment with the widely used platinum-based chemotherapeutic agent oxaliplatin (OX) at human-scaled doses (Housley et al., 2020). Previous work demonstrated that this abnormal firing arises from altered intrinsic membrane properties and can be reproduced in silico by reducing the balance of inward

to outward voltage-gated currents mediated by persistent sodium (NaV1.6) and Kv1 channels, respectively. Here, we tested whether restoring this balance can normalize motoneuron output and motor function. F344-Pirc rats, a genetic model of colon cancer, were treated with OX and studied in terminal experiments using intracellular recordings from spinal motoneurons obtained simultaneously with force measurements from their motor units. Two complementary approaches were used to reverse chronic firing deficits. First, systemic administration of the 5-HT2C receptor agonist lorcaserin, which enhances NaV1.6-mediated persistent inward current, restored sustained and regularly modulated motoneuron firing together with normal motor-unit force production. Second, dynamic-clamp manipulation of NaV1.6 and Kv1.1 conductances demonstrated that increasing the ratio of inward to outward current similarly restored normal firing and force profiles. Consistent with these physiological findings, systemic lorcaserin administration significantly improved ladder-rung walking performance in awake OX-treated rats. Collectively, these findings provide direct evidence that chronic oxaliplatin-induced motoneuron hypoexcitability results from an altered balance of voltage-gated inward and outward currents and can be rapidly reversed by targeted modulation of these channels. The results identify a potential therapeutic strategy for addressing gait impairment, muscle weakness, and fatigue associated with chronic chemotherapy-induced peripheral neuropathy.

Disclosures: P. Nardelli: None. **T.M. Rotterman:** None. **K. Bui:** None. **T.C. Cope:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.11/BB1

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant NS124820

Title: The Resting-State Organization of Lumbar Spinal Interneuron Networks and its Reconfiguration During Sensory-Evoked Motor Behaviors

Authors: *M. H. MOUSA, M. ZABACK, M. A. LEMAY, C. K. THOMPSON;
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Abstract: Spinal interneurons provide the primary source of synaptic input to motoneurons and are central in sensorimotor integration. While spinal networks remain active in the absence of overt sensory and motor drive, the organization of this resting-state activity is poorly understood. Therefore, it is entirely unknown how sensory drive transforms this resting state network activity. Here, we characterize the resting-state activity of large populations of lumbar spinal interneurons and track their network reorganization during sensory-evoked motor behaviors. Extracellular activity was recorded from lumbar spinal interneurons across eight spinal-intact decerebrate adult cats using two 64-channel microelectrode arrays implanted in rostral (L3-L4) and caudal (L5-L7) segments. Recordings of two to three minutes were obtained from laminae

VI-VII or laminae II-V at rest and during selective activation of hindlimb sensory pathways including groups Ia, Ib, II, low and high threshold ipsilateral and contralateral cutaneous afferents, through a combination of mechanical and electrical stimulation of various amplitudes. 2,847 interneurons were identified across all experiments, enabling longitudinal tracking of individual neurons between resting and stimulated conditions. Resting-state activity was characterized using measures of discharge variability, and functional connectivity was quantified using pairwise cross-correlation analyses across short (1 ms) and longer (400 ms) temporal scales. Our findings demonstrate that resting spinal circuitry exhibits sparse yet spatially and temporally structured connectivity. Interneuron discharge properties varied systematically with recording depth, with superficial neurons exhibiting higher and less variable firing rates than deeper neurons. Functional connectivity differed across temporal scales and anatomical regions, with short-timescale interactions concentrated near intermediate depths in caudal lumbar segments and longer-timescale interactions more prominent in deeper regions. Population and network level analyses identified functional ensembles, including widespread low-frequency common drive and localized subnetworks characterized by dense short-timescale connectivity. These findings establish the intrinsic organization of lumbar spinal networks and provide a framework for determining how identified neurons and ensembles are selectively recruited, suppressed, or reorganized by low- and high-threshold afferent activation arising from distinct peripheral nerve sources.

Disclosures: M.H. Mousa: None. **M. Zaback:** None. **M.A. Lemay:** None. **C.K. Thompson:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.12/BB2

Topic: F.09. Motor Neurons and Muscle

Support: NC State University Research Innovation Seed Funding (RISF)

Title: Focused ultrasound modulates spinally evoked motor responses in rats

Authors: X. XUE[1], N. HAKAM[2], M. CHEN[3], X. JIANG[4], *N. SHARMA[5];
[1]North Carolina State Univ., Raleigh, NC; [2]North Carolina State Univ., NC, NC; [3]North Carolina State Univ., RALEIGH, NC; [4]Mechanical and Aerospace Engin., North Carolina State Univ., North Carolina State University, NC; [5]North Carolina State Univ., Cary, NC

Abstract: Focused ultrasound (FUS) is an emerging approach for noninvasive neuromodulation, but its ability to regulate spinal motor output remains incompletely characterized. Here, we evaluated ultrasound spinal neuromodulation in rats using electromyography (EMG) as a quantitative readout of downstream limb muscle activity. First, we tested whether spinal FUS alone could activate motor output. A 3.5-MHz focused transducer was positioned over the spinal

cord, and hindlimb EMG was recorded during repeated baseline, FUS-on, and FUS-off periods at peak negative pressures of 0.4, 0.8, and 1.2 MPa. EMG signals were band-pass filtered and quantified using root-mean-square (RMS) amplitude. Across four rats, FUS significantly increased EMG RMS during ultrasound-on windows relative to ultrasound-off windows at each tested pressure. At the group level, EMG activation exhibited a monotonic increase with acoustic pressure, with mean on/off RMS fold changes of approximately 6, 10, and 12 at 0.4, 0.8, and 1.2 MPa, respectively. Second, we tested whether FUS could suppress electrically evoked motor responses. Electrical stimulation was applied to the spinal cord to generate repeatable EMG responses, while a 950-kHz FUS transducer was positioned over the T10-T12 spinal region. Hindlimb EMG was used as the test readout, and forelimb EMG was recorded as a control. Evoked EMG responses were compared across baseline, concurrent FUS, and recovery periods, and suppression was quantified as the percentage reduction in response amplitude during FUS relative to baseline. Across five rats, the mean suppression ratio was 12.4% at 0.4 MPa, 8.8% at 0.8 MPa, and 3.0% at 1.6 MPa, suggesting that low-to-moderate pressure FUS attenuated FES-evoked spinal motor responses more effectively than high-pressure stimulation. Together, these results show that spinal FUS can both activate EMG activity and suppress electrically evoked EMG responses depending on stimulation context and acoustic parameters. This work supports FUS as a tunable approach for spinal neuromodulation and establishes EMG-based metrics for optimizing ultrasound parameters in future motor-control and neurorehabilitation studies.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

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Program #/Poster #: PSTR140.13/BB3

Topic: F.09. Motor Neurons and Muscle

Support: NYSDOH SCIRB C37718GG
The Feinstein Institutes for Medical Research

Title: Improving hand function after spinal cord injury using AI-guided, paired neuromuscular and dorsal root stimulation

Authors: *E. IBROCI[1], R. P. HENDERSON[2], D. FRIED[2], C. MAFFEI[2], Z. ELIAS[2], A. JANGAM[2], A. B. STEIN[3], C. BOUTON[2];
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Abstract: Recent advancements in transcutaneous spinal cord stimulation (tSCS) and high-resolution neuromuscular electrical stimulation (NMES), coupled with rehabilitation activities, have led to improvements in motor recovery after spinal cord injury (SCI). However, the

combination of these two, especially guided by AI inference of user intention, has largely been unexplored. Here, for the first time, we evaluate novel AI-enabled, self-guided NMES and tSCS technologies for improving hand function in chronic SCI. Three participants with C5-6 SCI (AIS A/C/D) performed grasp-and-lift tasks (cylinders or weighted bottles) without, with, and post-stimulation. Custom high-density forearm and spinal electrode arrays delivered AI-enabled, self-guided NMES stimulation targeting improvement of hand opening (n=2) or closing (n=1). Setup time was <1 minute for the device, and participants independently operated the system after a single session of training. With the AI-guided NMES system, the participants are donned with the electrode array on the dorsal (SCI02-03) or volar (SCI04) surface of the forearm. They are subsequently trained to use the AI algorithms which track and recognize proximal arm reach trajectories in space to infer hand grasp intentions (e.g. cylindrical grasp vs. pinch grasp). Initial mapping of stimulation parameters to identify the desired grasp pattern took ~10 minutes, with patterns saved and reloaded in subsequent sessions, thereby eliminating the need to remap each session. For both functional tasks, a pass was defined as successfully grasping, lifting, and lowering the item without dropping or slipping. Scores and times were recorded pre-, during-, and post-NMES. With NMES, SCI02 achieved more passes with faster completion times (2.7 sec, 18 passes) for one of the larger cylinders (8.94 cm diameter) than without NMES (3.6 sec, 6 passes) in 1 session. Similarly, SCI03 successfully lifted a larger cylinder (4.58 cm) with the NMES system on than without (23 passes out of 32 attempts vs 1 pass out of 12 attempts in 2 sessions). SCI04 lifted all the bottle weights with a greater passing rate compared to without NMES, notably, the heaviest bottle was lifted with a 60% passing rate with NMES compared to a 0% without it. In this study we are collecting data and analyzing differences in ADL function with the NMES system on, as well as introducing paired tSCS, to allow for long-term plasticity changes. These preliminary findings demonstrate user-intent controlled NMES enables meaningful improvements in hand movement, with minimal training time, demonstrating strong potential for clinical translation for rehabilitation in clinical and at-home settings.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.14/BB4

Topic: F.09. Motor Neurons and Muscle

Support: R01DC017718-01A1

Title: Motor response asymmetry in Parkinson's disease after subthalamic nucleus-deep brain stimulation

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Abstract: In this study, we explore hemibody responses to bilateral subthalamic nucleus deep brain stimulation (STN-DBS) in a cohort of patients with Parkinson's disease (PD). Additionally, we categorized responses based on major subscore composites (bradykinesia, rigidity, axial, and tremor). Motor responses are characterized at 6 months and 12 months of STN-DBS in a prospective single-center cohort. Here, we focus on response asymmetry, longitudinal stability of responses, and DBS state differences.Seventy-five PD patients with bilateral STN-DBS were assessed at preoperative (baseline), 6- and 12-month postoperative time points, with stimulation ON and OFF at each postoperative visit. Linear Mixed-Effects modeling assessed changes in MDS-UPDRS scores and motor subscore composites. Motor symptom laterality was evaluated using hemibody motor score and onset side (i.e., where symptoms first manifested). Robustness analyses adjusted for demographics, baseline severity, stimulation magnitude, handedness, and dominant side at each time point.Stimulation showed steady and significant improvement in motor scores (MDS-UPDRS-III) postoperatively compared to baseline, by 19 at 6 months ($p<0.001$) and 18 at 12 months ($p<0.001$). largest score reduction was observed in tremor subscores ($\beta=-8$, $p<0.001$ at 6 months). Stim-OFF score increased by 5 over 12 months, driven mainly by bradykinesia ($\beta=5$, $p<0.001$). The hemibody corresponding to symptom onset showed greater DBS-related improvement than the opposite hemibody, particularly for bradykinesia and tremor; this asymmetry persisted after adjustment for demographics, baseline hemibody severity, stimulation magnitude (e-field), handedness, and current-dominant side.STN-DBS is effective in stable improvement of motor symptoms. Motor improvement was asymmetric relative to symptom-onset side, and this asymmetry persisted after adjustment for baseline severity, stimulation properties, and more-affected-side motor scores.

Disclosures: F. Tabasi: None. **I. Farmer:** None. **A. Rohl:** None. **L. Bergan:** None. **D.M. Corcos:** None. **C. Patterson:** None. **K. Tjaden:** None. **J.D. Greenlee:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.15/BB5

Topic: F.09. Motor Neurons and Muscle

Support: Wings for Life Spinal Cord Research Foundation, WFL-US-07/19:199

Title: Pulse Count and Frequency of Transcutaneous Spinal Stimulation Differentially Modulate Posterior Root Reflexes After Spinal Cord Injury

Authors: *B. J. SULLIVAN[1], E. GORDINEER[1], D. S. STOKIC[3], M. J. KRENN[2];
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Abstract: Transcutaneous spinal stimulation (TSS) is emerging as a noninvasive intervention to restore motor function after spinal cord injury (SCI). Some therapeutic protocols deliver trains of TSS pulses at subthreshold intensities; however, it is unclear how the number of pulses and pulse frequency within a train affect spinal circuitry. To address this, we examined the modulation of posterior root reflexes (PRR) with a conditioning TSS train, varying in number of pulses and pulse frequency. Methods: We recruited twenty individuals with chronic SCI (8 AIS A/B, 12 AIS C/D; median 2.7 [IQR: 1.7-4.8] years post-injury). TSS was delivered through skin electrodes over the T11/12 interspinous space (5×5 cm) and abdominal wall (15×10 cm), with participants resting in the supine position. PRRs were recorded from several leg muscles, including the soleus, which is presented here. Conditioning TSS was delivered with pulse number varied (1, 5, 10, 20 pulses) at a constant frequency (40 Hz), or with frequency varied (10, 20, 40, 80 Hz) at a constant pulse number (10 pulses), with intensity held constant at the median reflex threshold across all recorded muscles. The test pulse was delivered 25 ms after the last conditioning pulse at 1.5× reflex threshold. The outcome measure was the ratio of conditioned-to-unconditioned peak-to-peak PRR amplitude (values <1 indicate suppression). Separate linear mixed-effects models were applied, treating the conditioning parameter as a categorical fixed effect and participant as a random intercept. Results: TSS conditioning suppressed the soleus PRR across all configurations. Pulse number had a strong effect ($p<0.001$): a single pulse suppressed the test PRR to 0.58, whereas 5, 10, and 20 pulses produced further suppression to 0.38-0.41 ($p<0.001$). While frequencies of 10-80 Hz also strongly suppressed test PRR to 0.51-0.53 ($p<0.001$), the pairwise differences were not significant ($p=0.49$). Conclusion: These findings suggest that the temporal structure of near threshold TSS trains is important for modulation of the soleus PRR, which seems to be primarily driven by the first few pulses, whereas pulse frequency within a train has little effect. Understanding which stimulation parameters shape spinal circuitry may help guide the optimization of TSS protocols for improving outcomes after SCI.

Disclosures: B.J. Sullivan: None. **E. Gordineer:** None. **D.S. Stokic:** None. **M.J. Krenn:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.16/Web Only

Topic: F.09. Motor Neurons and Muscle

Title: Risk of sarcopenia among women with obesity

Authors: I. I. RAMOS-RODRÍGUEZ[1], *G. NOLASCO-ROSALES[2], I. E. JUAREZ-ROJOP, Jr.[3], Z. REYES LOPEZ[4], C. GUZMAN[5];
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Abstract: Sarcopenia, defined as the progressive loss of skeletal muscle mass and function, may coexist with obesity, configuring a clinical phenotype termed sarcopenic obesity (SO), which increases the risk of disability, metabolic syndrome, and mortality. In women, the menopausal transition accelerates both visceral fat accumulation and skeletal muscle deterioration, thereby amplifying their differential risk. Despite its clinical relevance, SO remains underdiagnosed in Mexican healthcare settings, where screening criteria have yet to be standardized for this population. The primary objective of this study is to identify the risk of sarcopenia in women with obesity through the application of validated screening tools and segmental body composition assessment. An analytical cross-sectional study is proposed in adult women aged 40-70 years with obesity (BMI ≥ 30 kg/m²). Initial screening will employ the SARC-F questionnaire. Upper limb muscle strength will be assessed by handgrip dynamometry (grip strength, kg), while lower limb muscle strength will be measured using the Sit-to-Stand (STS) test. Body composition will be determined by segmental bioelectrical impedance analysis (BIA) using an InBody device. A high proportion of the enrolled women is expected to present sarcopenia risk according to SARC-F, with greater prevalence among those aged 55 years and older. These findings would support the need to integrate SO screening protocols into routine clinical practice.

Disclosures: I.I. Ramos-Rodríguez: None. **G. Nolasco-Rosales:** None. **I.E. Juarez-Rojop:** None. **Z. Reyes Lopez:** None. **C. Guzman:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.17/BB6

Topic: F.09. Motor Neurons and Muscle

Support: Huntington's Disease Society of America, Human Biology Project 1335564
Infinitome Imaging Award 2021

Title: Selective Changes in Interhemispheric Connectivity in preclinical Huntington’s Disease Gene Expansion Carriers Using Single and Dual-Site Paired-Pulse TMS

Authors: E. WOODS[1], E. O'CONNOR[1], N. SULEYMAN[1], K. RUDDY[2], R. G. CARSON[3], ***R. MCMACKIN**[4];

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Abstract: Background: Paired-pulse transcranial magnetic stimulation (ppTMS) is a non-invasive technique for the interrogation of intracortical inhibitory and facilitatory circuitry[1-3]. These metrics have demonstrated considerable sensitivity in detecting early pathophysiology across a spectrum of neurodegenerative disorders, but have been minimally investigated in Huntington's disease. Dual-site paired-pulse transcranial magnetic stimulation (ds-ppTMS) facilitates evaluating the functional integrity of transcallosal projections, which are fundamental to coordinated interhemispheric communication[4]. Disruption of these pathways is established to occur prior to symptom onset in preclinical Huntington's disease gene expansion carriers (pHDGECs)[5]. However, ds-ppTMS measures have yet to be investigated in pHDGECs to date. **Methods:** Structural 3T MRI was collected from healthy adult participants (n=16) and pHDGECs (n=10). Test stimuli were applied to the dominant primary motor cortex, with threshold tracking of motor evoked potentials recorded from abductor pollicis brevis, targeting 200μV peak-to-peak amplitude. Conditioning pulses (120% of resting motor threshold) were applied over non-dominant motor, premotor (6a and 6d), or dorsolateral prefrontal (DLPFC, 8av, p9-46v and 46) regions to assess their influence on dominant primary motor cortex excitability. Short and long interval intracortical inhibition were measured, applying both conditioning and test stimuli to the dominant motor cortex, to assess tonic GABA, GABA-A and GABA-Bergic intrahemispheric inhibition. **Results:** Premotor (6d only) to primary motor interhemispheric inhibition was significantly reduced in pHDGECs compared to control participants ($p = 0.048$). Further, short interval intracortical inhibition (1ms interstimulus interval only) was also reduced in pHDGECs ($p = 0.0229$). No other measures reached statistical significance. **Conclusion:** This study demonstrates selective reductions in intracortical and interhemispheric inhibition in pHDGECs. These findings evidence inhibitory cortical circuit dysfunction before the onset of motor symptoms. These changes were temporally and region-specific, as opposed to widespread alterations across motor networks. These findings highlight the potential of these measures as early biomarkers for Huntington's disease. 1. Almohmadi et al. Brain Res Bull. 2025 1(225):111349 2. Taube et al. J Physiol. 2026 604(2):689-706 3. Vucic et al. Clin Neurophysiol Pract. 2018 1(3):164-72 4. Calvert et al., Clin Neurophysiol. 2020 131(11):2551-60 5. Di Paola et al., Cereb Cortex. 2012 22(12):2858-66

Disclosures: E. Woods: None. **E. O'Connor:** None. **N. Suleyman:** None. **K. ruddy:** None. **R.G. Carson:** None. **R. McMackin:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.18/BB7

Topic: F.09. Motor Neurons and Muscle

Support: Startup fund from University of Pittsburgh

Title: Neural mechanisms underlying spasticity and the potential of transcutaneous electrical stimulation to reduce it in children with cerebral palsy

Authors: *A. CEKO[1], P. LEKOVIC[2], E. ZAVACKY[4], Y. CHEN[3], B. PETERSEN[3], M. GORASSINI[5], G. PRAT ORTEGA[3];
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Abstract: Cerebral palsy (CP) is a spectrum of neurodevelopmental disorders caused by an early brain lesion and is the most common motor disability in children. Spasticity and hypertonia are major contributors to disability in CP characterized by involuntary muscle contractions resulting from hyperexcitability of the spinal circuits. Current treatments are often insufficient, highlighting the need for more effective treatments.Although the cerebral origin of CP is well established, the mechanisms leading to spinal hyperexcitability and thus spasticity, remain poorly understood. In particular, the contribution of corticospinal, sensory motor pathways, and motoneuron properties has yet to be determined, limiting the development of targeted therapies. While recent studies have shown that transcutaneous spinal cord stimulation (tSCS) can improve motor function in this population, its effects on spasticity have been inconsistent.Here, we investigated the contributions of corticospinal and sensory-motor pathways and motoneuron properties to spinal hyperexcitability using a set of human electrophysiological experiments. We also evaluated the potential of tSCS to reduce the contribution of each of these elements. Our preliminary results show that: 1) children with CP have hyperexcitable spinal circuits and 2) lumbar tSCS normalizes these aberrant responses, reducing spasticity. Interestingly, low stimulation amplitudes that likely do not directly recruit proprioceptive afferents, but instead recruit only cutaneous afferent, also produce a similar reduction in spasticity. Overall, these findings provide an electrophysiological characterization of spinal hyperexcitability and show that transcutaneous electrical stimulation may be a promising approach to reduce spasticity in children with CP.

Disclosures: A. Ceko: A. Employment/Salary (full or part-time):; University of Pittsburgh, Department of Neurological Surgery. 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.; Startup fund from University of Pittsburgh. **P. Lekovic:** None. **E. Zavacky:** None. **Y. Chen:** None. **B. Petersen:** None. **M. Gorassini:** None. **G. Prat Ortega:** None.

Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.19/BB8

Topic: F.09. Motor Neurons and Muscle

Title: Effects of Music Stimulation on Electroencephalography and Surface Electromyography Coupling During Deadlift Exercise

Authors: *G. D. LOPEZ-ARMAS[1], R. MAGAÑA-DIMAS[3], A. CANTON-MORENO[2], E. FREGOSO-CUARENTA[2], A. OSUNA-RODRIGUEZ[2], A. LOZANO-GARCIA[4];
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Abstract: Introduction: Listening to music during deadlift exercise may reduce fatigue and enhance performance by diverting attention from physical discomfort, such as muscle fatigue or shortness of breath, and by promoting dissociative thoughts. Exercise is widely recognized for its benefits to brain health, including reducing the risks of dementia, depression, and stress. Additionally, it contributes to the restoration and maintenance of cognitive function and metabolic control. This study aims to evaluate the effects of music on deadlift performance by assessing EEG waves and sEMG signals. **Methodology:** Twelve healthy male amateur weightlifters (aged 18-30) participated in this study and provided informed consent in compliance with the Helsinki guidelines. On the first day of testing (without music), the subject will perform a single deadlift repetition, gradually increasing the barbell weight until reaching their 1RM (one-rep maximum). Based on that 1RM, 60% is calculated as the average weight used in both tests. **Test A:** The subject performs deadlifts at 60% of their 1RM to failure, without listening to music. **Test B:** The subject will perform deadlifts at 60% of their 1RM to failure, listening to the songs that motivate them most while exercising. The tests are randomized: one subject starts with Test A and the other with Test B, to avoid affecting the results. Biopac MP36 hardware was used for EEG and sEMG acquisition with Ag/AgCl electrodes. For EEG, electrodes were placed in motor areas (C3, C4, Cz) according to the international 10-20 system; for sEMG, electrodes were placed on the lumbar spinal erectors and hamstring muscles. For statistical analysis, we used Python v.3.11, considering Root mean square (RMS), Power Spectral Density (PSD), and wavelet transforms on EEG and sEMG, applying spectral coherence in the beta band (10-40 Hz) and the band (20-450 Hz), respectively. Finally, using a Student's t-test, we compared the number of repetitions for each subject with and without music. **Results:** According to the number of deadlift repetitions performed with music are significant, with a p-value of < 0.001 (t-test); as for the EEG and sEMG biosignals, they show a significant correlation with the presence of music, mainly during the eccentric phase of the deadlift, as opposed to the concentric phase, thus demonstrating that music has a triggering effect on the performance of high-intensity exercises. **Conclusions:** The presence of music indicated motor cortex activation on EEG and was associated with increased muscle activation, as measured by sEMG, during deadlifts. Future research should investigate strategies to optimize training methods.

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Poster

PSTR140: Motor Neurons: Modulation, Injury, and Disease

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR140.20/BB9

Topic: F.09. Motor Neurons and Muscle

Title: Kidney-Brain Signaling and Motor Function: Associations Between Circulating Uromodulin (Tamm-Horsfall Protein, THP) and Human Performance

Authors: *M. L. SHAND[1], K. A. LAFAVERS[2];
[2]ACBP, [1]Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Background:Maintenance of motor function depends on tight regulation of oxidative stress within neural and musculoskeletal systems. Excess reactive oxygen species (ROS) disrupt calcium signaling, impair neuronal and muscular function, and contribute to age-related declines in motor performance. Uromodulin (Tamm-Horsfall protein; THP), a glycoprotein produced by the kidney and released into circulation, has been shown to attenuate oxidative stress through modulation of Transient Receptor Potential Melastatin 2 (TRPM2), a ROS-sensitive calcium-permeable ion channel expressed throughout the nervous system and peripheral tissues. Given the importance of TRPM2 signaling in cellular responses to oxidative stress, we examined whether circulating THP levels are associated with human motor performance.Methods:Serum samples were obtained from 48 participants enrolled in the Function, Imaging, and Testing (FIT) Core of the Indiana Center for Musculoskeletal Health. Participants were stratified by sex and age (20-34, 35-49, 50-64, and ≥65 years) and ranked according to composite motor performance scores derived from grip strength and 30-second chair stand testing. Within each sex, the highest- and lowest-performing quartiles (n=12/group) were designated as high- and low-performance cohorts. Circulating THP concentrations were quantified by ELISA. Associations between THP and performance metrics were evaluated using two-sample t-tests and multivariable regression analyses.Results:Circulating THP concentration positively correlated with average relative peak power across the study population (p=0.0053). Participants exhibiting superior motor performance demonstrated higher serum THP levels, with a trend toward significance when compared with lower-performing individuals (p=0.0526). Age-stratified analyses revealed the strongest association in adults aged 35-49 years, where high performers exhibited significantly elevated THP concentrations relative to low performers.Conclusion:These findings identify circulating THP as a potential biological correlate of human motor function. Given its reported regulation of ROS-sensitive TRPM2 signaling, THP may represent a previously unrecognized component of kidney-brain and kidney-muscle communication that supports motor performance. Ongoing studies in THP+/+ and THP−/− mice are investigating whether THP influences age-related motor decline through modulation of oxidative stress and calcium-dependent signaling pathways.

Disclosures: M.L. Shand: None. **K.A. LaFavers:** None.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.01/BB10

Topic: F.09. Motor Neurons and Muscle

Support: U24NS126936
R01NS109237

Title: Spatial Organization of Muscle Fiber Types Within and Across Compartments of the Mouse Triceps Brachii

Authors: *S. KILIC[1], A. JOSHI[2], A. L. JACOB[1], S. J. SOBER[1];
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Abstract: Skeletal muscles are composed of heterogeneous muscle fiber types, which are divided into two broad classes: slow-twitch (Type I) and fast-twitch (Type II) fibers, with distinct contractile speeds, force outputs, and fatigue resistance. How these muscle fiber types are structurally organized within and across compartments with different functional properties, and how this organization relates to CNS motor function, remain open questions. The mouse triceps brachii contains multiple compartments, the long and lateral heads, that work together to produce elbow extension but have distinct biomechanical roles and anatomy. Both heads share a distal insertion, but the long head spans both the shoulder and elbow, while the lateral head functions only at the elbow. To investigate the distribution of fiber types within and across these muscle compartments with biomechanical differences, we characterized fiber-type composition and cross-sectional area (CSA), along with their spatial distribution, using immunofluorescence targeting myosin heavy chain (MyHC) isoforms, combined with automated segmentation and quantitative spatial analysis. Preliminary findings show that the long head has more fibers overall with a higher proportion of Type IIa fibers (fast oxidative-glycolytic), consistent with its stabilizing role; meanwhile, Type IIb (fast glycolytic) fibers are the dominant fiber type in both heads. Additionally, fiber-type composition appears to vary along the proximal-distal axis within heads, suggesting that regional organization is structure-driven to meet functional demands. These findings suggest that region-specific muscle structure may contribute to the differential motor unit recruitment observed between triceps heads.

Disclosures: S. Kilic: None. **A. Joshi:** None. **A.L. Jacob:** None. **S.J. Sober:** None.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.02/BB11

Topic: F.09. Motor Neurons and Muscle

Support: SECIHTI (CF 1311312)
SECIHTI (AFH 1157306)

Title: Characterization of the reflex activity of the external urethral sphincter induced by selective mechanical stimulation of urethral regions in the female rabbit

Authors: *A. FLORES HERNANDEZ[1], S. SANCHEZ MENESES[2], F. CASTELÁN[3], M. MARTINEZ-GOMEZ[4], D. L. CORONA QUINTANILLA[2];
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Abstract: The control of the lower urinary tract depends on a complex network of reflexes that act in a coordinated and interdependent manner. Afferents from the bladder, transmitted primarily by the pelvic nerve, and from the urethra, carried by the pelvic and pudendal nerves, together with modulation by supraspinal centers, determine the activation and coordination of the reflex responses that regulate urinary continence and bladder emptying. During normal cycles of bladder filling and emptying, afferent fibers from the bladder transmit information regarding the distension and pressure exerted on the detrusor muscle. In turn, urethral afferents provide information about distension and intraurethral pressure. During the storage phase, this sensory information contributes to the activation of various structures responsible for maintaining urethral closure, notably the external urethral sphincter (EUS). The EUS is a ring-shaped striated muscle that surrounds the urethra; its activity can be controlled both voluntarily and by reflex, and it plays an important role in maintaining urinary continence. However, various studies have debated the extent to which this muscle contributes to the generation of urethral pressure along the length of the urethra and, consequently, its role in the urethral closure mechanism. In this regard, it is important to determine whether EUS activation varies depending on the stimulated urethral region and whether these differences might contribute differently to urethral closure. For this purpose, electromyographic recordings of the EUS were obtained from anesthetized female rabbits in response to selective mechanical stimulation of the proximal, medial, and distal regions of the urethra. The results demonstrated that mechanical distension of these regions triggers differential changes in both urethral pressure and EUS activity patterns.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.03/BB12

Topic: F.09. Motor Neurons and Muscle

Support: NIH-NINDS R01-NS047357
NIH-NINDS R21 NS106209
NIH-NINDS T32-NS096050
2026 Animal Research Tomorrow 3R Award

Title: Modulation of Reciprocal Inhibition and Excitation between Antagonist Motor Pools by Foxp2-Expressing V1 Interneurons and Renshaw Cells

Authors: *A. E. WORTHY[1], W. M. MCCALLUM[1], B. M. LUCADAMO[1], J. CHARLES[1], S. J. SOBER[2], F. J. ALVAREZ[1];
[1]Cell Biol., [2]Biol., Emory Univ., Atlanta, GA

Abstract: Reciprocal inhibition between antagonist motor pools is a canonical spinal circuit mechanism supporting coordinated flexion-extension movements. This pathway is classically attributed to Ia inhibitory interneurons (IaINs), but mounting evidence suggests that multiple inhibitory and excitatory interneuron classes shape its functional output. Here, we examined how Foxp2-expressing V1-derived IaINs (Foxp2-V1s) and Renshaw cells (RCs) interact to regulate reciprocal inhibition and excitation between antagonist motor pools.
We used intersectional genetic diphtheria toxin strategies to selectively ablate either RCs or Foxp2-V1s in mice. In decerebrate preparations, electromyographic (EMG) activity was recorded simultaneously from lateral gastrocnemius (LG) and tibialis anterior (TA) muscles. High-frequency (100 Hz) vibration of the LG was used to preferentially activate Ia afferents and engage reciprocal pathways onto TA motor pools.
In decerebrate mice, LG vibration elicited weak reciprocal excitation in the TA bulk EMG as opposed to pure reciprocal inhibition. Reciprocal excitation of TA motor pools was enhanced following ablation of Foxp2-V1s, indicating that these interneurons suppress reciprocal excitatory drive to antagonist motor pools in non-ablated mice. Reciprocal excitation was reduced, however, following ablation of RCs. Our results suggest that RC-mediated inhibition of IaINs may permit or amplify reciprocal facilitation in non-ablated mice. In parallel we confirmed extensive RC innervation of subpopulations of Foxp2-V1 interneurons.
Together, these results indicate that reciprocal motor output reflects a balance between inhibitory IaIN signaling and parallel excitatory pathways, likely mediated by intermediate zone interneurons receiving convergent sensory inputs. We propose that Foxp2-V1 IaINs normally mask reciprocal facilitation, while RC inhibition dynamically gates this masking, allowing reciprocal excitation to emerge when needed.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.04/BB13

Topic: F.09. Motor Neurons and Muscle

Support: R01-NS047357
R01-NS109237
R21-NS106209
U24NS126936
T32-NS09605

Title: The contribution of Renshaw Cells to limb movements during mouse locomotion.

Authors: *W. MCCALLUM[1], A. E. WORTHY[2], B. LUCADAMO[3], J. CHARLES[4], K. A. THOMAS[5], S. J. SOBER[5], F. J. ALVAREZ[4];
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Abstract: Although Renshaw Cells (RCs) were first described in the 1940's as a spinal interneuron forming a disynaptic circuit that provides recurrent inhibition to motoneurons, their exact role in motor control remains a matter of debate. Despite many advances in understanding their connectivity and electrophysiological properties, RC function during motor control in freely behaving animals has been difficult to decipher. Due to the lack of animal models to manipulate specifically RCs, studies investigating RC contributions to motor control have been largely based on correlational observations of the strength of RC firing and recurrent inhibition during different behaviors, or on computer modeling relying on many assumptions. To address this gap, we leveraged novel genetic mouse models to introduce diphtheria toxin receptor (DTR) specifically into RCs based on their expression of engrailed-1 (V1 derivation) and calbindin. For this purpose, we used a DTR allele expressed conditional to both flpo from the *en1* gene and a destabilized Cre from the *calb1* gene and that allows restricting cre recombination to only postnatal day 15 for specific RC targeting (RC-DTR). Diphtheria toxin was injected into the intrathecal space of adult RC-DTR mice using a hyperbaric solution to restrict the ablation to lumbosacral RCs. By combining 3D tracking with high-density electromyography (EMG) recordings of hindlimb muscles in animals before and after RC deletion, we quantify the contribution of RCs to limb movements and population spiking of hindlimb motor units during locomotion. Following RC removal, animals successfully locomote at multiple walking speeds. However, the step cycles have a shortened stance phase at all speeds, characterized by an earlier lift-off per step and by variations in joint angles at lift-off. Initial analyses of EMG recordings show increased motor unit bursting durations in both flexor and extensors during the stepping. Future and ongoing analysis of EMG activity will reveal the exact changes to lumbar motor output after the removal of RCs.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.05/BB14

Topic: F.09. Motor Neurons and Muscle

Support: NIH grant U24NS126936
NIH grant R01NS109237
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Title: Spinal circuits for locomotor flexibility

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Abstract: Central pattern generators (CPGs) in the spinal cord consist of six interneuron classes that generate the precise timing and patterns of muscle contraction underlying locomotion. Targeted perturbations of CPGs have identified how individual interneuron classes contribute to different aspects of locomotion, such as rhythmogenesis (excitatory V2a and V3), flexor-extensor muscle coordination (inhibitory V1 and V2b), and interlimb coordination (mixed V0, excitatory V2a and V3, and inhibitory V2b). However, it remains unclear whether and how these interneuron classes modulate motor unit recruitment and kinematic patterns to enable the striking locomotor flexibility animals exhibit across varying terrains and speeds. To identify the contributions of spinal CPG neuron classes to locomotor flexibility, we performed kinematic analyses and single-unit electromyography recordings via Myomatrix arrays in flexor (tibialis anterior) and extensor (lateral gastrocnemius) muscles of the mouse hindlimb. We combined these recordings with intersectional chemogenetics to selectively and transiently manipulate spinal V2a interneurons and quantify their contributions to behavior. Mice were tasked to cross a beam of varying widths (5, 12, 25 mm) or walk at varying treadmill speeds (6, 9, 12, 24, 36 cm/s), before and after administration of clozapine-N-oxide, which drives the activity of intersectionally expressed DREADDs, namely hM3Dq (activation) or hM4Di (silencing). Preliminary results show that narrowing beam widths increases flexor activation during stance and extensor activation during swing, thereby increasing co-contraction of the muscle pair; this likely reflects the increased demand for tonic muscle activation to maintain balance on a narrow surface. By contrast, flexor-extensor activation becomes more clearly separated as mice walk at increasing treadmill speeds. When V2a neurons are chemogenetically activated, mice start to display increased flexor activity and co-contraction throughout the step cycle while crossing a 25 mm beam, adopting the same pattern that control mice display only on the 5 mm beam. The resemblance in kinematic and muscular activity between the very narrow beam and V2a activation on wider beams suggests that V2a interneurons may have important contributions to balance control. However, activation of V2a interneurons has no detectable effect on performance on the treadmill. Together, these observations suggest a novel task-specific role for V2a interneurons in modulating muscle activity, being especially important in locomotor tasks that require postural control and finely tuned flexor-extensor coordination.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.06/BB15

Topic: F.09. Motor Neurons and Muscle

Title: Reproducibility of Motor Unit Modes Across Sessions: Evidence from Tracked Motor Units

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Abstract: The central nervous system controls voluntary actions by establishing low-dimensional neural modules, which at the motor unit (MU) are known as MU modes. MU modes are thought to reflect the strength of shared synaptic input onto spinal motor neurons. However, the extent to which MU modes are reproducible across sessions has not been established. The purpose of this study was to determine the reproducibility of MU modes across two sessions and whether a similar mode structure is preserved among tracked MUs. High-density surface electromyographic (EMG) recordings were obtained from the biceps femoris and semitendinosus muscles of a subset of healthy adults (n = 5; 1 female; 22.6 ± 2.1 yrs) during submaximal isometric contractions with the knee flexors. The target force was 10% of the maximal voluntary contraction force. MU discharge times were identified using a blind source separation technique (MUedit software), and the same MUs were tracked across sessions using a filter reapplication approach. Modes were extracted from smoothed steady-state discharge rates using factor analysis, with the number of modes determined by parallel analysis. Reliability was assessed using Tucker congruence coefficients comparing MU loading patterns between sessions. On average, 41.2 ± 9.7 and 40.4 ± 13.6 MUs were identified in each participant in the two sessions, respectively, with 14.2 ± 3.7 MUs tracked across sessions. Preliminary findings indicated that two modes were identified in all participants. Tucker congruence matrices showed clear diagonal dominance across sessions. The congruence coefficients for all MUs were 0.82 ± 0.07 (Mode 1) and 0.51 ± 0.26 (Mode 2), with low off-diagonal values (0.07 ± 0.08). Among tracked MUs, coefficients were 0.79 ± 0.14 (Mode 1) and 0.72 ± 0.18 (Mode 2), with off-diagonal values of 0.20 ± 0.08. These findings indicate that MU modes represent reproducible control modules that presumably reflect the proportion of shared synaptic input onto motor neurons that innervate two hamstring muscles during submaximal isometric contractions.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

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Program #/Poster #: PSTR141.07/BB16

Topic: F.09. Motor Neurons and Muscle

Support: NSERC

Title: Distinct motor unit recruitment patterns emerge during a novel chord learning task

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Abstract: Learning novel motor skills often requires acquiring novel muscle activation patterns. Much is known about how neural activity in motor cortical regions changes with motor learning. Less is known about how patterns of motor unit (MU) recruitment may change. The traditional view is that a single common descending input recruits all MUs within a muscle. Recently, a new model has been proposed in which MUs are organized into functional groups, within or across muscles, each driven by distinct inputs. Little is known about how these multiple inputs are selected for a given task, or modulated during learning. We investigated this question in the context of a chord learning task involving the 5 digits of the human hand. Seven participants practiced a chord production task in which they matched finger flexion or extension forces with the 5 digits of their right hand in a naturalistic open-grasp posture (Mindmaze Hummingbird). We recorded MU activity from the ring finger compartment of extensor digitorum communis using a 16 channel Myomatrix indwelling electrode array (NP-1x32-XZI-10). Participants practiced two chords over 12 blocks (240 trials/chord). The two chords required identical ring finger extension forces (1 ± 0.2 N, sustained for 0.6 s), but different force targets in the other 4 digits. Signals were acquired using Open Ephys, decomposed offline using EMUsort, and refined in Phy. Over 12 blocks, mean chord success rate improved by 32.5 % and average execution time decreased by 2.4 s. For each trial we constructed mean firing rate vectors for isolated MUs (n=105) during successful hold periods. We used cosine similarity to characterize how firing rate vectors changed over practice blocks both within and between chords. Within-chord cosine similarity increased across practice blocks, indicating increasingly stable motor unit recruitment patterns for repeated execution of the same chord. In contrast, between-chord cosine similarity decreased across blocks. This suggests a progressive differentiation of recruitment structure between chords, despite the fact that ring-finger force production was the same in both chords. These findings indicate that learning novel motor skills involves reorganization of spinal motor-unit recruitment into increasingly stable and chord-specific patterns.

Disclosures: P.M. Tilley: None. **P.L. Gribble:** None.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.08/BB17

Topic: F.09. Motor Neurons and Muscle

Title: The effects of training with different muscle contraction patterns on motor unit activity characteristics

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Abstract: [Abstract] Neural adaptations are considered a primary contributor to early performance improvements following resistance training, preceding measurable muscle hypertrophy. Although MU recruitment and discharge behavior have been investigated after isometric training, the extent to which contraction modality—specifically concentric and eccentric contractions—modulates neuromuscular control remains unclear. Therefore, this study aimed to determine how short-term, resistance training influences MU activity during both static and dynamic tasks, and whether these effects depend on contraction modality.HDEMG was used to record MU activity from the right tibialis anterior muscle in six healthy adult males. MVC during ankle dorsiflexion was assessed, and participants performed tasks on the BIODEX system at three ankle angles (plantar10°, 0°neutral, and dorsal10°) for isometric contractions, as well as isotonic contractions at 10% and 25% MVC intensities. Participants completed either concentric or eccentric training three times per week for two weeks, with a four-month washout period between conditions. MU activity was quantified using meanDR, RT, CV, and RMSE. [KN2] Muscle thickness was assessed using ultrasonography.No significant changes in muscle thickness were observed, indicating an absence of hypertrophic adaptation. In dynamic tasks, no consistent differences were detected between contraction modalities in meanDR, RT, CV, or RMSE. In contrast, during isometric contractions, differences in meanDR across joint angles were reduced following training. Additionally, meanDR increased after concentric training and decreased after eccentric training, with greater changes observed at 10% MVC compared to 25% MVC.These findings suggest that short-term contraction-specific training primarily induces neural adaptations rather than structural changes. The reduction in meanDR differences may reflect improved neural drive stability or enhanced MU coordination. Modality-dependent changes during dynamic tasks indicate rapid plasticity in neuromuscular control, particularly under low-force conditions, highlighting contraction modality as a key factor influencing early MU-level adaptations.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

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Topic: F.09. Motor Neurons and Muscle

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JSPS KAKENHI 25K14583
JST SPRING JPMJSP2108

Title: Influence of contralateral cooling on motor unit behavior during rapid contractions in humans

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Abstract: Temperature influences motor performance, including the rate of torque development (RTD). We previously observed that cooling of the lower limb decreased dorsiflexion RTD but was accompanied by earlier motor unit recruitment and a higher discharge rate in the tibialis anterior muscle during rapid contractions. However, it remains unclear whether these changes in motor unit behavior are primarily driven by peripheral factors (e.g., decreased muscle temperature) or by systemic neural modulations (e.g., altered spinal excitability associated with autonomic responses). In this study, we aimed to compare the influences of ipsilateral and contralateral cooling on RTD and motor unit behavior in humans. Fifteen healthy participants (five females) rested in a sitting position while immersing their lower legs in water of different temperatures (Control, ~33°C for both legs; Ipsilateral cooling, ~10°C for the right leg and ~33°C for the left leg; Contralateral cooling, ~33°C for the right leg and ~10°C for the left leg) for 20 min in each condition. Twitch contractions and H-reflexes of the right tibialis anterior muscle were evoked every 5 min throughout the experiment using supramaximal and submaximal common peroneal nerve stimulation, respectively. Participants then performed maximal voluntary isometric contractions, rapid contractions, and a low-intensity triangular contraction of dorsiflexors while maintaining water immersion. High-density surface electromyography was recorded from the tibialis anterior muscle and decomposed into individual motor unit spike trains. Electrocardiography was also recorded throughout the experiment. Ipsilateral cooling decreased RTD in both the early (0-50 ms after torque onset) and late (0-150 ms) phases, whereas contralateral cooling had no consistent effect. Motor unit recruitment time relative to torque onset and discharge rate at recruitment were comparable across conditions. We also observed no significant differences in H-reflex/M-wave ratio, ΔF (an indicator of persistent inward current), or autonomic indices derived from heart rate variability. However, individual responses to water immersion varied, such that decreases in recruitment time were associated with both decreases in low/high-frequency power ratio of heart rate variability and increases in early RTD. These findings suggest that contralateral cooling has little influence on motor unit behavior during rapid contractions, spinal excitability, or autonomic activity at the group level. However, individual variability in autonomic modulation may contribute to interindividual differences in motor unit responses to cooling.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

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Topic: F.09. Motor Neurons and Muscle

Support: DFF 123723

Title: Force field adaptation of lower limb muscle activity and kinematics during human bipedal walking

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Abstract: Walking in natural, complex environments requires ongoing, dynamic modulation of motor patterns to accommodate changing conditions. Here, we hypothesized that repeated stepping in an elastic force field would elicit time-dependent reorganization of muscle activation patterns and foot trajectory control, indicative of adaptive sensorimotor integration. Fifteen neurotypical adults (age range: 25-42 years) performed a visually- guided over-ground double-step task consisting of 50 baseline steps, 50 adaptation steps, and 20 after- effect steps. An elastic band was attached to the right foot, with a resistance corresponding to 20% of the maximum voluntary contraction force, to assist with dorsiflexion. The movement trajectories of the right foot and the rectified area under the curve of the electromyography (EMG) were analyzed for the tibialis anterior (TA), medial gastrocnemius (GM), and soleus (SOL) muscles during the swing phase prior to target hit. Linear mixed models revealed that foot trajectory and EMG activity of TA, GM, and SOL differed significantly across the three phases. Pairwise contrasts confirmed that the adaptation phase differed significantly from both baseline and washout for foot trajectory (in y and z direction, $p < 0.0001$), and muscle activity (TA and SOL, $p < 0.0001$) while baseline and washout were statistically comparable across these measures, suggesting restoration of pre-perturbation patterns following force field removal. Within the adaptation phase, paired comparisons between early (steps 51-60) and late (steps 91-100) revealed significant reductions in TA ($t(14) = 2.954$, $p = 0.011$), SOL ($t(14) = 2.626$, $p = 0.021$), and foot trajectory in z direction (Wilcoxon signed-rank: $W = 92$, $p = 0.014$), reflecting progressive modulation of neuromuscular output across force field exposure. These findings show that the neuromuscular system transiently adapts lower-limb muscle coordination and foot trajectories in response to external force perturbations, with motor patterns gradually adjusting during exposure and fully reverting after removal. This adaptability is critical for navigating complex environments and has implications for designing targeted rehabilitation and assistive interventions that involve adaptive motor recalibration.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

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Program #/Poster #: PSTR141.11/BB20

Topic: F.09. Motor Neurons and Muscle

Title: Pulsed direct current stimulation acutely enhances intermuscular coherence between rotator cuff and deltoid muscles during fatigue in patients with rotator cuff disease

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Abstract: Rotator cuff disease (RCD) is characterized by impaired neuromuscular coordination between the rotator cuff and deltoid muscles, leading to abnormal humeral head migration and persistent shoulder dysfunction. Whether peripheral electrical stimulation can acutely restore shared neural drive to glenohumeral stabilizers in this population is unknown. We examined the acute effects of pulsed direct current stimulation (PDCS) on intermuscular electromyographic (EMG-EMG) coherence, median frequency (MDF), maximal voluntary contraction (MVC) torque, and pain during a sustained fatiguing contraction in individuals with RCD. Eighteen participants with symptomatic RCD (10F/8M; 28 ± 6 yr) completed two randomized crossover sessions. In each session, a 20-minute PDCS (40 Hz, 460 μs) or sham was delivered to the supraspinatus (SS) and infraspinatus (IS), followed by sustained isometric shoulder abduction at 25% MVC until task failure. Surface EMG was recorded from IS and the middle deltoid (MD); fine-wire EMG was recorded from SS. Z-transformed pooled intermuscular coherence was computed for SS-IS, SS-MD, and IS-MD pairs in delta (1-5 Hz), alpha (5-15 Hz), and beta (15-35 Hz) bands during the initial and final 30 s of contraction, and analyzed with three-way repeated-measures ANOVA. A significant Intervention × Time interaction emerged in delta coherence ($P = 0.044$): under PDCS, SS-IS rose from 0.12 ± 0.03 to 0.24 ± 0.04 (mean ± SE; $P = 0.002$) and SS-MD from 0.16 ± 0.02 to 0.23 ± 0.04 ($P = 0.006$), with no significant change under sham. Alpha-band coherence showed a main effect of Intervention ($P = 0.012$), driven by elevated SS-IS coherence under PDCS (PDCS: 0.20 ± 0.01, Sham: 0.15 ± 0.01, $P < 0.001$). Beta SS-MD coherence was higher under PDCS in the initial phase (PDCS: 0.15 ± 0.01, Sham: 0.12 ± 0.01, $P = 0.010$). A significant MDF decline in SS (−0.08 ± 0.03 Hz/s) and IS (−0.05 ± 0.02 Hz/s) was shown under PDCS but absent under sham. PDCS also attenuated post-task MVC decline ($P = 0.040$). Endurance time did not differ significantly between sessions (PDCS: 4.4 ± 0.6, Sham: 4.7 ± 0.5 min, $P = 0.302$). The band-specific pattern suggests that PDCS engages multiple levels of the motor control hierarchy. A single PDCS session acutely enhances shared neural drive to glenohumeral stabilizers, redistributes activation toward the rotator cuff, and potentially preserves neuromuscular capacity in RCD. PDCS may serve as a non-invasive, neuromuscular-targeted adjunct to shoulder rehabilitation.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

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Program #/Poster #: PSTR141.12/BB21

Topic: F.09. Motor Neurons and Muscle

Support: Processo n°:408910/2022-4

Title: Persistent axonal peripheral nerve dysfunction following severe SARS-CoV-2 infection: an electroneuromyographic study

Authors: *M. R. P. REIS PRADO[1], F. SOUZA[1], I. S. MELO[3], A. PACHECO[2], A. S. JÚNIOR[5], Ê. BASSI[6], L. ANDERSON[7], O. W. CASTRO[4], A. M. SILVA[8]; [1]UNIVERSIDADE FEDERAL DE ALAGOAS - UFAL, Maceió, Brazil; [2]UNIVERSIDADE FEDERAL DE ALAGOAS - UFAL, maceió, Brazil; [3]Phisiology and Pharmacol., Federal Univ. of Alagoas, Maceio, Brazil; [4]Physiol., Federal Univ. of Alagoas, Maceió, Brazil; [5]Inst. de Ciências Biológicas e da Saúde, Univ. Federal de Alagoas, Maceió, Brazil; [6]Inst. de Ciências Biológicas e da Saúde/ICBS, [7]Inst. de Química e Biotecnologia, [8]Inst. de Ciências Biológicas e da Saúde, Univ. Federal de Alagoas, Maceió, Brazil

Abstract: Long COVID (LC) is frequently associated with persistent neurological and neuromuscular symptoms. However, objective evidence of long-term peripheral nervous system dysfunction remains limited, particularly among survivors of severe COVID-19. Here, we investigated electrophysiological abnormalities in individuals with LC one to four years after hospitalization for severe SARS-CoV-2 infection. The study was approved by the Institutional Review Board of the Federal University of Alagoas (CAAE: 68344823.2.0000.0155). Participants with confirmed SARS-CoV-2 infection between March 2020 and December 2022 underwent clinical evaluation and comprehensive electroneuromyography (ENMG), including motor and sensory nerve conduction studies, F-wave analyses, H-reflex testing, blink reflex evaluation, and needle electromyography. A total of 67 participants were enrolled, comprising 20 with prior mild/moderate COVID-19 and 47 with prior severe COVID-19. Electrophysiological abnormalities were detected in approximately 80% of severe COVID-19 survivors evaluated one to four years after acute infection. Focal neuropathies represented the most prevalent diagnosis (45%), followed by radiculopathies/multiradiculopathies (15%), mixed neuropathic disorders (9%), and polyneuropathies (9%). The predominant electrophysiological signature was an axonal neuropathic pattern characterized by reduced action potential amplitudes and evidence of chronic reinnervation. These findings demonstrate that objective neurophysiological abnormalities remain detectable long after resolution of the acute infection. Collectively, these results provide evidence of sustained peripheral nerve dysfunction following severe SARS-CoV-2 infection and identify axonal neuropathy as a prominent long-term neurological sequela of Long COVID. Our findings highlight the importance of neurophysiological assessment in patients with persistent neuromuscular symptoms and contribute to the understanding of the long-term neurological consequences of COVID-19.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

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Topic: F.09. Motor Neurons and Muscle

Support: NEA Grant 1879137-38

Title: Group therapeutic singing modifies muscle activity during swallow in people with Parkinson's disease

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Abstract: Dysphagia is a common symptom of Parkinson's disease (PD) that may lead to aspiration pneumonia, a leading cause of mortality in this population. Group therapeutic singing (GTS) may increase the duration of swallow-related muscle activity in people with PD, thus prolonging airway protection. However, previous studies were based on an 8-week intervention. The purpose of this study was to evaluate the effects of 16 weeks of one hour per week of GTS on swallow-related muscle activity in people with PD compared to a control period and healthy older adults (HOA). Electromyography (EMG) was recorded over the submental and laryngeal muscle groups during swallowing of thin and thick liquids at baseline, after 8 weeks of no intervention, after 8 weeks of once-weekly GTS, and after 16 weeks of GTS. Seventeen participants with idiopathic PD (9 female, age 72.6 ± 4.8 years, disease duration 7.7 ± 5.4 years) completed the GTS program and all data collection visits. Eleven HOA controls (5 female, age 71.0 ± 6.9 years) completed the swallow trials at the same 8-week intervals but did not complete GTS. Raw EMG data were low-pass filtered, DC-rectified, and smoothed using a second-order Butterworth filter. The duration and peak amplitude of swallow-related muscle activity were extracted from pre-processed EMG data using a combination of manual event identification and automatic peak picking. At baseline for thin liquids, participants with PD tended to have shorter muscle activity duration than HOAs at all four electrode sites, which is indicative of dysphagia. A linear mixed effects model revealed a main effect of group (t = -7.265) with the PD group demonstrating shorter swallow durations. There was a significant group x time interaction effect (t = 4.091) such that the PD group demonstrated in increase in muscle activity duration in post-intervention visits. Data processing and statistical analysis related to EMG amplitude are ongoing. The increased duration of swallow-related muscle activity is consistent with previous work on our lab and supports the efficacy of GTS to address dysphagia in people with PD.

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Poster

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Program #/Poster #: PSTR141.14/BB23

Topic: F.09. Motor Neurons and Muscle

Support: DoD HT9425-23-1-0678

Title: Electromyography Recorded from Sciatic Nerve RPNIs Shows Consistent Synergy Structure Across Walking Speeds in an Individual with Transfemoral Amputation

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Abstract: Transfemoral amputation (TFA) removes the distal muscles, limiting access to motor signals of the ankle and foot for powered prosthesis control. Regenerative Peripheral Nerve Interfaces (RPNIs), which are biological constructs amplifying neural signals via muscle grafts to amplify motor signals, provided stable upper-limb control in previous studies, yet lower-limb RPNI dynamics during locomotion remain unexplored. This study characterized sciatic nerve RPNI electromyography (EMG) synergies across treadmill walking speeds in a TFA individual, helping identify EMG coordinated patterns during walking. A 56-year-old man with TFA had five RPNIs created on his sciatic nerve, with intramuscular electrodes implanted into each. EMG was recorded from RPNIs at 30 kHz while the participant attempted to isolate lower-limb joint movement in a seated position and walked at three treadmill speeds (0.8, 1.1, and 1.5 m/s). EMG data were downsampled and filtered to obtain linear envelopes. Envelopes were then normalized by the average peak across cycles per speed. Pearson correlation evaluated cross-channel connectivity. Non-negative matrix factorization (NMF) extracted EMG synergies at each speed, with variance accounted for (VAF) determining synergy quantity, validated against temporally shuffled data. Cross-reconstruction assessed synergy generalizing across speeds. Finally, cosine similarity evaluated correlations between the synergy weight matrix and integrated EMG ratios from isolated joint movements. Results revealed moderate correlations across all five channels ($r=0.45$-0.64), whereas channels 2/3 and 4/5 exhibited strong correlations ($r=0.82$ and 0.72, respectively). Across speeds, three synergies explained >95% of total variance, with each RPNI channel reconstructed >75% VAF. Total VAF was significantly higher in original vs. shuffled data (96.30% vs. 85.72%), confirming structured EMG patterns rather than artifacts. High cross-reconstruction VAFs (>95%) and synergy weight cosine similarities across speeds indicated consistent synergy structures. While all five RPNIs exhibited moderate global correlation, channels 2/3 and 4/5 shared distinct localized patterns, and channel 1 dominated a standalone

synergy. Moreover, cosine similarity suggests that these synergies may relate to different aspects of the musculature, e.g., knee flexion and ankle dorsi/plantarflexion. These findings demonstrate that lower-limb RPNI EMG contains structured, task-consistent information during walking. Further the investigation of lower-limb RPNIs as a potential interface for decoding locomotor intent for powered prosthetic legs.

Disclosures: M. Li: None. **J. Kanetis:** None. **H. Razavi:** None. **B. Perlin:** None. **C.A. Chestek:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); P. Cederna and C. Chestek are inventors of patents US10314725 and US10779963 that are related to this work. This intellectual property is held by the University of Michigan and has been optioned by. **T.A. Kung:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); T. Kung, and P. Cederna are employed in leadership roles and hold equity in Blue Arbor Technologies, Inc., a company that makes prosthetic control systems. **P. Cederna:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); T. Kung, and P. Cederna are employed in leadership roles and hold equity in Blue Arbor Technologies, Inc., a company that makes prosthetic control systems., P. Cederna and C. Chestek are inventors of patents US10314725 and US10779963 that are related to this work. This intellectual property is held by the University of Michigan and has been optioned by. **D. Gates:** 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.; DoD HT9425-23-1-0678.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.15/BB24

Topic: F.09. Motor Neurons and Muscle

Support: NIH R01 Grant - GR0041002
NIH K01 Grant - GR0025544
NIH T32 Grant - NS126157-04

Title: Effects of tSCS amplitude on muscle recruitment and motor facilitation during single- and multi-joint movement in people with spinal cord injury

Authors: *C. ATKINSON[1,2], N. PHELPS[1,2], R. HAWTHORN[1,2], R. KEESEY[1,2], R. DE FREITAS[1,2], L. LOMBARDI[1,2], P. BRUNNER[1,2,3], S. HAROUTOUNIAN[3,4], I. SEÁÑEZ[1,2,3]; [1]Biomed. Engin., Washington Univ. in St. Louis, Saint Louis, MO; [2]Neurotechnology, [3]Neurosurg., [4]Anesthesiol., Washington Univ. Sch. of Med., Saint Louis, MO

Abstract: Transcutaneous spinal cord stimulation (tSCS), when paired with physical therapy, has been shown to improve motor outcomes in people with spinal cord injury (SCI), even in the chronic stage of injury. However, the therapeutic effects of tSCS vary widely across individuals and may depend on the tuning of stimulation parameters, with current approaches remaining poorly optimized. The amplitude at which stimulation is administered is inconsistent across studies, and is typically based on either participant tolerance, paresthesia, or threshold amplitudes for evoked muscle responses. Therefore, the effect of SCS amplitude on motor facilitation for both single-joint and multi-joint coordinated movement remains poorly understood. In this study, we examine the effect of tSCS amplitude on motor facilitation during single-joint isometric movement and multi-joint coordinated movement during cycling. Participants with incomplete (ASIA B-D) SCI completed isometric maximum voluntary contractions (MVCs) of the ankle, knee, and hip joints with and without tSCS at different tSCS amplitudes over five sessions. Magnitude of MVCs and EMG activation were used as primary outcome measures to determine the motor-enabling effect of tSCS. During a separate session, participants completed active (semi-assisted) and passive cycling with and without tSCS. To date, two participants have completed the protocol. Both participants exhibited a training effect, as movements got stronger over sessions. For one participant, there appeared to be a learning period in which they adapted to using tSCS for movement, and MVC amplitude was enhanced by tSCS only during sessions 3-5. EMG activation was enhanced at tSCS amplitudes between 70-100% of motor threshold, although higher stimulation amplitudes could cause co-contraction and decrease net torque output, or even cause torque generation in the opposite direction. Subthreshold tSCS at 35-66% of the motor threshold improved cycling movement smoothness compared to the no-stimulation condition. However, tSCS at 100% of motor threshold reduced this improvement due to widespread activation of leg muscles. Data collection for additional participants and further data analysis are ongoing and will be presented at the conference together with these results.

Disclosures: C. Atkinson: None. **N. Phelps:** None. **R. Hawthorn:** None. **R. Keesey:** None. **R. de Freitas:** None. **P. Brunner:** None. **S. Haroutounian:** None. **I. Seáñez:** None.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.16/BB25

Topic: F.09. Motor Neurons and Muscle

Support: NIH R01 Grant - GR0041002
NIH K01 Grant - GR0025544
NIH T32 Grant - NS126157-04

Title: Effect of frequency on torque output during transcutaneous spinal cord stimulation in individuals with spinal cord injury

Authors: *N. PHELPS[1,2], C. ATKINSON[1,2], L. LOMBARDI[1,2], R. HAWTHORN[1,2], R. KEESEY[1,2], R. DE FREITAS[1,2], P. BRUNNER[1,2,3], S. HAROUTOUNIAN[3,4], I. SEÁÑEZ[1,2,3]; [1]Biomed. Engin., [2]Neurotechnology, Washington Univ. in St. Louis, St. Louis, MO; [3]Neurosurg., [4]Anesthesiol., Washington Univ. Sch. of Med., St. Louis, MO

Abstract: Spinal cord stimulation (SCS) has demonstrated significant potential for improving motor function following spinal cord injury (SCI). While transcutaneous spinal cord stimulation (tSCS) offers a noninvasive means to activate leg muscles below the injury, neural recruitment suffers from low selectivity due to the long distance between the stimulation site and the targeted spinal neural structures. Consequently, the stimulation parameters required to achieve targeted motor activation with tSCS remain poorly understood. The focus of this study is to investigate how stimulation frequency modulates flexor- and extensor-related motor output during voluntary movement. We hypothesize that lower stimulation frequencies preferentially engage monosynaptic pathways, facilitating extensor-dominant motor output, whereas higher frequencies promote greater involvement of polysynaptic circuitry through temporal summation, enhancing flexor-dominant activation. To test this hypothesis, individuals with SCI perform maximum voluntary contractions (MVCs) of the ankle, knee, and hip joints during flexion and extension isometric tasks while receiving continuous tSCS at varying stimulation frequencies. Peak torque from MVCs at each joint is used as the primary outcome measure for motor facilitation. Frequency-dependent changes in torque and evoked responses via EMG are used to evaluate both the overall motor-enabling effects of stimulation and the potential preferential recruitment of flexor or extensor motor pools. If successful, results from this study could lead to selective activation of flexor vs extensor muscles by controlling tSCS frequency depending on movement phase, thus improving coordinated movement in people with SCI.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.17/BB26

Topic: F.09. Motor Neurons and Muscle

Support: NIH R01 Grant - GR0041002
NIH K01 Grant - GR0025544
NIH T32 Grant - NS126157-04

Title: Motor facilitation and neural mechanisms of transcutaneous spinal cord stimulation in people with spinal cord injury

Authors: *R. HAWTHORN[1], C. M. BERNABE CORREA[1], N. PHELPS[1], R. DE FREITAS[3,2], R. KEESEY[1], C. ATKINSON[1], I. SEÁÑEZ[1];
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Abstract: Transcutaneous spinal cord stimulation (tSCS) is a non-invasive approach that can immediately facilitate motor function after spinal cord injury (SCI). However, the magnitude of this immediate prosthetic effect and the neural mechanisms that enable it remain poorly understood. To characterize the motor-enabling effect of tSCS, we compared peak torque during isometric contractions performed with and without 30-Hz tSCS over the T11/T12 vertebral segments. Ten participants with chronic SCI (AIS C-D; injury levels between C3-L1; >1-year post-injury) performed five maximum voluntary contractions during hip, knee, and ankle flexion and extension, both with and without tSCS. Stimulation amplitude was set to either the target muscle's motor threshold or the maximum tolerable amplitude. Per-condition linear mixed models (peak torque ~ stimulation, random intercept per participant) revealed that tSCS significantly increased peak torque for hip extension (left +3.03 Nm, 95% CI [1.11, 4.96], $p = 0.006$; right +2.83 Nm, [0.74, 4.91], $p = 0.016$), ankle plantarflexion (left +1.43 Nm, [0.70, 2.17], $p < 0.001$), and ankle dorsiflexion (left +1.20 Nm, [0.67, 1.74], $p < 0.001$; right +0.91 Nm, [0.29, 1.53], $p = 0.010$), and significantly decreased it for right hip flexion (−2.96 Nm, [−4.57, −1.35], $p = 0.001$; Benjamini-Hochberg corrected across 12 conditions). Knee torque did not change significantly in any condition (all $p \geq 0.10$). A separate joint × direction mixed model revealed that tSCS facilitated extension over flexion at the hip (+4.17 Nm, [1.42, 6.92], $p = 0.003$) but not at the knee (+1.40 Nm, [−1.35, 4.15], $p = 0.32$) or ankle (−0.19 Nm, [−2.94, 2.56], $p = 0.89$). Extension facilitation was also significantly higher at the hip than at the ankle joint (4.36 Nm, [0.47, 8.25], $p = 0.028$). Ankle muscles typically required higher stimulation amplitudes to reach threshold. At these amplitudes, low-threshold proximal muscles may have been involuntarily activated, potentially interfering with participants' volitional attempts. We further examined interactions between supraspinal, voluntary drive and tSCS by comparing the likelihood of tSCS enabling EMG burst-like activity versus stimulation-evoked responses during the active contraction periods. Further data collection and analysis are currently ongoing. Together, findings presented at the conference will aim to quantify torque increases that can be expected with tSCS and provide insights into whether tSCS-mediated motor facilitation reflects a generalized increase in spinal excitability of voluntary gating of stimulation pulses acting on afferent fibers within the posterior roots.

Disclosures: R. Hawthorn: None. **C.M. Bernabe Correa:** None. **N. Phelps:** None. **R. de Freitas:** None. **R. Keesey:** None. **C. Atkinson:** None. **I. Seáñez:** None.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.18/BB27

Topic: F.09. Motor Neurons and Muscle

Support: NIH R01 Grant - GR0041002
NIH K01 Grant - GR0025544
NIH T32 Grant - NS126157-04

Title: Transcutaneous Spinal Cord Stimulation Paired with Activity-Based Training Differentially Drives Short-term Corticospinal, Reticulospinal and Spinal Excitability Changes

Authors: *C. M. BERNABE CORREA[1], R. M. HAWTHORN[2], C. LOPEZ MIRANDA[1], N. PHELPS[3], R. KEESEY[2], C. ATKINSON[2], R. DE FREITAS[4,5], I. SEÁÑEZ[6];
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Abstract: Spinal cord injury (SCI) causes a loss of motor and/or sensory functions. Transcutaneous spinal cord stimulation (tSCS) is a non-invasive method to activate dormant muscles below the injury and has shown functional improvements in chronic SCI when paired with activity-based training. However, how tSCS and activity-based training, alone and in combination, can modulate the excitability of corticospinal, reticulospinal, and spinal circuits, remains poorly understood. In a cross-over study design, we investigated short-term changes in neural excitability of the lower limbs as neurologically intact individuals (N = 18) completed 30-minute training sessions with: tSCS at the T11/T12 vertebral segments alone (tSCS), bilateral leg motor skill training (BoMi), tSCS combined with motor skill training (tSCS+BoMi), or tSCS plus high-intensity ankle resistance training (tSCS+resistance). Conditions were tested during separate sessions, and the order of testing was randomized. Corticospinal excitability was assessed by motor evoked potentials (MEPs) elicited with transcranial magnetic stimulation. Reticulospinal excitability was assessed by the reticulospinal gain during the StartReact task, a reduction in reaction time to a startling auditory cue. Spinal motoneuron excitability was analyzed via H-reflex/M-waves ratio (H/M) and F-wave amplitude/persistence of the right tibialis anterior using peripheral nerve stimulation. MEP amplitude (% Mmax) was modeled with a Gamma generalized linear mixed-effects model (log link). Motor skill training alone decreased MEP amplitude from pre to post (ratio = 1.13, $p = 0.003$), possibly reflecting the bilateral, multi-joint nature of the task. Adding tSCS to BoMi significantly altered the pre-to-post response relative to BoMi alone (pairwise interaction contrast, $\beta = 0.18$, $p = 0.002$), suggesting tSCS counteracted this reduction, when paired with BoMi. tSCS+resistance training significantly decreased MEP amplitude from pre to post (ratio = 1.24, $p < 0.0001$), and this pre-to-post change differed significantly from that of tSCS+BoMi (pairwise interaction contrast, $\beta = 0.23$, $p < 0.0001$). H/M ratio significantly increased after tSCS+BoMi ($t(17) = 2.07$, $p = 0.05$), but not during other conditions. The reticulospinal gain slightly decreased in extensors after tSCS+resistance ($t(14) = -2.01$, $p = 0.06$), although this change did not reach significance. This ongoing study clarifies short-term changes to neural excitability pathways related to training type, intensity, and stimulation.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.19/BB28

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant NS134834

Title: Lost in Time, then Lost in Translation: Evaluating Temporal Misalignment in EMG Decoding

Authors: *J. C. DEMATTEO[1], J. HUANG[2], L. H. CUBILLOS[1], O. G. LEE[1], I. B. TOWNE[1], A. I. HITE[1], H. TEMMAR[1], J. L. SIMONS[1], T. A. KUNG[1], P. S. CEDERNA[1], A. W. DRAELOS[1], V. GILJA[2], C. A. CHESTEK[1];
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Abstract: Myoelectric prostheses can restore motor function for individuals who have lost an upper limb. In mapping electromyographic (EMG) signals from implanted electrodes to known effector kinematics, neural networks outperform linear approaches in open-loop settings, where the user is not involved, but these gains have not yet translated to closed-loop control in people with amputations. We hypothesized that the absence of ground-truth kinematic labels due to limb loss is limiting clinical translation of such EMG "decoders." Here, we rigorously evaluated the negative impact that temporal misalignment of kinematic labels has on EMG decoder performance. We first investigated open-loop and closed-loop data from monkeys performing a finger movement task, in which we introduced systematic temporal misalignment (timing shifts, speed changes, and trajectory smoothing) to otherwise accurate kinematic labels. We showed that training with soft dynamic time warping (soft-DTW) loss, instead of mean squared error (MSE), effectively corrects label time misalignment and mitigates its effect in both open-loop and closed-loop contexts. We then performed closed-loop experiments in a person with a transradial amputation. Surprisingly, we discovered that even after successfully correcting for time misalignment with soft-DTW loss, neural network decoders are still unable to outperform a linear Kalman filter, even if they have much lower MSE on held-out data. We reveal that the Kalman filter effectively acts as a “movement direction” decoder, enabling a slower, simpler, and more directional control strategy that supports intuitive, feedback-driven corrections, in contrast to neural networks that produce realistic but less predictable velocity spikes. We also comment on alternative open-loop metrics that better predicted closed-loop performance in a human. Our study challenges the assumed correspondence between open-loop and closed-loop performance when ground-truth labels are unknown, exposing a fundamental mismatch between training conditions and real user interaction.

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holder, excluding diversified mutual funds); Blue Arbor Technologies. **A.W. Draelos:** None. **V. Gilja:** None. **C.A. Chestek:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Blue Arbor Technologies.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.20/BB29

Topic: F.09. Motor Neurons and Muscle

Support: 1926576 NSF-NCS
BWF CASI 1021865.01
UMICH M-BIOFAR
NIH R01NS134834
NSF-GRFP DGE-2241144

Title: A Multi-Camera Setup for Real-Time Markerless Non-Human Primate Hand Tracking

Authors: *J. JOSEPH[1], M. CERADINI[6], S. LIU[2], M. KELBERMAN[1], J. DEMATTEO[1], O. LEE[3], M. COPENHAVER[1], T. A. KUNG[4], C. A. CHESTEK[5], A. DRAELOS[1];
[1]Biomed. Engin., [2]Statistics, [3]Electrical Engin., [4]Plastic Surgery, Univ. of Michigan, Ann Arbor, MI; [5]Biomed. Engin., Univ. of Michigan, ANN ARBOR, MI; [6]Biorobotics Inst., Sant'Anna Sch. of Advanced Studies, Pisa, Italy

Abstract: Precise kinematic tracking of hand movement is essential for studies related to brain-machine interfaces (BMIs) and functional electrical stimulation (FES) aimed at restoring hand movements to spinal cord injury patients. Existing tracking methods, such as flex sensors or motion-capture gloves, limit the available degrees of freedom (DOF) or rely on restrictive hardware that is difficult to place on non-human primates (NHP). To address this, we propose a markerless, multi-camera system to track hand joint angles in real time. Raw video frames are captured from up to three cameras at once. Next, they are passed through a DeepLabCut (Mathis et al., 2018) pose-estimation network to produce 2D keypoint estimations and processed through a likelihood-based Kalman smoother. Finger positions are streamed to a separate Simulink Real Time computer that uses this and other inputs to run real-time neural decoding experiments. Data collection, analysis pipelines, and live experimental control are all integrated using the software platform improv (Draelos et al., 2025). Crucially, its modular architecture enabled parallelized inference across multiple camera views and synchronization of neural and camera data streams in real time. A single Rhesus Macaque performed multiple experiments with a two finger target acquisition task (Vaskov et al., 2018) where simultaneous flex sensor, implanted electromyographic (EMG) signals, and camera video were collected. We validated our systems' predicted hand keypoints against human labels, achieving high spatial accuracy (MAE 0.29 mm), substantially lower than the 2.5 mm diameter of an average NHP finger joint. Computationally,

the system operates faster than our camera's acquisition rate of 30 FPS, with a mean average processing time of 28.84 ms without accumulation of any lag after a typical session of 15 minutes. We used this system for a preliminary experiment using real-time, closed-loop neuroprosthetic control. An NHP successfully controlled a virtual hand during online experiments, using the markerless joint keypoints estimated by our system. We trained an EMG Kalman filter decoder using these kinematic features, enabling the monkey to successfully complete over 300 random target trials. These results establish our system could be used as a less restrictive alternative to bend sensors for BMI experiments. Future work will attempt to deploy this system to track individual fingers during natural movements without bend sensors or manipulandums, such as higher DOF foraging and grasping tasks, and provide real-time kinematic feedback for closed-loop FES control.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.21/BB30

Topic: F.09. Motor Neurons and Muscle

Support: NIH grant R01NS109237
NIH grant U24NS126936

Title: Computational Tools to Track Human Motor Unit Waveforms Across Changes in Joint Angle

Authors: *E. COREY[1], M. ASGHAR[2], M. PIASECKI[3], S. J. SOBER[4];
[1]Georgia Tech. and Emory Univ., Atlanta, GA; [3]Sch. of Med., [2]Univ. of Nottingham, Nottingham, United Kingdom; [4]Biol., Emory Univ., Atlanta, GA

Abstract: Motor units (MUs) are the basic elements of motor control. However, despite significant advances in high-density surface electromyography and intramuscular electrodes, we still have a poor understanding of how MU activity is coordinated during complex movements. A key reason for this is that as a muscle contracts or changes length, the muscle's cross-sectional area changes; therefore, the distance of each electrical source from the recording location is altered, complicating efforts to "track" the same MU's voltage output as the body and muscle change shape. To tackle the issue of MU tracking across joing angles, we developed a task that lets us monitor MU action potentials as they gradually change across postures. Participants are asked to produce a knee extension force at 10% of their maximum voluntary force production for 1 minute across a range of knee angles. We use Myomatrix multichannel intramuscular electrode arrays in the human Vastus Lateralis and Medialis to perform longitudinal recordings of these

muscles across each condition. To track individual MUs across changes in muscle shape, we first decompose each individual recording into MU clusters and firing times; then we take the median waveform of each channel and unit. The waveforms associated with individual MUs are compared across joint angles using Principal Components analysis and waveform correlation metrics, allowing a subset of units to be tracked across changes in knee angle. Extending these methods might allow the user to track motor units across the full range of body postures, providing insights into basic mechanisms of motor control and how these mechanisms are degraded in neuromuscular diseases.

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Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.22/BB31

Topic: F.09. Motor Neurons and Muscle

Support: NIH grant U24NS126936
NIH grant R01NS109237

Title: GravitySort: Rapid motor unit spike sorting for clinical and research applications

Authors: *K. RAMACHANDRA, M. WILLIAMS, S. J. SOBER;
Biol., Emory Univ., Atlanta, GA

Abstract: The nervous system controls the body using motor units, the subset of muscle fibers innervated by a single motor neuron. Accurate decomposition of electromyographic (EMG) signals into individual motor unit action potentials remain challenging because of waveform overlap, recording noise, and variability in motor unit morphology. Existing methods for EMG spike sorting require extensive user training and manual dataset curation, greatly reducing their usability in both clinical and research settings. We developed GravitySort, an automated EMG decomposition framework that represents isolated spike waveforms as particles interacting within a low-dimensional feature space according to simplified gravitational dynamics (W.E.Wright, 1977). Our method separates identification of isolated motor unit waveforms from subsequent resolution of overlapping waveforms, thus enhancing optimization of each step for better speed and usability. We applied GravitySort to EMG datasets recorded from humans, mice, and songbirds to evaluate its robustness across species, muscle groups, and recording conditions. Across these datasets, GravitySort successfully identified individual motor unit clusters while requiring minimal user intervention. Performance was maintained across species despite differences in motor unit waveform structure and firing patterns, suggesting that GravitySort can significantly accelerate motor unit spike sorting for clinical diagnosis and research purposes.

Disclosures: K. Ramachandra: None. **M. Williams:** None. **S.J. Sober:** None.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

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Program #/Poster #: PSTR141.23/BB32

Topic: F.09. Motor Neurons and Muscle

Support: NIH Grant R01DK133800

Title: Real-time 3D Innervation Zone Imaging via FEM-Guided Graph Transformers

Authors: *T. JIN, Y. ZHENG, Y. ZHANG;
Biomed. Engin., Univ. of Miami, Coral Gables, FL

Abstract: *In vivo* mapping of innervation zones (IZs) within the three-dimensional (3D) muscle volume provides clinically valuable information for precision interventions, including botulinum toxin injections, neuromodulation targeting, and neuromuscular assessment. Current 3D IZ imaging approaches rely on high-density surface EMG (HD-sEMG) and finite element modeling (FEM). However, the substantial computational burden of FEM-based inverse solutions limits their clinical translation and real-time applicability.To overcome this, we developed a FEM-constrained Graph Attention Transformer (FGAT), a hybrid framework that shifts the heavy computational burden to offline training while preserving biophysical fidelity. To facilitate robust clinical translation, the model was pre-trained on simulated HD-sEMG datasets, then fine-tuned using experimental HD-sEMG data, and validated using concurrently recorded intramuscular electromyography (iEMG) data. The FGAT architecture comprises a spatiotemporal encoder for motor unit action potential (MUAP) signals, fused with a Graph Attention Network (GAT) that incorporates mesh topology to preserve anatomical coherence. A Cross-Attention decoder then leverages these learned node embeddings to reconstruct 3D source activities from HD-sEMG signals, eliminating the need for subject-specific FEM computations. Optimized by a joint loss function embedding weighted minimum norm estimation (WMNE) and Pearson Correlation Coefficient (PCC) constraints, the network ensures physically valid solutions.FGAT achieved near real-time 3D IZ imaging (<50 ms) on simulated data at varying noise levels (10-30 dB SNR), dramatically outperforming traditional FEM-based iterative solvers that requires hours of computation for a single subject. FGAT also demonstrated superior spatial accuracy in clinical stroke datasets, with a mean IZ localization error of 6.00 ± 3.05 mm, and validated biophysical fidelity through iEMG reconstruction (PCC = 0.68 ± 0.15). By enabling rapid and accurate 3D IZ mapping, FGAT offers a powerful and clinically viable tool for real-time neuromuscular assessment.

Disclosures: T. Jin: None. **Y. zheng:** None. **Y. Zhang:** None.

Poster

PSTR141: Motor Units, Kinematics, and EMG

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR141.24/Web Only

Topic: F.09. Motor Neurons and Muscle

Support: RS-2026-25546078
RS-2025-03612975
RS-2025-23524370
RS-2026-25543545
RS-2026-25502214

Title: Nuclear-strain-guided design of soft, mesh microneedle electrodes for fibrosis-resistant neural biointerfaces

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Abstract: Chronic fibrotic encapsulation remains a major barrier to the long-term stability and electrophysiological performance of implantable neural and bioelectronic interfaces. Although soft porous electrodes improve chronic tissue integration, the mechanobiological effects of mesh pore geometry on fibrotic activation remain poorly understood. Here, we developed a soft mesh microneedle (smMN) electrode with pore sizes optimized through nuclear-strain-guided computational modeling. Finite element simulations were performed to investigate the confined migration of human dermal fibroblasts through mesh pores with varying dimensions. A viscoelastic cell model was used to quantify nuclear deformation during migration through mesh pores of varying sizes. Maximum principal nuclear strain was used as a mechanobiological metric of confinement-induced YAP activation and fibrotic mechanotransduction. Simulation results showed a safe pore-size regime of 10 - 16 μm that minimized nuclear deformation while preserving cellular infiltration, whereas smaller pores induced severe nuclear strain predicted to promote nuclear YAP translocation and fibrotic activation. smMN electrodes with optimized pore size were fabricated using a modified electrospinning process. Optimized smMN electrodes maintained structural integrity and conformal tissue contact owing to their ultrathin, compliant mesh architecture. To validate the computational predictions, human dermal fibroblasts were cultured on mesh substrates containing different pore dimensions under confined migration conditions. Fibrosis-associated activation was evaluated through immunostaining of YAP nuclear localization and α-SMA expression. Optimized mesh geometries suppressed nuclear YAP translocation and α-SMA expression relative to smaller-pore meshes and non-porous controls. Cells on optimized mesh architectures displayed enhanced regenerative signaling, with elevated VEGF and FGF-2 levels and reduced TGF-β1 expression. In vivo implantation studies demonstrated reduced fibrotic capsule formation and attenuated local inflammation around optimized electrodes compared with solid MN controls, consistent with the ultrathin porous mesh architecture. Reduced peri-implant fibrosis and improved tissue integration enabled enhanced long-term EMG recording stability. These findings establish nuclear-strain-guided pore

optimization as a mechanobiological strategy for fibrosis-resistant neural biointerfaces and support the use of smMN electrodes for reliable chronic electrophysiological recording.

Disclosures: P. Le: None. **J. Lee:** None. **G. Lim:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.01/CC1

Topic: G.01. Neuroethology

Support: AU ORCS Grant 75-201160

Title: Multifactorial modulation of phonotaxis in the house cricket Acheta domesticus

Authors: L. WIDDICOMBE[1,2], M. KIM[2], M. GIETSEL[4], D. N. MBUNGU[3], ***B. A. NAVIA**[2]; [1]Great Lakes Adventist Acad., Grand Ledge, MI; [2]Sch. of Life and Mol. Sci., Andrews Univ., Berrien Springs, MI; [3]Sch. of Life and Mol. Sci., Andrews Univ., Berrien Sprgs, MI; [4]Sch. of Med. Lab. Sci., ANDREWS UNIVERSITY, Berrien Springs, MI

Abstract: The phonotactic response of female crickets to the male's call is highly variable and influenced by multiple physiological and environmental factors. Although a neural model underlying call recognition has been proposed, the modulatory processes that shape phonotactic behavior are not fully understood. Previous studies have shown that young female *Acheta domesticus* selectively respond to conspecific male calls with syllable periods of 50-70 ms. However, as females age and juvenile hormone levels decline, their selectivity decreases, resulting in responsiveness to a broader range of syllable periods. Evidence from other insect models suggests that juvenile hormone III may exert its effects through signaling pathways involving protein kinases. To investigate the potential role of intracellular second-messenger systems in phonotactic behavior, we employed pharmacological agents known to modulate protein kinase signaling cascades. Injection of a membrane-permeable cGMP analog into the prothoracic ganglion altered female phonotactic behavior in a manner that paralleled changes in the spiking activity of the L3 auditory interneuron, previously shown to be critical for phonotaxis in *A. domesticus*. Treated females exhibited a significantly reduced phonotactic responsiveness with a narrower tuning preference, responding primarily to calls with syllable periods of 50 ms or less. Preliminary experiments reveal that females treated with reserpine (inhibitor of vesicular monoamine transport), also displayed reduced phonotactic responsiveness in a similarly restricted tuning profile centered on 50 ms calls. Although reserpine affects multiple aminergic systems, these findings are noteworthy because histamine has been implicated in sensory processing and phonotactic behavior in *A. domesticus*. Thus, aminergic depletion may influence auditory processing and phonotactic behavior in crickets. Lastly, we also examined the influence of male-derived cues on female phonotaxis. Females exposed to either calling males or muted males separated by a barrier preventing direct contact, exhibited more variable and erratic

phonotactic responses than age-matched, unexposed controls. In contrast, females exposed only to male pheromonal cues displayed phonotactic behavior more similar to that of unexposed females. Collectively, these findings support the hypothesis that phonotactic behavior in female *A. domesticus* is regulated by multifactorial mechanisms involving intracellular signaling pathways, aminergic modulation, and social cues, all of which may act on neural circuits responsible for auditory processing and behavioral decision-making.

Disclosures: L. Widdicombe: None. **M. Kim:** None. **M. Gietsel:** None. **D.N. Mbungu:** None. **B.A. Navia:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.02/CC2

Topic: G.01. Neuroethology

Support: KBRI basic research program 23-BR-01-01, 24-BR-01-01, and 25-BR-01-01
Japan Society for the Promotion of Science KAKENHI grant 23K06796

Title: A rebound from nighttime singing suppression drives intense morning singing in captive zebra finches and can explain the avian "dawn chorus"

Authors: *S. KOJIMA[1], E. BARROS DOS SANTOS[2], C. MORI[3], Y. KIM[1], R. O. TACHIBANA[4], O.-Y. JEONG[5], J. KIM[6];
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Abstract: Many birds sing vigorously at dawn, a phenomenon widely known as the "dawn chorus." While its adaptive functions have been extensively studied, the proximate mechanisms underlying this widespread phenomenon have remained largely unexplored. Here, we demonstrate that intense morning singing resembling the dawn chorus is evoked as a rebound from singing suppression prior to dawn in captive zebra finches. Our findings indicate that when birds become hormonally aroused in darkness well before dawn, the suppression of spontaneous singing by darkness enhances their intrinsic motivation to sing. This elevated motivation subsequently triggers a rebound of intense singing immediately upon an increase in ambient light. These results reveal mechanisms by which intense morning singing arises from the interaction between the bird's arousal state and ambient light, providing a plausible mechanistic explanation for the dawn chorus. Additionally, we found that rebound morning singing accelerates morning changes in song structure, supporting the existing hypothesis that the dawn chorus functions as a vocal warm-up to rapidly optimize song performance following nighttime

silence. Together, our findings provide both mechanistic and functional insights into the dawn chorus in songbirds.

Disclosures: S. Kojima: None. **E. Barros dos Santos:** None. **C. Mori:** None. **Y. Kim:** None. **R.O. Tachibana:** None. **O. Jeong:** None. **J. Kim:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.03/CC3

Topic: G.01. Neuroethology

Title: Dynamic Modulation of Co-Song Beat Gestures in Zebra Finches

Authors: E. OUYANG, *W.-C. LIU;
Colgate Univ., Hamilton, NY

Abstract: When we speak, we make simultaneous hand or head gestures: co-speech gestures. These gestures are dynamically modulated by our emotion, motivation, or cognitive states in order to enhance social communication. However, the neural mechanisms that underlie fine modulation and rhythmic coordination between speech and co-speech gestures remain largely unknown. Previously, our lab has demonstrated that a songbird, the zebra finch, has evolved a co-song beat gesture, which may offer an excellent model to explore its underlying neural or behavioral mechanisms. Using a combination of DeepLabCut and a 3D reconstruction framework, we are able to quantify and track the fine modulation of gesture movements. We discovered that under varying social contexts, male finches are able to dynamically modulate their beat gestures in magnitude, forms, and variance, perhaps to express or emphasize different meanings. The dynamic modulation of co-song gestures may be differentially regulated by neurotransmitters and under control of a coordinated cortical-basal ganglia circuit. This hypothesis is currently tested with bilateral Area X lesioning and administration of dopamine agonist and antagonist. Our study might shed new light on the circuit regulation and coordination of highly complex multi-sensorimotor behaviors.

Disclosures: E. Ouyang: None. **W. Liu:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.04/CC4

Topic: G.01. Neuroethology

Title: Investigating the Temporal Structure of Compound Calls and Vocal Interactions in Marmosets

Authors: *G. NANDY[1], L. ZHAO[2], X. WANG[3];
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Abstract: Common marmosets (Callithrix jacchus) are an excellent model for studying non-human primate vocalizations. Although many studies in marmoset vocalizations have focused on individual calls as isolated units, recent studies have begun to explore longer call sequences, including compound calls, i.e., calls composed of multiple phrases or syllables tightly organized together. However, the compositional structure and potential usage of compound calls have not been well characterized. Here, we investigated vocalizations from individual animals and systematically examined the structure of these compound calls. Four adult marmosets were simultaneously recorded in their home cages. For each marmoset, we quantified inter-phrase intervals (IPI) between consecutive vocal outputs. Using the five most common phrase types, we created phrase pairs with all permutations of the five phrase types. For the most frequent phrase-pair types, we modeled IPI distributions using Gaussian mixture models to identify thresholds separating within-call transitions from longer between-call intervals. These thresholds allowed us to classify each vocalization as either a simple call or part of a compound call. We then characterized how compound calls were distributed across days, individuals, and call types, and compared their usage to simple calls through normalized call-rate and proportion analyses. Next, we investigated the interactive use of their vocalizations between the four marmosets. Previous studies have focused mostly on antiphonal calling with phee calls. We sought to investigate whether there are significant vocal interactions for other call types. We computed a call-modulation index (CMI) to quantify changes in one monkey's call rate following a call from another monkey. Our preliminary analysis indicates that certain calls, especially trill calls, produced significant modulation in conspecific call rate. Together, these methods provide a framework for identifying structured multi-phrase compound calls and also testing the functional role of vocalizations in social communication.

Disclosures: G. Nandy: None. **L. Zhao:** None. **X. Wang:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.05/CC5

Topic: G.01. Neuroethology

Support: NIH R01009607

Title: Developmental trajectory of vocalizations in neonatal mice with and without sensorineural hearing impairment

Authors: *C.-T. CHEN, D. MUKHERJEE, P. O. KANOLD;
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Abstract: Mice extensively use ultrasonic vocalizations (USVs) for intra-species communication across diverse social contexts beginning early in development. Altered USVs in mouse pups are reported in mouse models of neurodevelopmental disorders associated with impaired social behaviors. However, the developmental trajectory of neonatal mouse USVs remains incompletely characterized. We recorded USVs from C57BL/6J mouse pups in the first and second postnatal weeks under isolated conditions and with the dam. USVs were classified using an automated tool (VocalMat) to extract spectrotemporal features, such as frequency, intensity, and duration of different vocalization types. To determine whether peripheral auditory input is required for normal USV development, we also recorded USVs in *Otoferlin*$^{-/-}$ pups with sensorineural hearing impairment. Our analysis revealed that all classified vocalization subtypes in adults were already present in pups during the first two postnatal weeks, even in the absence of early peripheral cochlear input, as in *Otoferlin*$^{-/-}$ pups. In addition, pups emitted fewer USVs when recorded within litters compared with isolated conditions, whereas low-frequency calls occurred more frequently within the litter. Together, our findings provide a comprehensive characterization of the developmental trajectory of mouse pup USVs and provide insights into how early self-generated vocalizations may contribute to neural development.

Disclosures: C. Chen: None. **D. Mukherjee:** None. **P.O. Kanold:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.06/CC6

Topic: G.01. Neuroethology

Title: Unsupervised Convolutional Autoencoder-based classification of mouse pup ultrasonic vocalizations reveals environment-dependent vocal pattern

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Abstract: Ultrasonic vocalizations (USVs) of mouse pups provide important information for inferring their behaviors and internal states during early developmental stages. However, due to their continuous nature, mouse USVs are difficult to fully characterize based on only simple acoustic features. To address these limitations, we developed an automated processing pipeline to detect, denoise, and classify mouse pup USVs recorded during isolation in the presence of

olfactory stimuli. Vocalizations were first extracted using the previously published USVSEG framework with a spectral peak-tracking method, which preserved the main time-frequency structure and intensity information while reducing background noise. Following vocalization detection, first, broadband vocalizations spanning the audible and ultrasonic frequency ranges ("squeaks") were identified based on their distinct acoustic features. The remaining vocalizations were then classified using an unsupervised approach.To capture the continuous acoustic features of mouse USVs, we trained a Convolutional Autoencoder (CAE) model to learn low-dimensional representations from the denoised USVs. Unsupervised clustering was subsequently performed using deep features extracted from the CAE model to identify distinct vocalization types. To evaluate classifier performance, we introduced an interpretable metric based on Earth Mover's Distance (EMD) to quantify the similarity of USVs within and across clusters. Using EMD-based evaluation, we identified the optimal clustering method and number of clusters. We applied this approach to USV recordings obtained from isolated P7-9 and P14-15 mouse pups and identified a diverse set of acoustic patterns. By integrating the clustering results with behavioral recordings, we found that USV composition differed depending on the olfactory stimuli presented during isolation, suggesting that vocalization patterns in young mice are shaped by environmental context.

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Poster

PSTR142: Neuroethology: Vocal/Social Communication

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Topic: G.01. Neuroethology

Support: UMBC GSA Research Grant
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ABS Student Research Grant
SICB Grant in Aid of Research
ECWG Exploration and Field Research Grant

Title: Testosterone induces early song crystallization in male and increases volume of song control nuclei in female grasshopper sparrows

Authors: *R. A. GLISSON[1,2], K. ODOM[4], B. LOHR[3], G. F. BALL[5];
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Abstract: As song is a learned behavior in songbirds, it is a popular model system for studying the neuroendocrine mechanisms regulating vocal development. However, few studies have

explored the mechanisms of song development in wild-caught songbird species. In temperate zone species, songs are memorized during an early sensory phase, then produced and modified throughout a sensorimotor phase during a bird's first breeding year. In most species this learning period ends with crystallization, when the song becomes stereotyped. Crystallization is typically preceded by a rise in circulating testosterone at the onset of sexual maturity. In some species, such as canaries, testosterone administration induces singing in females who normally do not produce songs, while in others, such as zebra finches, it has no effect on adult females. We studied the role of testosterone in song development in grasshopper sparrows, which have two distinct song types sung only by males of this species. The first song type, the "buzz", functions as the primary territorial song, while the second song type, the "warble" song, is typically sung by paired birds later in each breeding cycle. We captured wild grasshopper sparrows as juveniles (post sensory phase), implanted a subset of both male and female birds with testosterone early during the sensorimotor phase, and recorded their song output during this time. All males sang species-typical songs at the end of the sensorimotor phase after crystallization. Females implanted with testosterone produced crystallized song-like vocalizations with varying similarity to male songs. Further, males implanted with early testosterone crystallized both song types 8-10 weeks earlier than control males. Our behavioral results are similar to previous evidence suggesting that the administration of exogenous testosterone can induce premature song crystallization. Additionally, at the end of our behavioral study, we collected brain tissue to measure the volumes of nuclei within the song control system (SCS). Testosterone had a significant effect on the volume of SCS nuclei in grasshopper sparrow females, but not in males. Males had significantly larger volumes of SCS nuclei than females, including testosterone-implanted females. However, in our experimental paradigm all our males (i.e. T and non-T treated) were in spring breeding condition so they may have been at maximal SCS nuclear volume and endogenous T could not have additional effects. In addition, the sex difference we found in grasshopper sparrow nuclear volumes is relatively large compared to other species which lack female song, such as the related dark-eyed junco.

Disclosures: R.A. Glisson: A. Employment/Salary (full or part-time):; University of Maryland. **K. Odom:** A. Employment/Salary (full or part-time):; University of Pacific. **B. Lohr:** A. Employment/Salary (full or part-time):; University of Maryland, Baltimore County. **G.F. Ball:** A. Employment/Salary (full or part-time):; University of Maryland.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.08/CC8

Topic: G.01. Neuroethology

Support: U24NS126936
R01NS084844

Title: Multifunctional neural control of the songbird beak

Authors: *C. D. M. VARGAS, A. GRASSLER, S. J. SOBER;
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Abstract: Nervous systems can precisely, and flexibly, coordinate muscles to produce a large repertoire of behaviors with distinct functional goals. However, little is known about how brains represent different behaviors produced by one body part, or how circuits evolve to use a body part in new behaviors. Bird beaks, often studied for their many physical adaptations, provide an exemplary model of multifunctional motor control. The beak is involved in two behaviors important for birds' survival: eating and vocalizing. Similar orofacial muscles are used in both behaviors but with notable spatiotemporal differences. Seed eating occurs in three phases where birds peck a seed, husk the seed (analogous to mammal chewing), and then swallow the seed. When vocalizing, beak movements modulate the amplitude and frequency content of vocalizations. Vocalizations are comprised of calls, which are mostly unlearned, and song, which in songbirds is learned. Evolutionary studies propose that vocal behavior evolved after jaws arose, with learned song evolving even more recently in birds. This sequence suggests calls and songs co-opted pre-existing circuits for beak motor control. Anatomical studies in bird motor cortex show a region called AiL projects to beak motor circuits in the brainstem, while region RA, found only in song learning birds, projects both to brainstem circuits for vocal control and some overlapping targets with AiL for beak movement. Do the neural dynamics of these sequentially evolved regions share motor codes for similar beak movements, or is their activity unique to beak movements during eating or vocalizing? RA neural activity during song is well studied, but no prior studies have recorded from AiL. To address our question, we combined high resolution kinematics with recordings of populations of single neurons from AiL and RA in zebra finches. In AiL we identified neurons with activity modulation during eating, either increasing or decreasing activity. No AiL neurons recorded to date show vocal-related modulation relative to baseline, suggesting AiL is not a beak generalist and could sequence eating behaviors. In RA, we found precise activity for both song and different call types. In future work we will compare each region's activity between eating, calling, and singing to determine the region's degree of specialization. If AiL and RA use different dynamics for similar beak movement, it may be that evolving new pathways, like RA, allows motor systems to expand the motor codes available to control muscles and generate new behaviors. This work will provide a framework for multifunctional motor control across circuits, and how circuits evolve to support novel behaviors.

Disclosures: C.D.M. Vargas: None. **A. Grassler:** None. **S.J. Sober:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: G.01. Neuroethology

Support: DST CSRI
DST INDO-CZECH
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Title: Role of motor cortex in mouse vocalization sequence production

Authors: S. AGARWALLA[1], H. K. SRIVASTAVA[2], *S. BANDYOPADHYAY[3];
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Abstract: Pup isolation calls (PICs) and adult courtship ultrasonic vocalizations serve as an important behavioral readout for examining social communication abnormalities in mouse models of neurodevelopmental disorders. Here, we examined the sequential organization of ultrasonic vocalizations USVs and how it changes across development in a mouse model of ASD generated through prenatal exposure to valproic acid (VPA).We found that context-dependent USV sequences in typically developing (TD) mice contain predictive patterns during both infancy and adulthood. In contrast, VPA-exposed mice showed disrupted sequencing in both PICs and adult courtship USVs. These changes were behaviorally meaningful, as recipient animals, including mothers and virgin females, showed a preference for typical USV sequences over those produced by VPA-exposed mice.Previous work has shown that midbrain, brainstem, and diencephalic circuits are sufficient for generating mouse USVs. More recent evidence suggests that the cortex also contributes to USV production, with infragranular neurons in the primary motor cortex (M1) influencing USV acoustic features and projecting to subcortical centers that control laryngeal muscles. Using reversible pharmacological inhibition of infragranular M1, we demonstrate that M1 is necessary for producing the sequential structure of USVs.Further analysis of infragranular M1 microcircuitry using simultaneous glutamate uncaging and two-photon calcium imaging across developmental stages revealed altered circuit organization in VPA-exposed mice compared with TD mice. Together, these findings show that M1 plays an essential role in regulating a key component of mouse vocal communication, providing a basis for studying the neural mechanisms underlying vocal sequence-based communication and its disruption in neurodevelopmental disorders.

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Poster

PSTR142: Neuroethology: Vocal/Social Communication

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Program #/Poster #: PSTR142.10/CC10

Topic: G.01. Neuroethology

Support: NIH F32MH125562
NIH R01NS113071
NIH P40 OD010996

Title: Neural circuitry underlying the integration of social context and energy balance to regulate vocal display effort

Authors: *J. A. TRIPP[1], C. M. CERKEVICH[2], J. JANIK[1], S. M. PHELPS[3];
[1]Carleton Col., Northfield, MN; [2]Systems Neurosci. Ctr., Univ. Pittsburgh Sch. Med., Pittsburgh, PA; [3]Integrative Biol., Univ. of Texas at Austin, Austin, TX

Abstract: Social interactions are critical for health and well-being in humans and other animals, but the motivation driving social behaviors is not constant. It is influenced by a variety of factors including social environment and internal state. Animal vocal display behaviors have been found to be sensitive to social context and hormonal signals of internal states across a variety of species and provide a ready readout of social motivation. Alston's singing mouse (*Scotinomys teguina*) is a particularly valuable model for understanding the mechanisms that integrate external context and internal state. Their distinct vocalization is used in mate attraction and intrasexual competition, and their vocal effort is regulated by both social context and hormonal state. Leptin, which signals energy availability and satiety, promotes vocal display effort, but only in the presence of perceived social partners (song playback). In order to better understand the mechanisms integrating social environment and energy balance, we sought to identify the circuitry controlling singing mouse vocalization, as well as the cell types within that circuit that are active in response to social and energetic cues. First, we used retrograde rabies virus tracing of inputs to the cricothyroid, a muscle dedicated to frequency modulation in vocalization. This study revealed a multisynaptic circuit comprised of regions previously associated with vocalization, social behavior, and energy homeostasis including the lateral periaqueductal gray, paraventricular nucleus of the hypothalamus, arcuate nucleus and medial preoptic area. Next, we performed a playback study in which mice received injection of leptin or vehicle followed by playback of conspecific songs or control tones. Our behavioral results replicated our prior finding that leptin increases song effort in response to song playback. To identify cells within the circuit that integrate social context and leptin signaling, we used single-nucleus RNA-sequencing to reconstruct cell types and measure expression of activity-dependent genes following hormonal manipulation and playback, focusing on hypothalamic nuclei identified by our tracing study and prior research. Together, these experiments unveil the likely neural substrates involved in integrating cues of social environment and internal state to regulate motivation and investment in social display and provide promising candidates for future manipulation studies.

Disclosures: J.A. Tripp: A. Employment/Salary (full or part-time):; Carleton College. B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; University of Texas. **C.M. Cerkevich:** A. Employment/Salary (full or part-time):; University of Pittsburgh. **J. Janik:** None. **S.M. Phelps:** A. Employment/Salary (full or part-time):; University of Texas.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.11/CC11

Topic: G.01. Neuroethology

Support: NSF IOS 2154646
NINDS-NIH R01 NS140062

Title: Efficient-efficient dense burst-pause codes in a songbird

Authors: *L. E. S. TAVARES[1], B. M. ZEMEL[3], M. FARIAS-VIRGENS[2], C. V. MELLO[4], H. P. VON GERSDORFF[1];
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Abstract: Avian brains control fast, precise, and complex behaviors using 3-fold less energy per neuron than mammalian brains. How is this high performance achieved with such low energy cost? One intriguing mechanism links higher avian brain temperature (~40°C) to energy efficiency. Using a biophysical model constrained by in vitro recordings from song motor control neurons in zebra finches, we found an exquisite coordination among ionic currents at 40°C that minimizes Na+ influx during spike firings. We then used in vivo spike recordings from singing birds to model their temperature-dependent burst-pause firing statistics. Elevated temperatures facilitated higher firing frequencies, revealing a remarkable tradeoff that renders energy efficiency only weakly temperature-dependent from 30°C to 40°C. Importantly, we find an additional >3-fold energy cost during singing compared to silent periods, a difference that stems mainly from the plastic synaptic currents required to drive burst spiking during songs, and, surprisingly, not from intrinsic neuronal excitability. Songbirds thus utilize specialized cortical neurons with dense, precise and energy-efficient spike codes during song production.

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Poster

PSTR142: Neuroethology: Vocal/Social Communication

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Topic: G.01. Neuroethology

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NIH/NINDS R00NS102520
HHMI Freeman Hrabowski Award

Klingenstein Fellowship Award
Searle Scholar Award

Title: A Complete Song System Without Song: Anatomical Connectivity in Female Zebra Finches

Authors: *J. E. BURKE[1], H. CHEN[1], M. ESWARAN[1], A. YAGIELSKI[3], V. GADAGKAR[2]; [2]Zuckerman Mind Brain Behavior Inst., [1]Columbia Univ., New York, NY; [3]None., New York, NY

Abstract: In male zebra finches, song learning and production depend on a well-studied neural circuit known as the song system. This circuit includes a motor pathway, required for song production, and an anterior forebrain pathway, required for song learning. Although female zebra finches do not sing, they have the same brain regions within this circuit, raising the question of whether the female song system is organized in the same way as the male song system. To investigate the anatomical organization of the song system in non-singing female zebra finches, we performed targeted tracer injections into nuclei in both major pathways. We injected HVC and RA, two key nuclei in the motor pathway, as well as LMAN and Area X, two nuclei in the anterior forebrain pathway, and compared the resulting connectivity patterns to the known organization of the male song system. We found that despite the absence of learned song production, females possess an anatomically complete song system with connectivity across both the motor and anterior forebrain pathways. While the existence of many of these areas have been documented in females before, it was unknown whether they were connected the same way as males. These findings suggest that the female song system may not simply be a reduced or disconnected version of the male circuit, but may in fact play a functional role in behavior, like the evaluation of males during courtship. This work builds on existing anatomical tracing in female songbirds and provides a stronger foundation for future studies investigating the role of the song system in non-singing females.

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Poster

PSTR142: Neuroethology: Vocal/Social Communication

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Program #/Poster #: PSTR142.13/CC13

Topic: G.01. Neuroethology

Support: R01NS108424

Title: Introductory Notes as Motor Preparatory Gestures Underlying Zebra Finch Song

Authors: *S. ASADOORIAN[1], K. BIEN[1], A. R. MAGEE[1], M. NGUYEN[3], R. ABRAM[2], R. ARNOLD[1], J. MENDEZ[4], B. G. COOPER[1];

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Abstract: Neural and behavioral motor preparation facilitates the performance of voluntary, sequential motor acts. In male zebra finches, a vocal learning species, introductory notes (INs) are hypothesized to serve as a preparatory motor gesture for the upcoming stereotyped song syllable sequence (motif). INs and song syllables are produced during exhalation, and inspirations are silent gaps between vocalizations. Male birds sing more INs when singing to a female (directed) compared to the song produced in isolation, and the IN sequence becomes increasingly stereotyped immediately prior to song onset. We developed a novel method to identify variable INs produced exclusively by the male bird in a directed singing session by filtering subsyringeal air pressure to isolate only the male's vocalizations. We used the sound-silence-sound pattern of each bird's INs to trigger the playback of either a low-intensity (60 dB, 100 ms; n=9 birds) or a high-intensity (90 dB, 500 ms; n=8 birds) disruptive, white-noise stimulus. The two sound stimuli were also presented during the first song motif. Our hypothesis is that a disruptive stimulus presented during motor preparation (e.g., the IN sequence) would induce a motor delay, but would not cause a delay if presented during motor execution. Consistent with this hypothesis, during IN singing a low- or high-intensity disruptive stimulus caused atypical vocal pauses (range=100-300 ms) following sound playback. In contrast, such pauses were not observed during motif production in response to the low- or high-intensity sound playback. However, the high-intensity sound caused birds to terminate their song (3 of 6 birds tested). In a separate experiment, song respiration was recorded in seven zebra finches, and multiple features of respiratory motor gestures across the sequence of the terminal 4 INs (i.e., before song onset) were quantified. The terminal IN inspiration closely approximated the first motor gesture of the first song inspiration. The inspiratory phase of respiration became shorter duration, increased amplitude, and more stereotyped. The results are consistent with the view that INs function as a preparatory motor gesture that is flexible and modifiable in response to external stimuli, whereas song execution is inflexible. The flexibility may allow for vocal timing changes in song onset in response to conspecific behaviors. The correlation between respiratory features during IN progression and similarity to song is also consistent with preparatory motor patterns. We suggest that a critical role of INs is to overcome the inertia of the thoracic cavity before the bird engages in the temporally stereotyped song respiration.

Disclosures: S. Asadoorian: None. **K. Bien:** None. **A.R. Magee:** None. **M. Nguyen:** None. **R. Abram:** None. **R. Arnold:** None. **J. Mendez:** None. **B.G. Cooper:** None.

Poster

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Topic: G.01. Neuroethology

Support: Simons Foundation Society of Fellows

Title: Two-scale temporal organization of vocal communication in Mongolian gerbil families

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Abstract: Vocal communication in social mammals often relies on structured sequences in which information is encoded not only in individual elements, but also in their temporal arrangement. We characterize the vocalization repertoire of Mongolian gerbil (Meriones unguiculatus) families, focusing on call transition dynamics and the stereotyped structure of alarm bouts. We conducted continuous audio-video recordings from five separate families (2 parents and 4 pups) housed in a semi-naturalistic environment with two large above-ground enclosures, an underground burrow, and a nest. This dataset yielded over 1.5 million calls, 64.7% of which were emitted underground. We found that bouts displayed two temporal scales. At short inter-call intervals of ≤0.05s, transitions were predominantly heterotypic, linking different call types into combinatorial motifs. At longer intervals of 0.05-2s, transitions shifted toward homotypic repetition, with a rhythmic structure. The most robust temporal structure emerged during alarm behavior, a multimodal signal composed of vocal calls coupled with rhythmic foot drumming. Alarm calls occurred primarily underground, at 85% of instances, and often led other family members to flee to the nest and emit alarm signals. Alarm bout durations were highly skewed: 65% of alarm events consisted of a single call, while multi-call events (n=2,991 bouts comprising >18,000 calls) extended up to 46.6 min. In extended bouts, alarm calls eventually gave way to exclusive foot drumming. Alarm bouts showed strong rhythmic regularity, with median inter-call-interval CVs of 0.39-0.56 across families, and a distinct bimodal distribution with a mode near 0.35, highlighting the gerbils' capacity for high-precision temporal signaling. In addition, call duration decreased systematically from bout onset, with shortening in 67% of bouts, suggesting that call duration may encode elapsed time since the initial threat. Together, these results reveal that gerbil vocal communication is organized across multiple temporal scales, from rapid combinatorial call transitions to prolonged, rhythmic multimodal signaling.

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Poster

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Topic: G.01. Neuroethology

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Title: Forward suppression of neural responses to ethologically relevant vocalizations in the zebra finch auditory telencephalon

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Abstract: In auditory processing, segmentation of sounds into distinct auditory objects relies on cues such as silences between sounds and acoustic transitions. Forward masking is a psychological phenomenon whereby the perception of a sound can be masked by a preceding counterpart; e.g., unconsciously, speech signals are often masked due to the quick succession of speech sounds. A closely related physiological phenomenon that may explain forward masking is forward suppression (FS): where a stimulus-evoked response is suppressed proportionally to the silence gap between it and a preceding sound. While FS is typically studied in rodents using simple, closely spaced sounds (e.g., clicks/tones), many species produce learned, ethologically relevant vocalizations with rapidly successive elements. Zebra finches (ZF; *Taeniopygia guttata*), a species of songbird, produce stereotyped, learned vocalizations for social and mating communication, with songs composed of introductory notes and syllables combined into repeated motifs. The ZF *caudomedial nidopallium* (NCM) is a higher auditory region that forms memories, tracks statistical regularities in sounds, and discriminates conspecific sounds. A hallmark feature of NCM is stimulus-specific adaptation (SSA), whereby evoked activity decreases as a function of stimulus repetition, a process that recurs each time a new stimulus is encountered. The potential interaction between FS and SSA over different time scales for natural stimuli is largely unexplored. We here employ high-density, *in vivo* NCM electrophysiology to study FS in response to two different stimulus sets: 1) ZF call duplets with varying intervening silences (5, 50, or 100mS), and 2) novel conspecific songs that naturally include silences between syllables (~50mS on average). Single-unit analysis revealed suppression that is proportional to duplet silence length, and more rapid adaptation than with singlet call stimuli; this is seen in both narrow- and wide-spiking neurons. Robust adaptation may be facilitated by the processing of duplets as two renditions of the same stimulus rather than a single object. Although song-evoked activity is typically analyzed over the entire song duration, we show it can be parsed by component, with each element exhibiting adaptation. Further, evoked activity to each successive song component followed a “see-saw” shape, suggesting that activity levels undergo alternating suppression and facilitation depending on the preceding response state. Together, the results show that FS is detectable in NCM with a typical FS assay and can be studied in an established model for speech-sound processing. Support from NIH R01NS082179.

Disclosures: B. Furest Cataldo: None. **D.S. Vicario:** None. **L. Remage-Healey:** None.

Poster

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Title: Spiking activity during inter-syllable interval reveals predictive structure in vocal sequences

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Abstract: Temporal integration plays an important role for interpreting auditory information. The combination of acoustic elements and the silent intervals between them make a meaningful acoustic/sequence structure. Mouse ultrasonic vocalizations(USVs) are increasingly used as a model system to study the neural mechanisms underlying vocal communication and aspects relevant to human speech. However, using USVs as a tool to study translational aspects requires a deeper understanding of their temporal and sequential organization. In this study, we investigated the neural encoding of context-specific USV sequences to determine how sequence structure is represented in the auditory cortex with particular emphasis on the role of the inter syllable silence intervals.
Single-unit extracellular recordings from the auditory cortex (ACX) of typically developing (TD) female mice were analyzed in response to predictive natural USV sequences and randomized USV sequences. Incorporating spiking activity during the inter-syllable interval (ISI) revealed increased sequence selectivity for natural sequences (SN), while randomized sequences (SR) showed the opposite trend. Interestingly, male exposure further enhanced the ISI-dependent difference in sequence selectivity between SN and SR. Thus experience dependent plasticity in representation of natural predictive courtship sequences in the female mouse auditory cortex is also enhanced further with incorporation of neural activity between syllables.
To better understand the contribution of ISI to sequence structure, we created a set of stimuli with identical syllable content, S, J, H, and O. Each syllable was repeated six times with silence gaps of 45, 90, 180, and 270 ms inserted between repetitions, resulting in a total of 16 stimuli. When responses during the ISI were included in the analysis, selectivity for H and O sequences was significantly higher than for S and J sequences across all ISI durations. This difference was not evident when the analysis was restricted to syllable-evoked responses alone. Thus the study shows that silence plays an important role in the predicting the socially relevant sequences.

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Poster

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Topic: G.01. Neuroethology

Title: Investigation Posture-Dependent Modulation of Ultrasonic Vocalization Structure

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Abstract: Effective social communication requires the coordinated use of vocal and non-vocal signals. Although such multimodal interactions are widespread across species, how non-vocal sensory inputs regulate vocal production during ongoing social behavior remains poorly understood. Mouse ultrasonic vocalizations provide a powerful system in which to address this question, because mice emit USVs during active social investigation, when vocal output and chemosensory sampling are temporally coupled.
Here we developed an automated behavioral and acoustic analysis pipeline combining DeepLabCut pose estimation, SimBA behavioral classification, and DeepSqueak USV detection to quantify social investigation and vocal behavior in freely moving mice. In this assay, mice investigated a caged conspecific while their interaction patterns and USVs were measured with high temporal resolution. Consistent with previous observations, USVs occurred predominantly during direct social contact and declined after conspecific introduction. However, finer segmentation of social behavior revealed that USV structure depended strongly on the type of interaction. Calls emitted during nose-to-anogenital investigation were significantly longer than those produced during nose-to-nose contact, reorientation, or non-contact periods.
Because nose-to-anogenital investigation provides enriched access to social chemosensory cues, these findings suggest that olfactory input modulates the structure of vocal output during social interaction. Thus, USV production is not simply a correlate of social proximity or generalized arousal, but is dynamically shaped by the sensory context in which vocalization occurs.
To investigate the neural basis of this chemosensory-vocal coupling, we are recording calcium activity in the periaqueductal gray, a brainstem region required for USV generation. We hypothesize that PAG activity reflects not only the motor execution of vocalization, but also the influence of social sensory context on call structure. Ongoing fiber photometry experiments align PAG activity with specific interaction types, USV onset, and call duration to identify neural correlates of olfactory-dependent vocal modulation.
Together, these data identify a behavioral link between chemosensory investigation and vocal structure during social interaction. They further suggest that the PAG may act as a site where social sensory information is incorporated into vocal motor commands.

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Poster

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Konishi Neuroethology Research Award (MFV)

Title: Habitat transmission and annual variations of vocalizations in black jacobin hummingbirds

Authors: *C. R. OLSON[1], **C. V. MELLO**[2], C. DUCA[3], S. RODRIGUES SILVA[4], L. FALK[5], M. DA SILVA[6], A. RICO-GUEVARA[7], M. FARIAS-VIRGENS[8];
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Abstract: Black jacobins are hummingbirds from the basal Topaz clade, common in the Atlantic Forest of Brazil. Their vocalizations have a mean fundamental frequency of 11.5 kHz with rapid oscillations in the ~10-14 kHz range, which is remarkable as this is well above the established limit of typical avian hearing (<8-9 kHz). Black jacobins vocalize during inflight displays at short distance to conspecifics, whereas we have not observed them vocalizing to other species, or responses from other species. Their vocalizations are unexpected in the Atlantic Forest, where high-frequency sound is expected to transmit poorly. In a playback-rerecording experiment we tested: 1) jacobin vocalizations in open vs. dense habitats, 2) natural vs. frequency-shifted vocalizations (5.6, 3.6 kHz), and 3) natural vocalizations vs. matched artificial vibrato and tones. Re-recorded sounds 0.6-20 m from the speaker were analyzed (BaRulho in R) to obtain blur ratio (BR), excess attenuation (EA), and signal to noise ratio (SN). We found that: 1) dense habitat had higher EA and BR; 2) low-frequency vocalizations had higher SN and lower EA and penetrated understory better; 3) tones had lower BR compared to vocalizations and vibrato, but vocalizations had higher SN compared to other sounds. Jacobin vocalizations are thus poorly suited for long-distance communication yet transmit better than artificial sounds. Based on recordings from captive individuals, vocalizations are produced by both sexes and old juveniles and are represented by a single song type per individual. We have also compared vocalizations at the Instituto Nacional da Mata Atlantica over the past decade (2015 - 2025). In 2015-16 the most common pattern was a 3-syllable triplet, each syllable with distinct features that varied across birds. Starting in 2019 we noted the occurrence of 2- and 3-syllable vocalizations, and by 2022 the 3-syllable utterances had been entirely replaced by 2-syllable ones, a pattern that continued in 2024. We also noted seemingly transitional vocalizations in 2019, where the first two syllables seemed to merge into a longer 1st syllable, followed by a short 2nd syllable. This pattern was also in roughly half the vocalizations in 2022, whereas the remainder were two syllables of identical duration and structure. The ability to produce and perceive these fine temporal patterns points to remarkable vocal-motor and sensory abilities. The data set the stage for more extensive investigation of the acoustic biology of this species and the possible role of vocal learning. They

also present a valuable conceptual model for studying the behavioral ecology of avian vocal communication in complex environments.

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Poster

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Title: Sex Differences in Cell Type Composition and Molecular Specializations in a Vocal Motor Circuit

Authors: *M. FARIAS-VIRGENS[1], L. E. TAVARES[2], H. P. VON GERSDORFF[2], C. V. MELLO[3];
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Abstract: Brain sex differences are broadly understood to influence health outcomes and behavior, including sex differences in risk for, and presentation of, neuropsychiatric and neurological disorders. Yet the neurogenetic mechanisms that generate enduring sex differences in brain physiology and behavior remain poorly defined. Addressing these questions requires a model organism in which discrete, accessible brain regions control a sexually dimorphic, complex, and readily quantifiable behavior with relevance to human cognition. The zebra finch (ZF) offers an exceptional system for this purpose, as only males learn and produce song, reflecting profound sexual dimorphism within song-related neural pathways. Our work closely examines the sexual differentiation of a major ZF vocal-motor nucleus, the robust nucleus of the arcopallium (RA). RA integrates afferent input from cortical and basal ganglia vocal areas and projects directly to brainstem neurons that innervate the syrinx, the bird's vocal organ, thereby guiding song production in a manner analogous to the role of the human laryngeal motor cortex in speech. RA develops similarly in males and females until approximately 20 days post-hatch (dph). Thereafter, RA volume increases more than twofold in males, with cells becoming larger and more widely spaced, and growth plateauing by approximately 50 dph; in females, RA instead regresses. Using single-nucleus RNA sequencing and in situ hybridization analysis of selected markers in adult zebra finches (>100 dph), we identified previously uncharacterized cell

types and molecular specializations of female RA in contrast to males and the neighboring dorsal intermediate arcopallium, a region that supports broader sensorimotor functions. This approach allowed us to identify candidate molecular drivers of the development and physiology of RA projection neurons that innervate brainstem nuclei controlling vocal production, which may account for these neurons' distinctive morphological and electrophysiological properties. Our work provides mechanistic insight into how developmental programs and hormone signaling sculpt specific cell types to produce sexual dimorphism in a cortical-like circuit that supports vocal behavior. By defining the genetic regulation of brain sex differences at cellular resolution, the songbird model can help ground more precise approaches to sex-related interventions, including those relating to menopause, disorders of sexual development, and gender affirmation.

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Poster

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Searle Scholar Award

Title: A Sensorimotor Role for the Female Song System in Social Evaluation

Authors: *H. S. CHEN, J. E. BURKE, M. P. ESWARAN, A. J. YAGIELSKI, V. GADAGKAR;
Columbia Univ., New York, NY

Abstract: During social interactions, we must evaluate the behavior of others to respond appropriately. Here, we investigate the neural computations underlying social evaluation in zebra finches, a songbird species in which females choose their mates based on courtship songs. Decades of research have focused on the neural circuitry for song production in males (the "song system"), yet little is known about how song is evaluated in females. Remarkably, although females do not sing, they have an intact song system. This raises the exciting possibility that while the male song system is used for song production, the female song system is used for song evaluation. With the first-ever Neuropixels recordings in female HVC and downstream nucleus

RA, we examine how this key pathway of the song system encodes courtship-relevant vocal signals. During courtship, females must internally represent male songs to evaluate potential mates, with whom they interact using short, innate calls. We find that the female song system is strongly engaged during both perception and production: HVC exhibits time-locked firing patterns in response to male song, and both HVC and RA show premotor activity preceding calling. These dual functions seem to mirror male HVC activity, where neurons fire at precise moments during singing and also prior to calling. Additionally, precise syllable-level perturbations of male songs demonstrate that female HVC detects deviations from expected song structure, suggesting HVC in females plays a role in encoding song structure and detecting errors during song evaluation. Together, our findings challenge the traditional view of the female song system as a vestigial counterpart to the male song system. They instead support an emerging view of this circuit having functionality in females, where HVC plays a key sensorimotor role in linking male vocal signals, internal expectations, and female vocal responses. This work establishes female songbirds as a promising model for the neural basis of social evaluation.

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Poster

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Program #/Poster #: PSTR142.21/CC21

Topic: G.01. Neuroethology

Title: Acoustic structure of female squeaks impacts male mouse behavioral responses

Authors: *S. M. KEESOM, M. HILDRETH, F. MARTINEZ;
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Abstract: House mice (*Mus musculus*) are social animals that emit a range of vocal signals, including ultrasonic vocalizations (USVs) and broadband squeaks. A rise in the study of mouse USVs over the last two decades has allowed *Mus musculus* to become a valuable model organism for neuroscientific research focusing on vocal communication. In contrast, mouse squeaks have received less attention, although the current evidence points to the social relevance of squeaks for mice. During courtship, females are the main producers of squeaks, and previous studies demonstrate that squeaks affect male USVs. Furthermore, squeaks may convey information about the reproductive state of the female, since squeaks possess longer-duration nonlinear elements when female mice are in estrus. Whether male mice respond differently to squeaks depending on nonlinear content has yet to be thoroughly investigated, however. We therefore conducted this experiment to determine the extent to which nonlinearities in female squeaks affect male mouse behaviors. To do this, we used a split-cage assay to present 9 male mice with a novel female paired with one of three playback conditions (nonlinear squeaks, linear squeaks, and background noise as a control) in a repeated-measures design. Audio and video

recordings were subsequently analyzed, blind to playback treatment. We found that male USVs were significantly suppressed in response to nonlinear squeaks compared to background noise. There was a trend towards greater production of 50-kHz harmonic USVs, a subtype associated with male reproductive behaviors, following presentation of nonlinear squeaks compared to the other playback types. Lastly, we quantified male investigation of the perforated barrier separating the two mice as a proxy measure of male investigation of the female. Males spent significantly more time investigating the barrier during nonlinear squeak playback compared to linear squeak playback. Given that nonlinear segments are increased in the squeaks of estrous females and that nonlinearities increased male mouse behavioral responses to squeaks in the current study, this provides tentative support for the hypothesis that nonlinear elements in female squeaks convey information about female receptivity to males. More broadly, this would indicate that, during courtship, female mice emit context-dependent vocal signals to which males respond with appropriate behaviors. These findings also lend further support to the idea that mouse squeaks have much to offer as an instrument for studying the neural mechanisms of vocal communication, as well as communication disorders.

Disclosures: S.M. Keesom: None. **M. Hildreth:** None. **F. Martinez:** None.

Poster

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Program #/Poster #: PSTR142.22/CC22

Topic: G.01. Neuroethology

Title: Until we squeak again: Impacts of squeak playback on next-day courtship encounters in house mice

Authors: *A. BOROWIEC, F. MARTINEZ, M. HILDRETH, S. M. KEESOM;
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Abstract: Prior experience is a significant modifier of future behavior across animal species. This is particularly relevant in reproductive contexts, in which experience with courtship signals can shape responses to potential mates. For example, previous exposure to birdsong influences female preferences for male singing. Vocal interaction also makes an important contribution to courtship in house mice (*Mus musculus*). In this context, female mice mainly produce human-audible squeaks whereas male mice emit most of the ultrasonic vocalizations (USVs). Vocal playback impacts mouse behaviors while the playback is ongoing, but whether acoustic experience affects future social behavior has been relatively unexplored in mice. We therefore conducted a study to investigate whether mouse courtship is affected by prior exposure to squeaks, a vocal signal that corresponds to female defensive behaviors, but may also convey female receptivity via acoustic variation. On the first day, male (n = 6) and female (n = 6) mice were placed in a divided arena and presented with one of four 5-min playback conditions: linear squeaks, nonlinear squeaks, background noise, and no playback. One day after playback, the

same male and female mice were paired for 15 minutes in the male's home-cage. A blind observer imported videos into BORIS and quantified the following behaviors: approaches, male mounts, and female repels of the male. There was no significant effect of the prior day's playback on male approaches to the female or mounting. In contrast, female repelling was greater the day after either type of squeak playback, compared to playbacks that did not include squeaks. Interestingly, female approaches to the male were greatest in the days following playback of nonlinear squeaks, which are more likely to be produced by receptive females. If supported by additional data collection, this finding would suggest that prior exposure to squeaks in conjunction with a male mouse has long-lasting effects on the female response to the same male during a subsequent interaction. This would highlight the importance of experience with social sounds in shaping female reproductive behavior in a commonly studied laboratory animal.

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Poster

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Title: Dynamic Population Coding of Social Behavioral States in Hippocampal Area CA2

Authors: *D. PANDE[1,2], A. Y. MA[1,2], J. D. TURK[2,3], J. P. NEUNUEBEL[2,1,3];
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Abstract: Dorsal CA2, a hippocampal subregion important for social recognition memory (Hitti & Siegelbaum, 2014), exhibits social- and novel-context-dependent changes in spatial representations (Alexander et al., 2016). However, how CA2 encodes naturalistic social experiences, including ultrasonic vocalizations (USVs), remains unclear. To address this, we combined a sound source localization system (Warren et al., 2018) and wireless in vivo electrophysiology to simultaneously record behaviors, USVs, and dCA2 activity while adult male mice (n = 5, C57BL/6J) implanted with 32-channel silicon probes freely interacted with one male and two female partners. Dyadic social interactions were automatically identified using a previously described method (Clein et al., 2024), and USVs were assigned to individual mice. Preliminary analyses from a single recording session revealed significantly higher firing rates in neurons (n = 66) during social interactions (n = 487 bouts) than during an equal number of duration-matched non-interaction periods (Wilcoxon signed-rank, $p < 0.0001$). Using a support vector machine classifier (SVM), we decoded interaction versus non-interaction states from population activity with an accuracy significantly above chance (permutation test, $p < 0.001$).

Among 239 male-male interactions, single-neuron firing rates were similar during vocal (49) and silent (190) bouts (Wilcoxon signed-rank, $p = 0.59$). Despite the absence of firing-rate differences, an SVM classifier distinguished vocal and silent interactions with an accuracy significantly above chance ($p < 0.001$). Using a JAABA-trained classifier (Kabra et al., 2013), we identified investigation bouts. Firing rates were significantly higher when the implanted mouse was investigated by the male partner (56 bouts) than when the implanted mouse investigated the male partner (18 bouts; Wilcoxon signed-rank, $p < 0.01$). An SVM classifier decoded periods when the male partner investigated the implanted mouse from sample-matched non-investigation periods with an accuracy significantly above chance (permutation test, $p < 0.001$), whereas decoding periods when the implanted mouse investigated the male partner was not significant (permutation test, $p = 0.08$). Together, these preliminary results suggest that dCA2 population activity may encode social interaction states, distinguish vocal from silent interactions, and preferentially represent social behaviors directed toward the recorded animal.

Disclosures: D. Pande: None. **A.Y. Ma:** None. **J.D. Turk:** None. **J.P. Neunuebel:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.24/CC24

Topic: G.01. Neuroethology

Title: Parallel dopamine signals support hierarchical reinforcement learning of motor sequences

Authors: *A. RAHA[1], J. U. KASDIN[2], A. DUFFY[3], N. NADLER[4], A. L. FAIRHALL[5], K. STACHENFELD[6], V. GADAGKAR[2];
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Abstract: Across species and environments, the ability to chain complex motor actions into fluid sequences is essential for sophisticated behavior. Zebra finch song learning provides a powerful model for studying such sequence acquisition. Songs are composed of syllables that must be both learned individually and organized into a stereotyped sequence. Previous work has shown that dopamine (DA) signals in the basal ganglia reflect performance prediction errors. Functionally, these act as reinforcement learning (RL)-style reward prediction errors (RPEs) guiding the development of individual syllables via internal feedback, without external rewards. However, the role of DA in the process of learning syllable *order* remains unknown. Using longitudinal recordings across natural learning, we show DA encodes an order-related error independent of syllable-level error. To explain these findings, we propose a hierarchical RL model in which basal ganglia-thalamocortical circuits implement parallel actor-critic processes: one for learning individual syllables and another for chaining syllables into ordered sequences. Simulations recapitulate our findings in the data and reproduce behavioral features of song learning,

including the gradual emergence of new syllables and the dissociation between syllable and sequence learning. Our model yields further testable predictions for how circuit lesions and alternate sequence error formulations should influence syllable formation and sequencing. Overall, we provide experimental evidence supporting dopaminergic hierarchical RL in the brain and a computational framework for how parallel DA signals can jointly support robust acquisition of complex motor sequences.

Disclosures: A. Raha: None. **J.U. Kasdin:** None. **A. Duffy:** None. **N. Nadler:** None. **A.L. Fairhall:** None. **K. Stachenfeld:** None. **V. Gadagkar:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.25/CC25

Topic: G.01. Neuroethology

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Ting Tsung and Wei Fong Chao Foundation

Title: Frequency-dependent cerebellar circuits independently gate social vocalizations and movement

Authors: *C. BRANDENBURG[1], S. SRIVASTAVA[1], B. R. ARENKIEL[2], R. V. SILLITOE[3]; [2]Mol. & Human Genetis and Neurosci., [3]Pathology & Immunol., [1]Baylor Col. of Med., Houston, TX

Abstract: Language acquisition and social communication rely on distributed neural circuits that integrate motor and cognitive processes. While cortical networks governing language have been extensively studied, the cerebellum has historically been overlooked in models of communication despite growing evidence for its involvement in language, cognition, and neurodevelopmental disorders such as autism. A major unresolved question is whether cerebellar circuits that influence communication are separable from those controlling movement, or whether motor and non-motor behaviors are embedded within shared cerebellar pathways. Here, we asked whether the cerebellum directly regulates adult social vocalizations and whether such

control can be dissociated from motor output. Using ultrasonic vocalizations (USVs) in mice as a sensitive behavioral proxy for social communication, we demonstrate that optogenetic activation of defined cerebellar output pathways rapidly and reversibly suppresses ongoing vocalizations during social interaction. Activation of excitatory cerebellar projections through the superior cerebellar peduncle (SCP) silenced USVs with potency that scaled with stimulation frequency. Systematic mapping across cerebellar lobules, nuclei, and genetically defined cell types revealed that vocal suppression can occur without overt motor impairment, indicating that communication deficits are not secondary to disrupted movement. We next asked which downstream circuits mediate cerebellar control of vocal behavior and identified the periaqueductal gray (PAG), a conserved midbrain vocal control center, as a critical target. Optogenetic stimulation of cerebellar terminals within the PAG reduced vocalizations without altering locomotion, dissociating vocal gating from motor output. In contrast, stimulation of multiple cerebellar regions at 10 Hz robustly induced tremor, yet only a subset suppressed vocalizations, revealing frequency- and pathway-specific separation of motor and non-motor cerebellar functions. Finally, we tested whether vocal deficits arising from cerebellar dysfunction could be bypassed. In a Purkinje cell complex spike knockout model exhibiting severe motor impairment and reduced vocalizations, deep brain stimulation of the PAG restored vocal output without rescuing motor coordination. Together, these findings establish a causal cerebellar-midbrain pathway that gates social vocal communication independently of movement and reveal frequency-dependent circuit mechanisms through which the cerebellum differentially regulates motor and non-motor behaviors.

Disclosures: C. Brandenburg: None. **S. Srivastava:** None. **B.R. Arenkiel:** None. **R.V. Sillitoe:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.26/CC26

Topic: G.01. Neuroethology

Title: Cooling HVC in the Bengalese finch reduces the complexity of song syntax

Authors: *J. SCHUESSLER[1], A. ZENDER[1], Y. S. ZHANG[2], D. Z. JIN[1];
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Abstract: Bengalese finch songs consist of stereotyped syllables sequenced according to probabilistic syntactic rules. Syllable transition probabilities can be context-dependent: from the same syllable, the transition probabilities to other syllables can depend on the preceding syllable sequence. Such syntax can be described by a partially observable Markov model (POMM), which is a state-transition model in which each state is associated with one syllable. The state transitions are Markovian, so the transition probabilities do not depend on the preceding

sequence of state transitions. However, multiple states can be associated with the same syllable. Through this many-to-one mapping from states to syllables, POMMs can generate syllable sequences that contain context-dependent syllable transitions. We recently showed how to infer, from observed Bengalese finch songs, minimal POMMs that have the fewest possible states and can generate syllable sequences that are statistically equivalent to the observed Bengalese finch songs (Lu & Surendralal et al., 2025). Previous work that cooled HVC in Bengalese finches showed that cooling reduced the number of syllable repetitions and randomized syllable transition probabilities (Zhang et al., 2017). To examine whether HVC cooling affects context-dependent syllable transitions, we inferred POMMs for songs produced under both normal and cooled conditions in five adult birds. Context dependency was quantified by the number of extra states associated with syllables. Cooling significantly reduced the number of extra states in three birds, whereas the remaining two birds showed no significant change. These individual differences can be related to the complexity of song syntax under normal conditions. Previous work showed that cooling the left HVC is more effective than cooling the right HVC in slowing song syllables (Zhang et al., 2017). For context dependence, however, cooling either the left or right HVC was effective. Our results suggest that HVC plays an important role in controlling context-dependent syllable transitions and that both hemispheres contribute.

Disclosures: J. Schuessler: None. **A. Zender:** None. **Y.S. Zhang:** None. **D.Z. Jin:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.27/CC27

Topic: G.01. Neuroethology

Title: A NIf-HVC Model of the Emergence of Structured Inhibition During Song Learning

Authors: *D. SEDERMAN, I. MANZO-WENDEL, D. Z. JIN;
Penn State Univ., State College, PA

Abstract: Singing in the zebra finch is driven by an ultra-sparse sequence of bursts in HVC (proper name) neurons that project to RA (the robust nucleus of the arcopallium). Inhibitory neurons in HVC fire throughout the song. Although HVC(I) neurons are less reliable and precise in their timing than HVC(RA) neurons, they exhibit temporal structure (Kosche et al., 2015), and HVC(RA) neurons tend to burst during periods of reduced inhibition (Kosche et al., 2015; Khare et al., 2026). How such a structure arises remains unclear. Here, we propose that inputs from NIf (the nucleus interfacialis of the nidopallium) to HVC play an important role in shaping the HVC(I) firing structure during the formation of protosyllable sequences in HVC at the onset of song learning. In particular, NIf inputs to HVC(I) neurons create a gapped activity scaffold during protosyllable HVC sequence formation. Driven by NIf activity, HVC(RA) neurons self-organize into a synaptic-chain network by recruiting immature HVC(RA) neurons into a growing sequence (Tupikov & Jin, 2021). The recruited HVC(RA) neurons form connections to nearby

active HVC(I) neurons, thereby solidifying the inhibitory scaffold initially provided by NIf. Spontaneous activity is crucial for chain formation. Therefore, HVC(RA) neurons tend to be less inhibited when they are recruited into the growing sequence. Our model consists of more than 20,000 compartmental Hodgkin-Huxley neurons, including HVC(RA) and HVC(I) neurons, and builds on a recent observation that NIf plays an important role in HVC sequence formation (Mackevicius et al., 2020). We model NIf as a generic recurrent neural network. Driven by random Poisson spike trains representing unstructured external input, NIf neurons fire reliably at syllable onsets and exhibit roughly consistent temporal dynamics that provide the timing critical for HVC(I) activity.

Disclosures: D. Sederman: None. **I. Manzo-Wendel:** None. **D.Z. Jin:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR142.28/CC28

Topic: G.01. Neuroethology

Title: Are X projecting HVC neurons critical for the HVC sequence generation?

Authors: *A. KHARE, D. Z. JIN;
Dept. of Physics, The Pennsylvania State Univ., University Park, PA

Abstract: Zebra finch song is driven by an ultra-sparse sequence of projection neurons in the premotor nucleus HVC (proper name). There are two types of projection neurons. HVC(RA) neurons project to RA (Robust Nucleus of the Arcopallium) and burst once at a precise time during the song motif. HVC(X) neurons project to Area X and burst 2 to 4 times at precise times during the motif. HVC(I) neurons are inhibitory interneurons that control HVC dynamics. An HVC(I) neuron fires more randomly during the motif but also exhibits rough preferred spiking times. A canonical model of the HVC(RA) burst sequence posits that HVC(RA) neurons are wired into a synaptic chain network (Jin et al 2007; Long et al 2010). Burst propagation along this chain produces the ultra-sparse and precisely timed sequences in these neurons. However, this model is challenged by recent work suggesting that the HVC sequence is generated through the alternating activations of HVC(RA) and HVC(X) neurons (Trusel et al 2026). Key evidence cited in support of this “relay” model is that stimulating HVC(X) neurons is more effective, as it stops the song with a shorter latency than HVC(RA) stimulation. Using a computational model, we show that the relay model contradicts known facts about HVC sequences. This relay model inevitably introduces gaps in the firing times of HVC(RA) neurons due to axonal delays and integration in HVC(RA) and HVC(X) neurons. However, prior experiments have shown that such gaps do not exist (Egger & Tupikov et al 2020). Moreover, the relay model is more consistent with HVC(X) neurons firing only once during the motif, like HVC(RA) neurons. Attempting to make them fire 2 to 4 times, as observed, makes the relay model highly sensitive to the tuning of network parameters. We propose an extension of the canonical model that

includes HVC(X) neurons. In this model, HVC(X) neurons receive inputs from HVC(RA) neurons such that they fire 2 to 4 times during the motif. They also connect to HVC(I) neurons. However, there are no HVC(X)-to-HVC(RA) connections. Stimulating HVC(X) neurons stops the song because they activate HVC(I) neurons, which in turn suppress HVC(RA) neurons. Stimulating HVC(RA) neurons also stops the song through the activation of HVC(X) and HVC(I) neurons, and is more effective. For minimally effective stimulations, the latency of song stopping can be longer for HVC(RA) stimulation than for HVC(X) stimulation because minimal HVC(RA) stimulation requires recruiting HVC(X) neurons. We suggest that HVC(X) neurons are not direct participants of HVC sequence generation. Experiments that probe their roles must take into account secondary effects through HVC(I) neurons.

Disclosures: A. Khare: None. **D.Z. Jin:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: G.01. Neuroethology

Support: Cornell University Klarman Postdoctoral Fellowship
Simons Postdoctoral Fellowship
Cornell University Department of Neurobiology & Behavior Excellence Fellowship

Title: Neural Evidence for an Acoustically-Organized Mirror System in Parrots

Authors: *M. VANCHISWAR[1,2], Z. ZHAO[3,2], T. YU[2], E. ITAHANA[2], J. H. GOLDBERG[2]; [2]Neurobio. and Behavior, [1]Cornell Univ., Ithaca, NY; [3]Inst. of Zoology, Chinese Acad. of Sci., Beijing, China

Abstract: Social imitation requires the motor system to transform perceived sensory signals into matching behavioral outputs. This process may rely on internal models that map perceptual representations onto premotor commands. A leading candidate for this mapping is "mirroring," where individual neurons exhibit selective activity for an action regardless of whether it is observed or produced (Rizzolatti et al, 1996). Budgerigar parrots are open-ended vocal learners that acquire complex sequences throughout life, providing a powerful model for studying mechanisms of imitation. We recently identified a frontal cortical nucleus, MO, that exhibits an acoustically-grounded premotor code: during singing, individual MO neurons exhibit high selectivity for specific acoustic features, independent of syllable category or vocal context. In this exploratory study we asked whether MO also serves a perceptual role by recording neural activity during natural social exchanges between socially bonded partners with converged warble repertoire. In preliminary recordings from a single adult male budgerigar, we isolated 40 MO single units and quantified per-neuron acoustic selectivity by kernel density estimation relative to

trial-shuffled distributions. Eleven of these neurons responded selectively to the partner's song above the shuffle mean and survived Benjamini-Hochberg correction (false discovery rate $q < 0.05$), each displaying the same precise acoustic selectivity observed during self-generated singing. Recording and analyses from additional birds are ongoing to assess the generality of this representation and any sex differences. These findings suggest that MO contains an acoustically-organized mirror system, potentially providing the neural scaffold for vocal imitation and flexible social communication.

Disclosures: M. Vanchiswar: None. **Z. Zhao:** None. **T. Yu:** None. **E. Itahana:** None. **J.H. Goldberg:** None.

Poster

PSTR142: Neuroethology: Vocal/Social Communication

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: G.01. Neuroethology

Support: Cornell University Klarman Postdoctoral Fellowship
Simons Postdoctoral Fellowship

Title: Characterization of song-related discharge in frontal cortical nuclei of the parrot

Authors: *L. M. CIRONE[1], M. VANCHISWAR[1], Z. ZHAO[1,2], J. H. GOLDBERG[1];
[1]Neurobio. and Behavior, Cornell Univ., Ithaca, NY; [2]Inst. of Zoology, Chinese Acad. of Sci., Beijing, China

Abstract: How the brain generates and refines complex learned vocalizations is a central question in systems neuroscience. Songbirds have provided a powerful model: sparse, temporally precise activity in HVC (posterior forebrain pathway, PFP) drives learned acoustic structure, while bursty, variable discharge in LMAN (anterior forebrain pathway, AFP) generates the vocal variability required for learning. Whether these circuit mechanisms generalize across species with more elaborate vocal repertoires — and what neural strategies support lifelong, open-ended vocal learning — remains unknown. Budgerigar parrots (*Melopsittacus undulatus*) offer a compelling comparative system. Having diverged from songbirds over 50 million years ago, budgerigars learn vast vocal repertoires throughout life and produce flexible, complex warble songs. Like songbirds, they possess a nucleated song system with segregated AFP and PFP, but with greater recurrent connectivity and additional nuclei whose functional correspondence to songbird circuits is largely untested. Critically, the frontal cortical nuclei of the parrot AFP have never been physiologically characterized. To address this gap, we present the first electrophysiological recordings from the parrot AFP during singing. Using moveable electrode arrays in freely behaving budgerigars, we sampled a broad dorsoventral extent of the frontal song system in single penetrations, spanning the oval nucleus of the mesopallium (MO), the magnocellular nucleus of the anterior nidopallium (NAO; a candidate LMAN analog), and the

medial striatum (MMSt; a putative Area X analog). As in songbirds, parrot AFP neurons show dramatic firing-rate changes at singing onset and offset. However, we observe representational diversity not previously described in zebra finch LMAN: sparse neurons highly selective for specific acoustic elements in both MO and NAO, alongside a distinct high-firing-rate, bursty population in NAO. Current analyses also examine whether MMSt activity parallels Area X dynamics. These recordings reveal a richer, more heterogeneous set of singing-related signals in the parrot AFP than in songbird LMAN, and begin to define the cell types and circuit dynamics that may support complex, lifelong vocal learning — with implications for understanding the neural basis of flexible sequence learning more broadly.

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Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.01/DD1

Topic: G.03. Stress and the Brain

Title: AMC-F1-mediated mitochondria-autophagy crosstalk promotes neurological resilience in a mouse model of Leigh syndrome

Authors: *O. MCCARTY;
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Abstract: Olivia Y. McCarty, Raksha Rao, Andrew Fanous, and Nami McCarty
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Leigh syndrome is the most common pediatric mitochondrial disease (~1 in 40,000 live births) and is characterized by progressive neurodegeneration, motor dysfunction, respiratory failure, and premature death. Mutations in NDUFS4, an accessory subunit of mitochondrial complex I, account for a subset of Leigh syndrome cases and result in profound defects in mitochondrial function. Despite being a primary mitochondrial disorder, activation of autophagy by rapamycin partially ameliorates disease progression in *Ndufs4*$^{-/-}$ mice, suggesting that mitochondrial quality control pathways can modify neurological outcomes. However, the mechanisms coordinating mitochondrial adaptation and autophagy in neurological disease remain poorly understood.
We recently discovered AMC-F1 (Autophagy-mitochondria coupling factor-1;TRIM44) as a novel regulator that bidirectionally coordinates mitochondrial and autophagic programs (*Nature Communications*, in press). We therefore hypothesized that AMC-F1 promotes resilience to mitochondrial dysfunction by enhancing adaptive mitochondria-autophagy crosstalk. To test this hypothesis, we generated whole-body AMC-F1 knock-in mice (*Sox2-Cre;Amcf1KI*) and crossed them with *Ndufs4*$^{-/-}$ mice.
Consistent with previous reports, *Ndufs4*$^{-/-}$ mice developed progressive decline beginning at

approximately P30-40 and succumbed by approximately P70. In contrast, *Amcf1KI*;*Ndufs4*$^{-/-}$ mice exhibited marked improvements in disease progression, including increased body weight and size, reversal of dorsal hair loss, and improved overall health status. Importantly, rotarod testing demonstrated significantly improved motor coordination, while open-field analysis revealed enhanced exploratory behavior and locomotor activity, indicating improved neurological function. Metabolic phenotyping further demonstrated increased oxygen consumption, with similar trends toward increased energy expenditure. Collectively, these findings identify AMC-F1 as a modifier of neurological disease progression in Leigh syndrome and suggest that coordinated regulation of mitochondrial and autophagic programs promotes adaptation to chronic complex I deficiency. These results establish AMC-F1-mediated mitochondria-autophagy as a potential therapeutic target for Leigh syndrome and potentially other mitochondrial neurodegenerative disorders.

Disclosures: O. McCarty: None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.02/DD2

Topic: G.03. Stress and the Brain

Support: NIAAA Grant P50AA017823

Title: Impact of stress on mouse fetal development and gene expression in brain and placenta

Authors: H. SAWAL, T. A. DORMAN, S. Y. LAGUE, S. ALIBEKOVA, S. FANG, O. HAN, *K. E. BOSCHEN;
Upstate Med. Univ., Syracuse, NY

Abstract: Prenatal alcohol exposure (PAE) causes a range of physical, behavioral, and cognitive impairments and prenatal stress (PS) has also been associated with adverse fetal outcomes. Previously, combined PAE and PS exacerbated developmental defects and increased fetal demise. Here, we investigated the independent effects of PS on fetal health and mechanisms through which PS may alter susceptibility to PAE. Pregnant C57BL/6J mice were divided into PS (single housing, low bedding) or control groups (group housed, normal bedding) from embryonic day (E) 0 to E17. Placental and fetal tissues were collected at two time points: E7 or E17. E7 tissue was used for bulk RNA-seq which revealed a robust placental response to PS with upregulation of Wnt signaling, ER stress, glycosylation, angiogenesis, and proteolytic regulation pathways and downregulation of mitochondrial organization, oxidative phosphorylation, aerobic respiration, ribosome biogenesis, and innate immune regulation pathways. Effects were highly sex-specific, with female placentas exhibiting substantially greater transcriptional disruption than male placentas. In E7 embryos, enriched biological pathways were driven by prolactin genes and included immune effector regulation, JAK-STAT signaling, embryonic-placental development,

and leukocyte-mediated immune function. Again, a marked sex difference was observed as females exhibited a greater transcriptional response than males. Shared genes between placenta and embryo revealed changes to lipid metabolism, cell size, and activin signaling in both tissues. Ligand-receptor interaction analysis also supported altered inter-tissue communication, characterized by pairs regulating trophoblast survival, angiogenesis, vascular development, extracellular matrix remodeling, and immune signaling. These findings indicate that PS triggers a coordinated and sex-dependent transcriptomic response in the placenta and embryo during early development. On E17, fetuses were evaluated for developmental defects, and fetal brain and placentas analyzed for gene expression. This analysis confirmed prolonged disruptions to glucocorticoid and immune signaling across the maternal-fetal interface and fetal growth deficits after PS. PS caused downregulated *Il6ra* in brain, and upregulated *Hsd11b2* and downregulated *Hsd11b1, Nr3c1*, and *Abcb1a*/*c1* in placenta. These findings suggest that PS may impair placental glucocorticoid buffering and transport, potentially increasing fetal exposure to maternal glucocorticoids and inflammatory cytokines. Changes in placental transport capacity may contribute to adverse developmental outcomes after PS.

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Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.03/DD3

Topic: G.03. Stress and the Brain

Support: TCU College of Science & Engineering SERC Grant

Title: Interactive effects of diet quality and food source reliability on inflammation and behavior in a mouse model of food insecurity

Authors: *L. P. GUNDERSON[1], J. A. SUAREZ[1], L. EDDLEMAN[2], M. J. CHUMLEY[2], G. W. BOEHM[1];
[1]Psychology, [2]Biol., Texas Christian Univ., Fort Worth, TX

Abstract: More than 6 million households with children in the U.S. experience food insecurity, the majority of which are insecure without hunger. Food insecurity is associated with significant negative health outcomes, such as impaired immune function, anxiety/eating disorders, malnutrition, and delayed language acquisition. Prior studies have attempted to model food insecurity in rodent models to investigate the factors underlying this association, with mixed results. An ideal study design to answer this question would expose mice to a food source that is truly unpredictable and of poor nutritional value, however, much of the prior work has either not been able to make a truly unpredictable food source or utilized a food source that is both unpredictable and less-than-healthy. To address these limitations and improve generalizability,

the present study aimed to ensure that the rodent's food source was truly unpredictable by randomly assigning periods of limited food access across each week of the study. At weaning, male and female C57BL/6J mice were either given ad libitum food access or were food insecure, where their otherwise full food-hopper would be reduced to 25% of their baseline consumption three or four randomly selected nights each week until the following morning. Additionally, mice were also randomly assigned to be fed either a standard chow, a “typical American diet” chow, or a high-fat/high-sugar chow. At 7 months, the mice underwent a battery of behavioral tests to assess anxiety-like behavior and spatial memory capabilities. Samples were then collected from the brain (hippocampus, prefrontal cortex, and cerebellum), liver, small intestine, and adipose tissue for subsequent analysis of the inflammatory response as noted by altered peripheral tissue morphology and changes in TNF-α and IL-6 expression, in particular. This study establishes a novel paradigm to induce a food insecure state in rodents that closely mirrors that which is seen in human populations and provides a robust analysis of the behavioral and immunological changes resulting from chronic exposure to a truly unpredictable and nutritionally poor food source.

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Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

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Topic: G.03. Stress and the Brain

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Animal Behavior Society GIAR
Society for Neuroscience, Neuroscience Scholars Program Fellowship
NIH T32 5T32MH018931-35 (Training Program in Emotions Research)

Title: The Effects of Early Life Adversity on Affective Touch Sensitivity and Socioemotional Development

Authors: *J. E. BOYCE[1], R. RAJU[3], C. A. MARLER[2];
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Abstract: Background: Affective touch is one of the first mammalian sensory experiences after birth and supports neurodevelopment and socioemotional development in infants. However, parental separation, such as NICU hospitalization or orphanage rearing, creates an early environment deprived of touch. Childhood separation from caregivers reduces pleasantness to affective touch, and up to 42% of maltreated children exhibit hypersensitivity to affective touch

(tactile defensiveness, TD). However, the mechanisms underlying the consequences of early life parental separation remain unknown.Methods: We use the Peromyscus californicus because it is biparental and monogamous. We induced early life touch deprivation through biparental separation (BS) from P2-P17 for three hours each day. To study sensitivity to affective touch, we developed a Tactile Defensiveness Assay (TDA) to test pups at P10 and P17. We adapted the Evaluation in Ayres Sensory Integration (EASI) to quantify aversion, locomotion, and soothing behaviors. Lastly, we observed differences in the status of pups latching to their mother, which may be associated with socioemotional development. We divided these observations into four categories and quantified the frequency of each status from P2-P10.Results: The average Rodent-EASI scores were calculated and compared using an unpaired, two-tailed t-test. BS pups exhibited a significantly elevated R-EASI score at both P10 ($p<0.0001$) and P17 ($p=0.01$). Chi-squared analysis of latch status identified a significant difference between the “not latched” and “tightly latched” categories ($p<0.0001$). Fisher’s Exact Test identified that BS pups were more frequently “not latched” ($p=0.0028$) and less frequently “tightly latched” ($p<0.0001$) than controls.Conclusions: Children who have experienced parental separation or maltreatment report reduced pleasantness to affective touch and TD. We developed a novel affective touch assay and present evidence that BS induces hypersensitivity to affective touch at P10 and P17. We also present evidence that BS increases the frequency of pups not being latched and reduces the frequency of pups being tightly latched to their mothers. These results suggest that parental separation may affect somatosensory and socioemotional development.

Disclosures: J.E. Boyce: None. **R. Raju:** None. **C.A. Marler:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.05/DD5

Topic: G.03. Stress and the Brain

Title: Early life stress alters mitochondrial plasticity in the medial prefrontal cortex of adolescence rats

Authors: *S. MALLICK, A. DODGE, F. HOSSAIN, C. P. BASTOS, A. JEFFERS, S. MITRA; Oklahoma State Univ. Ctr. for Hlth. Sci., Tulsa, OK

Abstract: Adolescence is a critical developmental window characterized by significant cognitive and emotional development. Early life stress (ELS) is a traumatic experience during childhood, which can lead to long-term mental and physical health problems later in life, causing depression, anxiety, and a wide range of physical health issues throughout a person's life. In the case of rodents, Limited bedding and nesting (LBN) triggers fragmented care and physical abuse from pup-rearing dams receiving low bedding and nesting material. ELS significantly alters the medial prefrontal cortex (mPFC), disrupting its development and connectivity, leading to impaired emotional regulation, heightened anxiety, and attention issues. However, this condition

can be mitigated by several positive environmental factors. Mitochondria are highly dynamic organelles that readily sense and respond to internal and environmental change but, its role in ELS is not well understood. Mitochondrial DNA (mtDNA) was isolated from the mPFC tissue of adolescent rats (PND 45-47) exposed to standard and LBN rearing conditions with or without exposure to favorable environmental factors. For environmental enrichment (EE), pups are provided with lofts and toys (PND 22-47), and for cross-fostering (CF), pups are reared by alternate dams (PND 10-21). To detect the mitochondrial damage, COMET assay was performed, and the relative copy number (RCN) of mtDNA was estimated by qPCR assay. RT-PCR was performed with primers of several mitochondrial genes, and immunofluorescence was observed with fusion and fission antibodies. mtDNA damage and RCN of mtDNA significantly increased in the mPFC of LBN animals compared to naïve controls. Additionally, mitochondrial fusion and fission were dysregulated in LBN animals. Finally, mitochondrial respiration, volume, and mitochondrial interactions with endoplasmic reticulum (ER) were altered in LBN. On the contrary, both EE and CF significantly reduced mtDNA damage and mtDNA RCN in LBN-exposed mPFC tissues. Overall, our results indicate maladaptive mitochondrial plasticity underlying LBN stress that might underlie behavioral dysregulation.

Disclosures: S. Mallick: None. **A. Dodge:** None. **F. Hossain:** None. **C.P. Bastos:** None. **A. Jeffers:** None. **S. Mitra:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.06/DD6

Topic: G.03. Stress and the Brain

Support: Trem2 grant 1R01MH136490
R01 MH130825

Title: Early-Life Adversity Induces Transcriptional and Epigenetic Remodeling in Hippocampal Microglia

Authors: *T. PASAM[1], J. GIEGERICH[2], J. MUNOZ-MARTIN[3], S. AHMED[4], A. PASTOR[5], A. KAFFMAN[6];
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Abstract: Childhood neglect and deprivation (CND) is the most common form of childhood adversity and is associated with severe cognitive deficits that are often more pronounced than those observed following other forms of adversity, such as sexual or physical abuse. The mechanisms by which CND causes long-term cognitive impairments, and how early-life

enrichment can reverse some of these deficits, remain poorly understood. To address these questions, we recently showed that mouse pups raised under prolonged impoverished conditions using the limited bedding (LB) paradigm exhibit deficits resembling those observed in children exposed to CND, including avoidant attachment, hyperactivity, cortical thinning, and abnormal hippocampal function. Deficits in synaptic connectivity and hippocampal function in adolescent LB mice were caused by impaired microglia-mediated synaptic pruning during the second and third weeks of life, when synaptic pruning peaks in the developing hippocampus. Restoring microglial function during this critical developmental period through brief environmental enrichment or chemogenetic activation normalized deficits in synaptic connectivity and hippocampal function later in life, highlighting a critical role for microglia in mediating the effects of deprivation and enrichment during a specific early developmental window. To further clarify the mechanisms by which LB and enrichment alter microglia-mediated synaptic pruning, we utilized the tamoxifen-inducible microglia-specific NuTRAP reporter system (Tmem119-CreERT2::NuTRAP), which enables simultaneous isolation of microglia-specific translating mRNA and nuclei for epigenomic profiling. Mice were exposed to control (CTL) or LB conditions from birth (P0) and received a single tamoxifen injection at P10 to induce NuTRAP expression in microglia. At P17, when synaptic pruning peaks in the hippocampus, hippocampal tissue was collected for isolation of microglia-enriched translating RNA and nuclei. Initial validation studies confirmed that this approach yields highly enriched microglia-specific transcripts and a microglia-specific DNA methylation signature identified by whole-genome bisulfite sequencing. These studies provide novel genomic insights into the mechanisms by which microglial function is altered during a critical developmental period in a mouse model of CND and highlight the utility of NuTRAP-based multi-omic approaches for defining cell type-specific neuroimmune mechanisms linking early-life experiences to long-term alterations in brain function.

Disclosures: T. Pasam: None. **J. Giegerich:** None. **J. Munoz-Martin:** None. **S. Ahmed:** None. **A. Pastor:** None. **A. Kaffman:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR143.07/DD7

Topic: G.03. Stress and the Brain

Support: R01 MH132680
P50 MH096889
T32 NS045540

Title: Is paraventricular thalamus corticotropin-releasing hormone receptor 1 required for cell-type specific neuronal activation by early-life adversity?

Authors: *J. M. MENDOZA[1], A. FLORIOU-SERVOU[2], Y. CHEN[3], M. HARDY[4], L. ZAMAN[6], T. Z. BARAM[5];
[1]UC Irvine Sch. of Med., Irvine, CA; [2]Dept. of Anat. & Neurobio., UC Irvine, Irvine, CA; [3]Pediatrics, Dept. of Pediatrics, Univ. of California-Irvine, Irvine, CA; [5]Anatomy/Neurobiology; Pediatrics, [4]Univ. of California Irvine, Irvine, CA; [6]Univ. of California, Irvine, Irvine, CA

Abstract: **Rationale:** Early-life adversity (ELA) is associated with increased vulnerability to mental illness characterized by disrupted reward behaviors such as anhedonia or drug use disorders. However, the mechanisms by which transient experiences lead to enduring disruptions to reward-related behaviors remain unresolved. Using a model of ELA established in our lab, limited bedding and nesting, we find persistent sex-dependent disruptions to adult reward behavior and have identified the paraventricular thalamus (PVT) as a key mediator of this process. Specifically, among all brain regions tested, PVT cells uniquely were preferentially activated by ELA compared to standard rearing (controls). Importantly, silencing in adult ELA mice of the same PVT neurons activated early in life restored normal reward behaviors. Surprisingly, we found that a higher proportion of activated neurons expressed corticotropin-releasing hormone receptor 1 (CRHR1) in ELA mice compared to control mice. However, it is unknown if activation of CRHR1 itself is required for this neuronal activation, as well as for the subsequent disruption of adult behaviors. Here, we test the hypotheses that 1) PVT CRHR1 cells activation during ELA requires CRH ligand-CRHR1 signaling and 2) blocking CRH-CRHR1 signaling prevents disruptions to reward behavior following ELA. **Methods:** To quantify PVT cells activated during the first week of life, Fos-Cre^{ERT2} x tdTomato mice pups exposed to ELA or standard rearing receive tamoxifen subcutaneously, enabling cre recombination and a permanent tdTomato labeling. To determine whether CRHR1 signaling is required for receptor expressing neuron activation (cfos expression) we administer a CRHR1 antagonist (NBI-30775), into the cerebral ventricle. We perform these manipulations on P6, during the midpoint of our ELA paradigm. On P10 all mice are returned to home cages. When adult, mice are tested in several tasks of reward behaviors including palatable food consumption under low and high effort in their home cage using the FED3 device and protocols. Mice are then euthanized and perfused and the number of PVT cells expressing tdTomato is quantified. **Results and Conclusions:** The experiments are ongoing. Preliminary results indicate feasibility of the experimental design, with excellent pup survival. Results of these experiments will be presented during SfN and should be informative regardless of their outcome. They will answer the key question if CRH-induced CRHR1 signaling is required for the mechanism by which ELA leads to aberrant reward behaviors. **Funding:** This work was supported by the National Institutes of Health, R01MH132680, P50 MH096889 and T32NS045540

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Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.08/DD8

Topic: G.03. Stress and the Brain

Support: New York Stem Cell Foundation (NYSCF) Robertson Neuroscience Investigator Award
R01 MH129643
Princeton Neuroscience Institute Research Innovator Award

Title: Single-nucleus multiomic profiling of the nucleus accumbens reveals widespread, cell-type-specific molecular effects of early life stress persisting into adulthood

Authors: *S. BERKE[1], R. L. RASHFORD[3], R. LIN[2], M. DEBERARDINE[1], C. J. PENA[4]; [2]Neurosci., [1]Princeton Univ., Princeton, NJ; [4]Princeton Neurosci. Inst., [3]Princeton Neurosci. Inst., Princeton, NJ

Abstract: The nucleus accumbens (NAc) is central to motivation and reward circuitry and a known site of stress-induced molecular plasticity, yet how early life stress (ELS) reshapes its molecular landscape at cell-type resolution remains poorly defined. In this exploratory study, male and female C57BL/6J mice underwent ELS (postnatal days 10-17), and NAc tissue was collected in adulthood (~P60; n = 8 ELS and 8 standard-reared animals, both sexes, across 8 pooled multiome libraries), and single-nucleus multiome-sequencing (snRNA-seq + snATAC-seq) was performed. Integrating and clustering 68,200 high-quality nuclei in dimensionally reduced transcriptomic space resolved 19 transcriptionally distinct clusters spanning 11 cell types (Louvain, resolution = 0.4), including the expected predominance of medium spiny neurons (MSNs). Cell-type-resolved differential expression was assessed by animal-level pseudobulk with DESeq2, with sex modeled as a covariate (Benjamini-Hochberg-corrected $p < 0.05$, $|\log2 \text{ fold change}| > 0.5$), yielding hundreds of differentially expressed genes between ELS and standard-reared animals across all cell types. D2-type MSNs showed the largest transcriptional response: genes upregulated by ELS were enriched for synaptic and histone-modification pathways, whereas standard-reared animals showed comparatively elevated translational and energy-metabolic pathways. Among the top ELS-upregulated genes in the largest D2-MSN cluster were Gab2, Dpp10, and Nr4a3, implicating receptor signal transduction, neuronal excitability, and activity-dependent neuronal survival and development, respectively, as molecular processes disrupted by ELS. Together, these results provide a cell-type-resolved map of ELS-driven transcriptional dysregulation in the NAc and establish D2-MSNs as a focal point for dissecting the gene regulatory programs through which early life experience is molecularly encoded.

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Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.09/DD9

Topic: G.03. Stress and the Brain

Support: PNI Research Innovator Award
New York Stem Cell Foundation
Robin Chemers Neustein Fellowship

Title: Thyroid hormone rescues the epigenomic effects of early-life stress

Authors: *Z. M. ZEMMEL, S. N. BENNETT, R. LIN, C. J. PENA;
Princeton Neurosci. Inst., Princeton Univ., Princeton, NJ

Abstract: Early-life stress (ELS) dramatically elevates lifetime risk for a broad range of psychiatric disorders. Identifying therapeutics that reverse or compensate for the effects of ELS on brain development is a major open challenge in neuroscience. Thyroid hormone signaling may present an unusually accessible entry point. In mice, ELS suppresses thyroid function during a critical postnatal window, and post-ELS supplementation with the synthetic thyroid hormone levothyroxine restores behavioral resilience. How this transient suppression affects gene regulation and expression in the brain remains unknown.
To determine the role of thyroid hormone signaling in the ELS response, we studied four groups of mice at four weeks postnatal: (1) standard-reared, (2) ELS-exposed, (3) pharmacologically thyroid-suppressed, and (4) ELS-exposed subsequently treated with levothyroxine. We performed integrated single-nucleus RNA and chromatin accessibility sequencing (multiomic snRNA-seq + snATAC-seq) of the basolateral amygdala, a key site for associative emotional learning. ELS produced robust changes in chromatin accessibility and gene expression, particularly (but not exclusively) in glutamatergic neurons. These changes largely did not overlap with those produced by pharmacological thyroid suppression. Strikingly, though, at every ELS-altered differentially accessible region in glutamatergic neurons, levothyroxine shifted chromatin accessibility back toward the standard-reared baseline, demonstrating that ELS-induced epigenomic remodeling is broadly reversible by thyroid hormone. At the transcriptional level, levothyroxine treatment attenuated the magnitude of ELS-induced expression changes by approximately 30-70%, depending on the neuronal or glial cell type. Examining the regulatory logic of these changes, we discovered that thyroid hormone supplementation likely returns ELS-affected loci toward baseline by engaging a distinct basic helix-loop-helix neurodevelopmental chromatin program rather than by reversing the regulatory effects that ELS originally produced. Taken together, our results suggest that early adversity does not cause epigenomic injury via a single, uniform process. Instead, it creates separable thyroid-responsive and thyroid-independent components, the former of which is correctable with levothyroxine treatment after the cessation of stress.

Disclosures: Z.M. Zemmel: 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.; Autobahn Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind

support); Autobahn Therapeutics. **S.N. Bennett:** None. **R. Lin:** None. **C.J. Pena:** 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.; Autobahn Therapeutics. C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Autobahn Therapeutics. F. Consulting Fees (e.g., advisory boards); Autobahn Therapeutics.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.10/DD10

Topic: G.03. Stress and the Brain

Support: MH108286
HD105771

Title: Maternal extracellular vesicles as modulators of preimplantation embryo developmental rates and early brain development

Authors: *K. C. CREUTZBERG, B. STOCCHERO, N. A. LEU, T. L. BALE;
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Abstract: Early embryonic development is characterized by coordinated events that drive the progression from zygote to blastocyst formation. During this preimplantation period, before placental formation, the embryo develops within the reproductive tract and may be directly exposed to maternal circulating signals, including extracellular vesicles (EVs). Disruptions in embryo developmental timing have been associated with impaired implantation potential, suggesting that developmental rates may be sensitive to environmental and physiological signals, such as maternal stress. However, the mechanistic link between stress exposure and embryonic developmental rates remains poorly understood. To mechanistically examine this, we investigated whether EVs isolated from stressed dams can alter preimplantation embryo developmental rates, and if those alterations result in changes in brain development and ultimately impact sensory sensitivity in postnatal life. Utilizing our stress chemogenetic approach, the Designer Receptor Exclusively Activated by Designer Drugs (DREADD) receptor is expressed in CRF neurons, allowing chronic drug-induced activation of stress-responsive circuitry. Following chronic stress, plasma EVs were isolated and characterized to validate an increased EV concentration and changes in EV protein cargo. Embryos were generated and cultured under controlled conditions, and incubated with maternal control or stressed EVs, from the zygote to the blastocyst stage to assess the influence of stress-associated EVs on embryo developmental timing. Time-lapse imaging was used to quantify developmental rates. To determine how stress-associated EV effects differ by embryo sex, we used the D4/XEGFP transgenic reporter line in which X-linked EGFP fluorescence enables identification of female embryos, allowing sex-specific comparison at early developmental stages. These studies identify

maternal EVs as important mechanistic mediators of stress-induced changes to early embryo developmental rates in a sex-specific manner.

Disclosures: K.C. Creutzberg: None. **B. Stocchero:** None. **N.A. Leu:** None. **T.L. Bale:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

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Program #/Poster #: PSTR143.11/DD11

Topic: G.03. Stress and the Brain

Support: 5R01HD097093-06
T32HD007186

Title: Chemogenetic activation of postpartum maternal stress circuitry alters circulating EV protein cargo and engagement with peripheral immune cell populations in mice

Authors: *G. DUNN, C. N. EPPERSON, T. L. BALE;
Psychiatry, CU Anschutz, Aurora, CO

Abstract: One in seven women experiences postpartum depressive symptoms, with rates doubling over the last decade, profoundly impacting both maternal morbidity and offspring development. However, highly heterogenous clinical presentations necessitate a deeper mechanistic understanding and an urgent need for biomarkers predictive of mental health risk. Maternal stress dysregulation is a key factor influencing postpartum depression, where disruptions to homeostatic control are tightly integrated with immune system dysfunction. In the neuropsychiatry biomarker space, extracellular vesicles (EVs) have recently emerged as key integrators of systemic communication, vital to organismal homeostasis. Indeed, a primary target of circulating EVs is the immune system, with up to 60% of circulating EVs sequestered by immune cells or lymphoid tissues (e.g. liver/spleen). This immunomodulatory capacity is especially relevant in perinatal physiology as maternal EV concentrations increase 4-to-5-fold during pregnancy and then decrease dramatically in early postpartum. However, how EV postpartum dynamics may influence maternal brain health are not understood. Therefore, we examined how chronic stress alters circulating EV cargo and immune cell populations in postpartum mice. We hypothesized that maternal postpartum stress elicits systemic immune dysregulation via remodeling of circulating EV protein cargo. During postpartum days 2-12, we utilized our chemogenetic approach of chronic stress to specifically activate corticotropin-releasing factor (CRF) neurons in the maternal brain. Following PBMC isolation and characterization via multi-parameter flow cytometry, we detected distinct compositional changes across control maternal postpartum immune cell populations. We hypothesize that an impact of stress is remodeling cell populations toward a more proinflammatory and activated immune state. Concurrently, isolated circulating EVs from nonpregnant, pregnant, and postpartum mice displayed unique proteomic cargo profiles characterized by proteins associated with key

homeostatic functions including glucose regulation and inflammatory signaling. We expect the introduction of postpartum stress to modulate EV protein cargo to differentially alter EV proteins related to complement and inflammatory signaling pathways. Together, these findings indicate that stress-induced remodeling of EV protein cargo and immune cell profiles represents a compelling mechanism through which peripheral homeostatic integrators modulate maternal postpartum neurobiology.

Disclosures: G. Dunn: None. **C.N. Epperson:** None. **T.L. Bale:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.12/DD12

Topic: G.03. Stress and the Brain

Title: Vitamin d deficiency alters maternal outcomes and produces sex-specific impacts on offspring temporal discrimination

Authors: *C. M. LAMBERT[1], L. LUTHER[2], M. NICODEMUS[2], I. LINTON[3], K. E. MORRISON[1];
[1]Psychology, [2]West Virginia Univ., Morgantown, WV; [3]West Virginia Univ., Glen Dale, WV

Abstract: Vitamin D is important for the maintenance of bodily and brain health, especially during early development. The effects of vitamin D deficiency have been studied in rodent models, including the developmental-vitamin D-deficiency (DVD) model. In this model, vitamin D is removed from the diets of female mice prior to breeding and throughout gestation, and offspring are examined. DVD offspring exhibit a hyperactive behavioral phenotype, with an increased tendency towards premature responding in operant-conditioning tasks and general learning deficits. As rodents tend to adopt a time-based response strategy on such operant-conditioning tasks, alterations in temporal discrimination abilities could result in premature responding. Little is known to whether changes in offspring health and behavior are due solely to the lack of vitamin D, as potential alterations to maternal care during the postpartum period might also influence offspring development. Additionally, the effects of this procedure on maternal health and behavior have been largely overlooked. Both a lack of vitamin D and being postpartum have been associated with increased anhedonia in humans. Here, vitamin D deficiency was induced in adult female mice beginning six weeks before breeding and throughout gestation. Behavioral and physiological measures relevant to postpartum depressive-like state were conducted with postpartum dams. Dams underwent a pup-retrieval task on postnatal day (PN) 2 and a sucrose-preference test from PN 2-6. Two hypothalamic-pituitary-adrenal (HPA) axis assessments were conducted: one in response to a pup-retrieval task (PN2) and one in response to a 15-min restraint stress (PN21). Dam brains were collected at PN31. To evaluate temporal discrimination abilities, a peak-interval procedure was conducted in the adult offspring. We measured genes related to vitamin D and dopamine in the brains of dams and

offspring. Vitamin D deficient adult male offspring had accelerated temporal discrimination, where responding began earlier than the responding of control animals and females. Additionally, vitamin D deficient dams consumed less total water, and relatively more sucrose, during the dark phase of the test, and had lasting disruptions to their HPA axis response. These results indicate that vitamin D deprivation during gestation has enduring impacts on both the dam and the offspring. These findings further inform how offspring, through both lack of vitamin D and exposure to altered maternal behavior and physiology, may be left with deficits in temporal discrimination and increased risk for a variety of maladaptive behaviors.

Disclosures: C.M. Lambert: None. **L. Luther:** None. **M. Nicodemus:** None. **I. Linton:** None. **K.E. Morrison:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.13/DD13

Topic: G.03. Stress and the Brain

Support: NIH Grant ES028202
NIH Grant HD091376

Title: Interaction of stress during puberty with later adulthood pregnancy on extracellular vesicle small RNA expression in mice

Authors: *L. A. M. LUTHER[1], T. L. BALE[2], K. E. MORRISON[1];
[1]Psychology, West Virginia Univ., Morgantown, WV; [2]Psychiatry, Univ. of Colorado Anschutz Med. Sch., Aurora, CO

Abstract: Experiencing stress during the critical developmental period of puberty puts women at risk for affective disorders and stress dysregulation, and this risk is heightened if they become pregnant in adulthood. We previously demonstrated that stress during puberty followed by pregnancy in adulthood led to a blunted response of the hypothalamic-pituitary-adrenal (HPA) axis which is responsible for initiating and maintaining the hormonal stress response in both mice and humans. Separately, we found that women who reported experiencing adverse childhood events displayed a blunted HPA-axis response when presented with a maternally-relevant stressor. We have since sought to uncover the biological mechanisms that may be contributing to the lasting effect of early life stress on physiological and behavioral outcomes throughout the lifespan. One biological system shown to be altered in response to a specific stressor is extracellular vesicles (EVs). EVs are cell-derived membranous particles that carry a variety of cargo, including proteins and nucleic acids, and are secreted by every tissue in the body. When EVs reach their target tissue, this cargo can influence local cellular functions. We previously showed that the developmental timing of trauma exposure produced significant changes to the proteome of EVs in human women. Trauma exposure during adolescence

produced a distinct protein signature compared to the signature found in no trauma, childhood trauma, or adulthood trauma groups. Here, we used our mouse model to further understand how early life stress and becoming pregnant in adulthood impact EV cargo. Specifically, we measured EV small RNA expression in mice who either underwent stress or not during puberty and then either became pregnant or remained virgin in adulthood. Beginning at postnatal day (PN) 21, mice were exposed to 14 days of chronic variable stress (CVS). Because there is evidence that social support buffers the adverse effects of stress, a subset of stressed mice were group housed each day following exposure to stress (CVS + social interaction). Blood was collected at baseline (non-stimulated) from CVS, CVS + social interaction, and control female mice who were either pregnant or virgin. EVs were isolated from blood plasma and prepared for small RNA sequencing. Sequencing results were analyzed for the impact of pubertal stress and pregnancy state on the number of differentially expressed genes. These findings will add to our understanding of the molecular underpinnings of the risk for affective disorders and stress dysregulation throughout the lifespan of females.

Disclosures: L.A.M. Luther: None. **T.L. Bale:** None. **K.E. Morrison:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.14/DD14

Topic: G.03. Stress and the Brain

Support: NIH grant HD091376

Title: Early life stress alters the behavioral, physiological, and molecular risk for peripartum dysfunction following adult gestational stress

Authors: *M. NICODEMUS[1], L. LUTHER[1], M. MILLER[2], M. FOUAL[1], I. LINTON[1], K. E. MORRISON[2];
[2]Psychology, [1]West Virginia Univ., Morgantown, WV

Abstract: Women are at increased risk for anxiety or mood disorders, although this is not uniform across the lifespan. Risk generally increases during the peripartum window, and both preconception and gestational stress have been associated with a greater risk of peripartum mental health issues. However, it is unclear how exposure to stress at different developmental timepoints may interact across the lifespan. We use a well-established mouse model designed to capture experiences pertinent to the female lifespan. Mice undergo stress during the onset of puberty, a window during which females may be more sensitive than males to the effects of stress. In adulthood, these mice become pregnant. Previously, we found that pubertal stress interacted with pregnancy to lead to a disrupted glucocorticoid response to stress during the peripartum window, as well as lasting transcriptional and epigenetic responses in the paraventricular nucleus of the hypothalamus (PVN). However, whether these findings are related

to altered behavior has yet to be determined. In addition, it is unknown how this disrupted glucocorticoid response might affect the response to a second period of chronic stress during gestation. Here, we addressed these gaps by examining how chronic stress at different windows in the female lifespan might uniquely impact the physiological stress response and behavior. Female mice were exposed to chronic variable stress or not during the onset of puberty and became pregnant in adulthood. During gestation, a mild limited nesting material (LNM) stressor was applied, where mice received half of the standard nesting material. In late pregnancy, mice were tested for pup retrieval, depressive- and anxiety-like behavior (sucrose preference, open field, social interaction, and splash tests), and corticosterone response to the pup retrieval task. Preliminary results showed a striking increase in sucrose preference in mice who underwent both pubertal and gestational stress. In addition, we found that mice who underwent LNM showed increased grooming in the splash test. Key genes in stress- and reward-related brain regions will be examined. However, an attempt to replicate procedures across cohorts revealed differences in physiology and behavior, potentially due to unplanned disruptions to animal facility housing conditions (light, temperature) at a key moment in the experiment. These findings provide insight into the impact of varying levels of stress during key developmental windows in the female lifespan on behavior and physiology and inform a broader understanding of how stress compounds across the female lifespan to influence risk for anxiety and mood disorders.

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Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.15/DD15

Topic: G.03. Stress and the Brain

Title: Modulation of hypothalamic Bdnf, cortical kynurenic acid, and glutamate levels by an enriched environment during early life stages in mice.

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Abstract: An enriched environment (EE) is an experimental strategy that can modulate the brain's response to diverse stressors. Early exposure to an EE promotes processes associated with brain-derived neurotrophic factor (Bdnf), such as neuronal plasticity, synaptogenesis, neurogenesis, and hippocampal long-term potentiation. However, the neurochemical mechanisms that mediate these protective effects are not fully understood. In this context, it has been reported that prenatal or early postnatal stress induces behavioral alterations such as anxiety or depression in adulthood, which are associated with changes in kynurenic acid (KYNA) levels. Hence, it is relevant to evaluate whether the EE modulates KYNA and glutamate levels and whether this regulation could contribute to beneficial effects on brain function. Accordingly, this work aimed to characterize the effects of exposure to an EE during early life stages on KYNA and glutamate levels in the prefrontal cortex (pCx), as well as on the hypothalamic Bdnf expression. To achieve this objective, 30-day-old male and female mice were exposed to an enriched environment for 45 days. At the end of the exposure period, burrowing behavior was evaluated using the marble-burying test, and social interaction was evaluated using the Crawley test. KYNA and glutamate levels were determined in the pCx by HPLC, and Bdnf expression levels in the hypothalamus (Hp) were measured by RT-qPCR. The results showed that mice of both sexes exposed to an EE were able to manipulate a greater number of marbles compared to the control group, which could reflect greater exploratory activity rather than repetitive-compulsive behavior. In the social interaction test, both groups showed a greater preference for the social stimulus than for empty box. Bdnf expression increased significantly in the Hp of both females and males exposed to EE compared to the control group. In the pCx KYNA levels decreased in both sexes after EE exposure. Furthermore, glutamate levels showed a trend toward an increase in the female Cx, although this did not reach statistical significance, while in males, the increase was significant ($p<0.05$). In conclusion, exposure to EE during early developmental stages promotes Bdnf expression in Hp and modulates cortical neurochemical balance by decreasing KYNA levels and increasing glutamate levels. These changes could be related to enhanced exploratory activity and neuronal plasticity mechanisms induced by enriched environments. Overall, these results suggest that enriched environments regulate key components of glutamatergic neurotransmission and the kynurenine pathway during early developmental stages.

Disclosures: D. Ramírez Ortega: None. **C. Flores León:** None. **K. Meza-Sosa:** None. **D. Gonzalez:** None. **G. Perez de la Cruz:** None. **A. Salazar:** None. **B. Pineda olvera:** None. **V. Perez De La Cruz:** None.

Poster

PSTR143: Early-Life Stress: Molecular and Cellular Mechanisms

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR143.16/DD16

Topic: G.03. Stress and the Brain

Support: Illinois Sociogenomics Initiative
NSF Graduate Research Fellowship
University of Illinois Urbana Champaign Predoctoral Aspire Fellowship

Title: Effects of acute heat stress and chronic social isolation on behavior and brain gene expression in honey bees

Authors: *M. E. FLORES[1,2], G. E. ROBINSON[1,2,3];
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Abstract: Adult worker honey bees exhibit highly stereotyped shifts in behavior associated with age, and this behavioral maturation is also associated with distinct changes in brain structure, chemistry, and gene expression. Various forms of stress are known to accelerate behavioral maturation, including chronic social isolation. However, the combined effects of early-life social isolation and environmental factors such as acute heat stress ("heat shock") have not been previously studied.To address this question, we compared behavior and brain gene expression in groups of non- and heat-shocked sister bees that experienced one of three levels of isolation. One-day-old adult bees were fully socially housed and reared in groups of 8 in the laboratory for one week. On the same day that control groups were housed, a subset of individuals were isolated. Partially isolated and reunited individuals were caged in isolation for 5 days and then "reunified" with one another for 2 days, while fully isolated individuals were reared in isolation for the duration. On the seventh day, half of the adults in each isolation group were heat shocked. We quantified aggression toward unrelated individuals in an intruder assay as the focal behavior because bees typically become increasingly aggressive as they age. In addition, increased aggression is associated with well-characterized changes in brain gene expression. Full social isolation caused increased aggression, but heat shock did not. Partially isolated individuals had levels of aggression similar to controls, but partial isolation had some effect, inducing more individuals per cage to engage with the intruder or one another compared to controls.Because there was no effect of heat shock on behavior, we explored the effects of social isolation on brain gene expression using bulk RNA sequencing by comparing heat-shocked animals. We compared low-aggression individuals that did not experience social isolation and high-aggression individuals that were partially or fully isolated. Surprisingly, there were very few differences in brain gene expression among the three groups, and most of the differentially expressed genes encode heat shock response proteins. It appears that acute heat stress "overwhelmed" the expected transcriptomic differences between high- and low-aggression bees as well as the hypothesized effects of social isolation—even though heat shock had no detectable behavioral effect. Future transcriptomic studies are expanding on these findings by performing a full factorial analysis on the effects of social isolation and heat shock on brain gene expression of low- and high-aggression individuals.

Disclosures: M.E. Flores: None. **G.E. Robinson:** None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.01/DD17

Topic: G.03. Stress and the Brain

Support: SIUE startup funding

Title: Impact of chronic intermittent ethanol on the adult Drosophila head transcriptome and behavior

Authors: *E. PETRUCCELLI;
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Abstract: Chronic alcohol use can lead to addiction behavior, but identifying molecular targets for treatment remains challenging. *Drosophila melanogaster* is a powerful model for studying the underlying genetics and behaviors associated with Alcohol Use Disorder (AUD), though the effects of chronic intermittent ethanol (CIE) exposure on the fly transcriptome are not well characterized. Here, we developed a new 7-day CIE paradigm consisting of three daily 50% ethanol vapor exposures and on the eighth day performed bulk, short-read RNA-seq to examine transcriptomic changes in adult fly heads. Differential expression following CIE exposure was assessed at the gene (DEG), transcript (DET), transcript usage (DTU), and alternative splicing (DAS) levels. CIE significantly affected expression of 2,894 genes, 664 corresponding to human orthologs, at least 12 of which have been recently implicated in human AUD - *CHI3L1*, *TTLL6*, *SUSD2* and more. Gene ontology analysis showed enrichment of pathways associated with cilia, which is not typically investigated in fly AUD models. Notably, DTU and DAS analyses revealed splicing-related changes missed by standard differential analysis. For example, predicted consequential alterations were identified in *GABAR* (metabotropic GABA receptor) and *orb* (CPEB RNA-binding protein) transcripts. Ongoing work is examining how CIE exposure impacts behaviors - longevity, fertility, ethanol sedation, ethanol locomotion, and ethanol preference. Overall, this work establishes a foundational fly model for studying chronic intermittent ethanol exposure and testing AUD targets for therapy.

Disclosures: E. Petruccelli: None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.02/DD18

Topic: G.03. Stress and the Brain

Support: NIGMS Center for Nervous System COBRE (5P20GM103645) Pilot Award

Title: Impacts of Acute Shock Trauma on Gene Regulation and Behavior in Drosophila

Authors: *S. Z. MOGES[1], J. S. HERNANDEZ[1], A. WATERMAN[1], B. LEVESQUE[1], S. STEA[1,2], R. AZANCHI[1], K. R. KAUN[1];
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Abstract: Stressful experiences can produce long-lasting changes in behavior that influence how organisms respond to future experiences and environments. In *Drosophila melanogaster*, electric shock conditioning has been extensively used to study associative learning and memory, but less is known about how exposure to acute repeated shock influences molecular changes in the brain and corresponding behavioral output. Remarkably, there are no characterized molecular markers for behavioral stress in *Drosophila*, despite the existence of well-established markers in mammalian models. Our goal was to identify molecular and behavioral markers of stress by investigating how acute trauma induced by aversive electric shock impacted brain gene expression, locomotion, thigmotaxis, and food-odor seeking in *Drosophila*. We used a shock paradigm that induces memory for the shock experience for up to 7 days. Following repeated electric shock exposure, behavioral responses and whole head bulk RNA sequencing were assessed at 0, 24, 48, and 72 hours post-shock. We found major sex differences in shock-induced transcription of genes associated with sensory perception, synaptic signaling and splicing. Interestingly, males showed more non-splicing transcriptional changes following shock, whereas females showed more splicing associated changes. These molecular changes correlate with behavioral changes. Shock altered conserved behaviors used to quantify anxiety-like states observed across species, including thigmotaxis, or wall-hugging, food-odor seeking and locomotor behaviors. As hypothesized, shock enhanced thigmotaxis and food-odor seeking, while reducing locomotion. Whereas behavioral responses were not sexually dimorphic, gene expression was, suggesting that males and females employ different transcriptional strategies that induce similar behavioral strategies to cope with acute trauma. Overall, these findings suggest that shock alters behavior, and that males and females have distinct molecular strategies to promote adaptive stress responses. Future studies will investigate the functional consequences of altering shock-associated gene regulatory networks in specific cells to alter behaviors like social interaction and reward-related behavior. Ultimately, this line of work aims to elucidate the underlying neural and molecular mechanisms through which acute trauma influences behavior.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.03/DD19

Topic: G.03. Stress and the Brain

Support: NIDA Grant DA043572
NIDA Grant DA057836

NINDS Grant NS134981
Pilot Grant from Rutgers Addiction Research Center

Title: Lateral Habenula Glutamatergic Neurons Link Stress, Pain, and Fentanyl-Directed Behavior

Authors: *O. DEPASQUALE[1], C. O'BRIEN[2], D. DESAI[1], R. VEMIREDDY[1], M. LYTTLE[1], E. B. MARGOLIS[4], D. J. BARKER[3];
[2]Psychology, [1]Rutgers Univ., Piscataway, NJ; [3]Psychology, Rutgers Univ., Pisctaway, NJ; [4]Neurol., UCSF, San Francisco, CA

Abstract: A brief traumatic experience can produce long-lasting changes in pain sensitivity, motivation, and affect, but the circuit mechanisms that couple acute stress to persistent hypersensitivity and later opioid-directed behavior remain poorly understood. The lateral habenula (LHb) is a glutamatergic hub whose activity is modulated by aversion, reward, and pain, and is positioned to transform the neural consequences of stress and injury into persistent sensory and motivational dysfunction. Here, we tested whether LHb glutamatergic activity is necessary for stress- and injury-induced hypersensitivity and subsequent fentanyl-directed behavior. Adult male and female vGlut2-ires-Cre mice received intra-LHb AAV-DIO-hM4Di-mCherry or AAV-DIO-mCherry control virus. Following recovery, mice were treated with the DREADD agonist JHU37160 (J60) during foot shock stress or contextual control sessions. Behavior was then assessed in the absence of J60 using behavioral avoidance, sucrose preference, mechanical sensitivity, oral fentanyl self-administration, and fentanyl preference assays. LHb inhibition during foot shock prevented stress-induced mechanical hypersensitivity and reductions in sucrose preference without altering behavioral avoidance in the elevated plus maze or open field. Because these stress-induced phenotypes have been shown to predict fentanyl preference in a two-bottle choice paradigm, we next tested whether LHb inhibition during stress altered subsequent fentanyl intake and preference. Transient LHb inhibition reduced oral fentanyl preference 21 days later regardless of stress history, suggesting that brief suppression of LHb glutamatergic neurons may confer lasting protection against subsequent opioid-directed behavior. To examine therapeutic potential, we chronically inhibited the LHb by administering J60 in drinking water beginning one week after foot shock stress or immediately following nerve injury. This attenuated foot shock-induced mechanical hypersensitivity and prevented the development of nerve injury-induced mechanical and thermal hypersensitivity. In an independent cohort, LHb inhibition was not reinforcing in a place conditioning assay regardless of stress exposure, supporting its potential as a low abuse-liability intervention. Together, these findings identify LHb glutamatergic activity as a causal contributor to stress- and injury-induced sensory-affective dysfunction and later fentanyl preference, while motivating ongoing work to define the neuromodulatory signals and LHb circuits that transform acute stress and injury into persistent sensory and opioid-related vulnerability.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.04/DD20

Topic: G.03. Stress and the Brain

Support: NIH/NIMH Grant R21 MH132136

Title: Neuroanatomical and behavioral characterization of corticotropin releasing factor-expressing lateral habenula neurons in mice

Authors: *E. H. THOMAS[1], W. J. FLERLAGE[2], S. C. SIMMONS[3], M. C. TSUDA[4], O. RUJAN[5], R. C. ARMSTRONG[6], L. IYER[7], E. PETRUS[8], B. M. COX[9], F. S. NUGENT[7]; [1]Uniformed Services Univ., Bethesda, MD; [2]Pharmacol., Uniformed Services Univ. of Hlth. Sci. Grad. Program In Neurosci., Bethesda, MD; [3]Pharmacol., Michigan State Univ., East Lansing, MI; [4]NIMH, Bethesda, MD; [5]USUHS, Bethesda, MD; [6]Dept Anatomy, Physiol. and Genet., Uniformed Services Univ. APG, Burtonsville, MD; [8]Anatomy, Physiol. and Genet., [7]Uniformed Services Univ. of the Hlth. Sci., Bethesda, MD; [9]Pharmacol., Brian Cox, Rockville, MD

Abstract: The lateral habenula (LHb) is a critical hub for value-based decision-making and stress-related behaviors. While the LHb is highly responsive to corticotropin-releasing factor (CRF), the specific sources of CRF inputs to this region have remained poorly defined. Here, we utilized high-resolution imaging, multiplexed RNAscope, and viral tracing to map CRF inputs to the LHb and discovered a novel, intrinsic subpopulation of LHb neurons expressing CRF (LHb^{CRF}). Molecular characterization revealed that the majority of LHb^{CRF} neurons are VGLUT2+, with a distinct rostral subpopulation co-expressing GAD2. Chemogenetic activation of LHb^{CRF} neurons in both sexes did not alter conditioned place preference, locomotion, or general anxiety-like behaviors. However, LHb^{CRF} activation selectively shifted defensive strategies toward passive responses during a Visual Looming Shadow Test (VLST). This was characterized by increased action-locking frequency and duration across both sexes, while specifically prolonging escape latencies in males and post-escape shelter stays in females. Using optogenetics and electrophysiology, we further identified significant sex-dependent divergence in the physiological phenotype of these neurons. While individual LHb^{CRF} neurons in males are more numerous and intrinsically excitable, female LHb^{CRF} neurons form significantly stronger local excitatory synaptic connections. These findings establish the LHb^{CRF} population as a novel, sexually dimorphic component of the LHb's heterogeneous circuit architecture that could contribute to bias towards defensive strategy selection of action-locking under threat and may underlie the sex-dependent variations in escape latency and post-escape shelter seeking observed during the VLST.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

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Program #/Poster #: PSTR144.05/DD21

Topic: G.03. Stress and the Brain

Support: CIHR Project Grant PJT-197845
OGS (JPL)
NSERC USRA (JPL)
I-CUREUS (JPL)
NSERC CGS D (PM)

Title: Fear suppression by zona incerta projections to the superior colliculus

Authors: *J. PHY-LIM, P. MILLER, T. LUONG, M. J. CHEE;
Carleton Univ., Ottawa, ON, Canada

Abstract: Wild animals must rapidly adapt to internal and external threats, but these threats may elicit opposing behaviors. For example, hungry animals are motivated to find food but must seek shelter to evade predators. One region integrating multisensory input including from internal states is the zona incerta (ZI) of the hypothalamus, as fasting increases ZI c-Fos expression. In turn, ZI activation coordinates adaptive survival behaviors to promote feeding and fear suppression. The ZI is primarily GABAergic, but a cluster of cells in the medial ZI also coexpress tyrosine hydroxylase (TH) and produce dopamine (DA). These ZI-GABA/DA cells primarily innervate midbrain motor regions, especially the medial motor-related superior colliculus (SCm) that promotes escape from perceived visual threats. Our preliminary findings indicated that ZI-GABA/DA projections can inhibit SCm cells, but it is not known if ZI projections can suppress escape or if fasting further suppresses escape. To determine if activating ZI-GABA/DA projections at the SCm suppressed escape, we transduced *Th-cre* ZI cells with a Cre-dependent virus encoding an excitatory hM3Dq DREADD. We placed mice in an arena comprising a home shelter and open space with food placed beneath a fixed dot. When the fixed dot looms, it rapidly induced escape to home. Intra-SCm infusion of the DREADD agonist Compound 21 (C21) did not alter time spent at food, home, or open space in fed or fasted mice. Interestingly, C21 delayed the latency to escape home in fasted but not sated male mice. To determine if GABA and/or DA release respectively suppressed escape, we co-infused C21 with D1 (SCH23390) and D2 (raclopride) receptor antagonists (SCH+RAC) or GABA-A receptor antagonist (bicuculline; BIC). Co-infusion of C21+BIC or C21+SCH+RAC in fasted male mice delayed home latency thus implicating both DA and GABA in escape suppression. Interestingly, C21 infusion alone did not suppress escape in fed or fasted female mice, but when co-infused with BIC, C21 delayed home latency when fasted and suggested that DA solely suppressed escape by females in a state-dependent manner. Together, chemogenetic activation of ZI projections in the SCm suppressed escape but only in the fasted state. Different neurotransmitter systems underlie escape suppression in male and female mice and suggested both state- and sex-dependent mechanisms in ZI-mediated behaviors. As wild mice must suppress fear responses to explore and seek food, our work points to a hypothalamic circuit that calibrates behavior in response to the energy state.

Disclosures: J. Phy-Lim: None. **P. Miller:** None. **T. Luong:** None. **M.J. Chee:** None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.06/DD22

Topic: G.03. Stress and the Brain

Support: NSERC CGS M (SV)
NSERC Discovery Grant RGPIN-2024-04133

Title: Neuroanatomical basis for monosynaptic projection from melanin-concentrating hormone neurons in the ventral tegmental area

Authors: *S. S. VIEIRA[1], U. PARAJULI[1], M. A. PAYANT[1], M. J. CHEE[2];
[1]Neurosci., [2]Carleton Univ., Ottawa, ON, Canada

Abstract: Melanin-concentrating hormone (MCH) is produced primarily by neurons in the lateral hypothalamic area. About half of MCH neurons coexpress additional neuropeptides, but nearly all MCH neurons can signal via the neurotransmitter glutamate. MCH neurons are critical for feeding and energy balance, as the deletion of MCH neurons yields leanness and hyperactivity. Loss of MCH or MCH receptor (MCHR1) recapitulated this increase in energy expenditure, which is related to a hyperdopaminergic state. Therefore, MCH signaling may suppress dopamine tone to regulate energy balance. We recently showed that MCH inhibits dopaminergic neurons in the ventral tegmental area (VTA) and suppresses dopamine release at VTA target sites. However, as MCH neurons also signal via glutamate, they may also regulate VTA neurons by glutamatergic transmission. Here, we used a Cre-dependent approach to determine the neuroanatomical basis for Pmch-Cre neurons to innervate VTA neurons. We first transduced Pmch-Cre neurons with a Cre-dependent virus encoding synaptophysin-EGFP and found punctate EGFP fluorescence distributed throughout the VTA. To determine if synaptophysin-labeled puncta represented potential sites of innervation, we employed the anterograde transsynaptic label based on antibody-like sensors (ATLAS) tracing strategy to label VTA cells receiving monosynaptic glutamatergic input from Pmch-Cre neurons. We transduced Pmch-Cre cells with a Cre-dependent virus encoding Flp recombinase fused to a GluA1-binding complex, which was released presynaptically and endocytosed when bound to the GluA1 subunit of postsynaptic AMPA receptors, as well as a Flp-dependent virus encoding mCherry at the VTA. We found mCherry-labeled neurons distributed throughout the VTA but were more common laterally and posteriorly. Importantly, half (52%) of mCherry-labeled VTA neurons expressed tyrosine hydroxylase (TH), a marker of dopaminergic neurons. Furthermore, half (54%) of these mCherry-labeled TH cells also expressed MCHR1 immunoreactivity at the primary cilium. These findings show that both MCH and glutamate release from MCH neurons may regulate dopaminergic VTA neurons. Together, this work provides the neuroanatomical basis for MCH neurons to innervate heterogenous VTA cell types by monosynaptic glutamate

release. Ongoing studies will determine the neurochemical identity of VTA neurons innervated by MCH neurons and investigate the contribution of MCH and glutamate to the regulation of energy expenditure via the VTA.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.07/DD23

Topic: G.03. Stress and the Brain

Support: NIH grant R01 MH136708

Title: Sex Differences in the Effects of Chronic Stress, Chronic Corticosterone and Prefrontal Cortical REDD1 Overexpression on Pavlovian Autoshaping Behavior in Rats

Authors: *B. KURTOGLU[1], D. OLIVEIRA[1], D. S. WHEELER[2], R. A. WHEELER[2], J. MANTSCH[1];
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Abstract: Approach motivation is motivation stemming from the expectation of reward and is classified in the Research Domain Criteria(RDoC) matrix under the positive valence systems domain. Deficits in approach motivation have been linked to neuropsychiatric disease states such as depression and addiction and result in reduced resilience to negative life events like stress. The prefrontal cortex (PFC) is important for regulating approach motivation behavior and chronic stress is known to produce structural and functional changes in PFC that might also contribute to disease states. To study the changes in approach motivation, we used an operant-based Pavlovian autoshaping task where a cue is associated with the subsequent delivery of a reward. Rats express the learned association between the lever and food delivery by approaching the cue. We find that chronic unpredictable stress (CUS) produces deficits in approach motivation using an operant-based Pavlovian autoshaping task, by attenuating CS+ approach in male ($p=0.002$) but not in female rats. However, what neural adaptations drive these deficits remain unclear. To gain more insight into this, our studies focus on the protein REDD1 (regulated in development and DNA damage responses-1) (aka DDIT4, Dig2, RTP801) as it is increased in post-mortem dorsolateral prefrontal cortex tissue from individuals diagnosed with depression. In line with these findings, we observed that there is an increase in REDD1 expression ($p=0.0001$) and a decrease in Raptor phosphorylation ($p=0.002$), one of the key elements of the mTORC1 complex, in the male but not female rat PFC after CUS, suggesting disrupted mTORC1 function. To determine if REDD1 overexpression is sufficient to produce deficits in Pavlovian autoshaping, we used a viral vector to overexpress REDD1 in the PFC of male rats. Similar to CUS, REDD1 overexpressing rats exhibited reduced anticipatory approach to the cue ($p<0.0001$). Because corticosterone (CORT) plays an important role in many of the

adaptive responses to stress observed in laboratory experiments, we examined whether a chronic CORT elevation is sufficient to reduce conditioned approach. CORT treated male rats showed deficits in Pavlovian autoshaping, evidenced by reduced CS+ approach (p=0.005). However, this deficit was not observed in female rats. The observation that CUS, REDD1 overexpression and chronic CORT elevation produce deficits in approach motivation likely has relevance for understanding a number of stress related disorders. Future research will determine whether female rats are similarly affected by REDD1 overexpression and necessity of disrupted mTORC1 for stress effects.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.08/DD24

Topic: G.03. Stress and the Brain

Title: The effects of brain serotonin deficiency on susceptibility to chronic restraint stress

Authors: *B. D. SACHS[1], D. ZEID[2], C. C. BAVLEY[2], M. E. WIMMER[3];
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Abstract: Neuropsychiatric and substance use disorders are widespread conditions that affect millions of Americans each year. Although the precise causes of these disorders are not known, both genetic factors and stress are thought to contribute to their development and progression. However, the genetic factors that confer susceptibility to stress remain largely unknown. Brain serotonin (5-HT) deficiency has long been theorized to contribute to mental illness, and genetic models of 5-HT deficiency have been shown to alter susceptibility to some stress paradigms, but not others. The current work used *tryptophan hydroxylase 2* (R439H) knock-in (Tph2KI) mice to determine the impact of brain 5-HT deficiency on responses to chronic restraint stress. Our results reveal that low levels of brain 5-HT increase susceptibility to stress-induced increases in binge-like alcohol consumption in females, but not males. In contrast, no significant genotype differences were observed in sensitivity to stress-induced changes in the elevated plus maze in either sex. Mice with low 5-HT were surprisingly protected from the effects of stress on weight loss and had significantly lower levels of corticosterone compared to WT littermates. RNA sequencing of samples collected from the raphe nucleus reveals that stress induced approximately half as many gene expression changes in 5-HT-deficient females as compared to the other three groups (WT females and both genotypes of males). In particular, serum/glucocorticoid-regulated kinase 1 (SGK1) was one of several genes that was upregulated in all groups except 5-HT-deficient females. Gene ontology analyses suggest that NGF-

stimulated transcription was the top pathway upregulated in both genotypes of males and in WT females, but this pathway was notably unaffected by stress in the 5-HT-deficient females. Similarly, glucocorticoid receptor (GR) signaling was listed among the top ten canonical pathways impacted by stress in each group other than 5-HT-deficient females. Together, these results suggest that low levels of brain 5-HT exacerbate some stress responses while blunting others and may do so in part by impacting NGF- and GR-dependent signaling, but future research is required to establish the requirement and/or sufficiency of these signaling changes.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.09/DD25

Topic: G.03. Stress and the Brain

Support: NSF GRFP

Title: Early Life Adversity Reshapes NAc Dopamine Dynamics During Methamphetamine Reward and Extinction

Authors: *B. L. WILLIAMS[1], H. R. HYLAND[2], K. G. BATH[3];
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Abstract: Experiencing early life adversity (ELA) increases the risk of substance use disorders (SUDs) and stress-induced relapse. Among SUDs, methamphetamine (MA) use and abuse has been steadily increasing and has emerged as a major public health concern with profound psychiatric, medical, and psychosocial complications. In 2021 alone, over 64% of MA users met criteria for MA-SUD for which there are currently no approved pharmacological treatments. Psychostimulants such as MA primarily exert their effects by increasing extracellular dopamine (DA), and the pursuit of reward and reinstatement (a model of relapse) has been shown to be mediated by DA release. Conditioned place preference (CPP) is an established model to study reward-related behaviors and the association of drugs of abuse with contextual cues, which has been implicated in context-induced craving and relapse. This association can be extinguished, and either drug injection or stress can elicit reinstatement of CPP. Prior studies have shown that entry into a drug-paired context evokes robust DA release in the nucleus accumbens (NAc) and activation of the D1R-mediated direct pathway. However, the impact of ELA on MA-induced CPP, extinction, and the underlying DA dynamics remains unclear. Using an 8-day CPP paradigm, I found that both control and ELA animals developed robust preference for the MA-paired chamber after 4 days of conditioning. At 1.0 mg/kg MA ($N = 69$), CPP was comparable between groups (n.s.), but at 2.0 mg/kg ($N = 46$), ELA animals showed heightened preference relative to controls ($p = .02$). During extinction, ELA animals showed faster reduction in CPP

than controls (Day 4, p= .008), but both groups reinstated to post-test levels after MA re-exposure (n.s.). To link these behavioral results to underlying DA dynamics, I used fiber photometry with the DA sensor dLight1.3b to measure real-time DA release in the nucleus accumbens during CPP, extinction, and reinstatement. Preliminary findings reveal that DA release patterns change over the course of extinction with ELA animals showing distinct temporal dynamics. Notably, animals distributed into divergent extinction phenotypes, and despite similar behavioral profiles between ELA and control animals within each phenotype, their DA signatures differed substantially. These findings suggest ELA alters behavioral sensitivity to MA dose and extinction dynamics via changes in NAc DA signaling. Together, these results may shed light on mechanisms underlying SUD risk in vulnerable populations and inform new intervention strategies.

Disclosures: B.L. Williams: None. **H.R. Hyland:** None. **K.G. Bath:** None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.10/DD26

Topic: G.03. Stress and the Brain

Support: T32-NS082145
VA #BX004693
VA #BX004646
T32 TR004545

Title: Neural circuit interactions underlying stress-induced dopamine system dysfunction

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Abstract: Stress is a major risk factor for neuropsychiatric disorders, in part through its ability to dysregulate mesolimbic dopamine signaling. Prior work has established that stress increases the number of spontaneously firing dopamine neurons in the midbrain, or dopamine neuron population activity, in the ventral tegmental area (VTA), and that inactivation of distinct neural circuits driven by the ventral hippocampus (vHipp) or the insular cortex (IC) can reverse this effect. However, the temporal dynamics and circuit hierarchy through which these regions interact to drive dopamine dysregulation remain unknown. Here, we investigate how vHipp and IC circuits interact with stress to regulate dopamine neuron population activity. Using chemogenetics and *in vivo* electrophysiology, we show that vHipp inactivation during stress blocks stress-induced increases in dopamine neuron population activity, while IC inactivation does not, establishing vHipp as the primary stress-responsive node in this circuit. Two-day chemogenetic activation of vHipp was sufficient to increase dopamine population activity 24

hours later and was resistant to acute IC inactivation. Conversely, two-day activation of IC also produced increases in dopamine population activity that were resistant to acute vHipp inactivation. Transcriptomic analyses revealed a robust increase in transcriptional activity in vHipp one hour following stress that was not sustained at 24 hours, suggesting that vHipp serves as an early, transient stress-responsive hub. Together, these findings support a model in which stress engages vHipp as an initial, necessary trigger that dysregulates the dopamine system downstream, which is then maintained independently of continued vHipp or IC activity. These results provide insight into the circuit mechanisms by which stress produces lasting changes in dopamine signaling, with implications for stress-related psychiatric conditions.

Disclosures: O. Yang: None. **S.M. Perez:** None. **D.J. Lodge:** None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

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Title: Stress accelerates instrumental learning in a KCC2 dependent manner

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Abstract: Stress is a major risk factor for psychiatric diseases, and a trigger for depression and addiction. Stress-induced changes to synaptic connectivity drive lasting modifications to brain function, producing behavioral adaptations that, while initially beneficial, can become maladaptive upon chronic exposure. However, mechanisms linking stress-induced synaptic plasticity to altered behavior remain unclear. We investigated whether operant learning adaptations are driven by the downregulation of the potassium-chloride co-transporter 2 (KCC2), a stress-triggered mechanism of inhibitory synaptic plasticity. During behavior, rats exposed to acute stress had a higher learning performance in an operant self-administration task when compared to control animals, showing an earlier preference for the reinforced lever. To investigate the underlying neural circuitry, we combined electrophysiological recordings with

pharmacological manipulation using Diazepam. This technique revealed increased synchronized inhibitory inputs onto dopaminergic projections, with a stress-induced enhancement of GABA release after Diazepam, a pharmacological response that indicates altered KCC2 function within these neurons. Acute stress selectively altered midbrain synaptic inputs projecting to striatal areas critical for associative and instrumental learning: the Dorsomedial Striatum and the Lateral Nucleus Accumbens. Finally, we administered CLP290 to enhance KCC2 functional expression during operant learning behavior. Preventing KCC2 downregulation effectively blocked the stress-induced potentiation of instrumental learning. Our findings demonstrate a functional link between acute stress, KCC2-mediated synaptic plasticity, and learning potentiation. Understanding such neural mechanisms provides a critical foundation for developing targeted interventions for stress-related neuropsychological disorders.

Disclosures: H.C. Schuch: None. **J. Woo:** None. **K. Jiang:** None. **A. Ostroumov:** None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: G.03. Stress and the Brain

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NIH Grant MH118388

Title: Pre-adolescent immune activation modulates stress-sensitive cognitive circuits in the adult mouse brain

Authors: *R. M. RAHN[1], D. CHOPRA[2], D. ROCKS[2], G. MANZANO NIEVES[4], V. BLOCK[5,2], C. PARKHURST[2], C. M. LISTON[3];
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Abstract: Neuroinflammation and immune circuits are well-known to play a role in stress-related psychiatric disorders. Epidemiological data suggest that infectious illness in childhood can increase the rate of subsequent mood disorder diagnosis in adulthood, but the exact circuit-level mechanisms underlying this contribution have not been established. We therefore examined how immune activation by lipopolysaccharide (LPS) at postnatal day (P)21 in mice affected adult cognitive behavior, multi-region calcium activity acquired by widefield functional imaging, and molecular and cellular metrics. The effects of P21 LPS were examined both alone and in combination with 7-day mild unpredictable stress in adulthood. All experiments compared 4 groups (LPS only, stress only, LPS+stress, and control) and data analyzed by 2-way ANOVA unless noted otherwise. A variable-effort reward assay was utilized in which C57BL/6J mice

were trained to lick for sucrose water reward, with the reward size increasing proportionally with the increase of on-task tone licks and reduction of pre-tone licks. LPS only, stress only, and LPS+stress mice all exhibited a reduction in learned effort compared to controls. A fixed-ratio (FR1) operant conditioning reward assay and simultaneous widefield calcium imaging were also performed on LPS+stress and control *Thy1*-GCaMP6s mice expressing the genetically encoded calcium indicator in excitatory pyramidal neurons. The calcium activity data was analyzed using a general linear model (GLM). The fixed-ratio reward behavior displayed a reduction in trials completed by LPS+stress mice compared to controls, while GLM analysis identified excitatory activity differences in regions including cingulate and frontal cortex during reward and tone periods. To determine the underlying mechanisms driving these changes, we also examined synaptic phagocytic capacity using flow cytometry in microglia populations after P21 LPS and adult stress. We labeled neuronal material that had been consumed by microglia using AAV-PHP.eb-CAG-tdTomato viral injections at 8 weeks of age, which were followed by adult stress and perfusion using PBS. Analysis was then performed on the left (whole) brain hemisphere, gating on live, $CD45^{int}$, CX_3CR1^+, $CD11b^+$, $Tmem119^+$ cells. We found P21 LPS increased adult microglial phagocytic capacity, and stress altered multiple microglia activity-related markers. Taken together, these data indicate that pre-adolescent immune activation has long-lasting effects on cognitive reward behavior and related excitatory neuronal activity and microglia function.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.13/DD29

Topic: G.03. Stress and the Brain

Support: NIH Grant R03 MH134181

Title: Social stress alters activity of medial and basolateral amygdala terminals in the infralimbic cortex

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Abstract: Neural activity within the infralimbic cortex (IL) plays an important role in regulating behavioral responses to stress. Previous work has shown that dominant Syrian hamsters display fewer stress-related behaviors than subordinate hamsters, which is dependent on defeat-induced activity of IL neurons. In addition, subordinate male and female hamsters show decreased IL calcium activity when displaying anxiety-like behaviors such as vigilance during social stress. However, it remains unclear what circuits are driving IL activation during social defeat to cause

a reduction in anxiety-like responses. In this study, we used dual-color fiber photometry to measure in vivo calcium transients in medial amygdala (MeA) and basolateral amygdala (BLA) terminals in the IL in male and female hamsters during social defeat exposure and subsequent anxiety testing. The MeA modulates aggressive and defensive behavior while the BLA regulates fear and anxiety responses. Therefore, we predict that dominant animals will have greater activity of a MeA-IL pathway compared to subordinates when they fight back during social defeat. Furthermore, we predict that subordinate animals will have greater activity of a BLA-IL pathway compared to dominants when being attacked and fleeing during social defeat. Preliminary data indicate that fighting back during social defeat increases MeA-IL activity but does not alter BLA-IL activity. Additionally, receiving attacks during social defeat causes an increase in BLA-IL activity and a decrease in MeA-IL activity. These findings demonstrate that social defeat exposure differentially modulates the stress-induced activity of MeA-IL and BLA-IL pathways, which helps to delineate the inputs to the IL that regulate stress vulnerability.

Disclosures: A.F. Radford: None. **A.A. Holmes:** None. **E.A. Kaminski:** None. **K.W. Dube:** None. **M.A. Cooper:** None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.14/DD30

Topic: G.03. Stress and the Brain

Support: R03 MH134181

Title: Estrogen receptor alpha in the medial amygdala modulates stress vulnerability and neural activity in the social behavior neural network

Authors: *B. KRIEG[1], E. HALLERAN[1], M. A. COOPER[3], E. KAMAU[2];
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Abstract: The posterior regions of the medial amygdala (MeA) contain gonadal steroid hormone receptors that modulate responses to social stress and contribute to sex differences in stress vulnerability. Previous work has demonstrated that androgen receptor expression in the MeA reduces stress-related behavior in males but not females. Although estrogen receptor alpha (ERα) is known to regulate aggressive, and defensive behaviors, its role in stress-related behavior remains unclear. In the present study, we used a Syrian hamster (*Mesocricetus auratus*) model to test the hypothesis that ERα expression in the MeA reduces stress-related behavior in females but not males. To test this hypothesis, we used an AAV-ERα-shRNA virus to knock down ERα expression in the MeA and an AAV-SCRAM-shRNA virus as a surgical control. Following surgery, male and female hamsters were evaluated in conditioned defeat and social avoidance

tests before and after social defeat exposure. Females receiving ERα-shRNA exhibited reduced latency to submit during social defeat, suggesting that ERα signaling in the MeA contributes to initial behavioral responses to social stress. Prior to defeat exposure, ERα-shRNA females also displayed increased social investigation of a novel conspeciflic during the social avoidance task. In contrast, ERα knockdown did not significantly alter anxiety-like behavior when compared with SCRAM-shRNA controls. These findings suggest that ERα expression in the MeA may influence pro-social behavior but not regulate defeat-induced anxiety-like responses in females. Consistent with our hypothesis, ERα knockdown had no detectable effect on anxiety-like behavior in males. Preliminary data indicate that ERα knockdown altered defeat-induced c-Fos immunoreactivity across multiple nodes of the social behavior neural network. Together, these findings indicate that ERα signaling in the MeA regulates social investigation and defensiveness during social stress in females, but not males. Overall, gonadal steroid hormone receptors within the MeA shape sex-specific responses to traumatic social stress and may contribute to sex differences in stress vulnerability.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR144.15/EE1

Topic: G.03. Stress and the Brain

Title: Stress and running interact to produce a unique striatal transcriptional state associated with persistent reductions in motivation for physical activity.

Authors: *O. P. ODIA[1], T. J. BUHR[4], L. CHU[2], J. S. RHODES[5], Z. V. JOHNSON[6], E. MCNEILL[3], H. BAI[1], P. J. CLARK[3];
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Abstract: Physical inactivity is the fourth leading risk factor for global mortality, yet the neural mechanisms underlying persistent reductions in motivation for physical activity remain poorly understood. Adverse experiences, including psychological stress, are strongly associated with sedentary lifestyles. We previously found that a single episode of uncontrollable tail shocks (acute stress) produces a persistent (>42 d), approximately 6-fold reduction in voluntary wheel running in rats without impairing forced physical activity, providing a model for investigating the biological mechanisms underlying chronic reductions in motivation for exercise. To identify molecular pathways associated with this phenotype, we performed single-nucleus RNA sequencing of the striatum from adult male rats exposed or not exposed to acute stress and subsequently housed with or without running wheels for 42 d. Analyses focused on medium

spiny neurons (MSNs), the principal neuronal population of the striatum and a key regulator of motivation, reward, and motor output. Differential expression analysis identified 320 genes exhibiting a significant Stress × Exercise interaction (FDR $q < 0.05$). Post hoc analyses revealed that 240 of 320 interaction genes (75%) were uniquely associated with stressed runners, whereas 63 genes reflected exercise-responsive programs observed only in unstressed runners. Gene ontology analysis demonstrated coordinated upregulation of ribosomal, oxidative phosphorylation, mitochondrial, and RNA-processing pathways together with downregulation of postsynaptic density, glutamatergic receptor, and synaptic plasticity pathways. Subcluster analyses further revealed prominent oxidative phosphorylation enrichment in D1-matrix MSNs, whereas D2-matrix neurons preferentially exhibited ion-channel and hypoxia-related pathway enrichment. These findings indicate that prior stress does not simply suppress exercise-responsive transcriptional programs but instead generates a distinct MSN molecular state characterized by enhanced biosynthetic and mitochondrial signaling coupled to reduced postsynaptic glutamatergic machinery. This transcriptional reorganization may represent a neural mechanism linking adverse experiences to persistent reductions in motivation for voluntary physical activity.

Disclosures: O.P. Odia: None. **T.J. Buhr:** None. **L. Chu:** None. **J.S. Rhodes:** None. **Z.V. Johnson:** None. **E. McNeill:** None. **H. Bai:** None. **P.J. Clark:** None.

Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: G.03. Stress and the Brain

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Title: Lifelong Low Social Status Leads to Lateralized Differences in Social and Visual Networks Functional Connectivity in Adult Rhesus Macaques

Authors: *R. A. TOBAR MOSQUEIRA[1], Z. A. KOVACS-BALINT[1], T. JONESTELLER[1], K. BAILEY[1], J. H. ACEVEDO-POLO[1], A. WANG[1], A. LANDSTEIN[1], N. BRING[1], E. FECZKO[2], E. EARL[3], D. A. FAIR[2], M. A. STYNER[4], R. VLASOVA[4], J. RAPER[1], M. C. ALVARADO[1], M. SANCHEZ[1];
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Abstract: Chronic social stress is associated with enduring alterations in the processing of socially relevant visual information, attention and threat detection, as well as emotional and reward regulation. However, the underlying neurobiological mechanisms remain unclear. Using a translational rhesus monkey model of low social status (social subordination -SUB-) as a form chronic social stress we have reported elevations in stress hormones and enlarged temporal lobe brain regions important for socioemotional and cognitive function, such as the hippocampus (HIPP) and amygdala (AMY) in SUB animals. Here we use additional neuroimaging tools to examine alterations in functional connectivity (FC) in social neurocircuits along the temporal lobe, and attention and social affiliation networks critical for social-visual information processing. Resting state functional brain MRI scans were collected in 26 adult female rhesus monkeys (12 dominant -DOM-, 14 SUB) living in large social groups, at 7 years of age. FC was analyzed along the visual Ventral Object and Motion Pathways *(VOP: V1-V3-TEO-TEp-AMY, VMP: V1-V3-MT-AST-AMY, respectively)* and Social Affiliation Network *(SAN: AMY, insula (INS), nucleus accumbens (NACC), anterior cingulate (ACC))* using repeated-measures ANOVA (rmANOVA) to assess the effects of RANK (DOM, SUB) and HEMISPHERE (Left, Right). In the VOP a RANK x HEMISPHERE interaction effect was found in V1-V3 FC with stronger Left than Right FC in SUB, but no laterality detected in DOM subjects (*$F (1,24) = 4.775$; $p = 0.039$; $\eta_p^2 = 0.166$).* A RANK x HEMISPHERE interaction was also detected in TEO-TEp FC with stronger Right than Left FC in SUB, but no laterality detected in DOM subjects *($F (1,24) = 4.306$; $p = 0.049$; $\eta_p^2 = 0.152$*). No other effects were detected. Additional main LATERALITY effects were detected in the VMP, where AST-AMY FC was stronger in the Left than Right hemisphere *($F (1,24) = 5.643$; $p = 0.028$; $\eta_p^2 = .185$*); in the SAN, where NACC-INS FC was stronger in the Left than Right ($F (1,24) = 4.780$; $p = 0.039$; $\eta_p^2 = 0.166$), and INS-AMY FC was stronger in the Right than Left ($F (1,24) = 7.051$; $p = 0.014$; $\eta_p^2 = 0.227$). Overall, these findings indicate that lifelong low social status (SUB) results in differences in temporal visual social network FC that are also hemisphere specific. This difference appears not only on primary visual processing circuits (V1-V3), but also along higher-order temporal cortex processing regions (TEO-TEp). We are currently analyzing the associations between FC along these social circuits and social behavior function.

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Poster

PSTR144: Stress-Modulated Pathways: Reward and Motivational Drive Circuits

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: G.03. Stress and the Brain

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Title: Effects of low social status on adult neural systems that control stress and emotional regulation in rhesus monkeys

Authors: R. NEWTON[1], Z. KOVACS-BALINT[1], R. TOBAR MOSQUEIRA[1], K. LOVE[1], T. JONESTELLER[1], K. BAILEY[1], R. VLASOVA[2], M. A. STYNER[2], E. FECZKO[3], E. EARL[4], D. A. FAIR[3], J. BACHEVALIER[1], M. C. ALVARADO[1], J. RAPER[1], *M. SANCHEZ[1];
[1]Emory Univ., Atlanta, GA; [2]Univ. of North Carolina, Chapel Hill, NC; [3]Univ. of Minnesota, Minneapolis, MN; [4]Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: Chronic social stress is a risk factor for physical and mental illness, impaired socio-emotional regulation and accelerated neurocognitive aging contributing to dementia. This study uses a life-span longitudinal design in a rhesus monkey model to examine the neurobiological mechanisms underlying stress and emotional dysregulation. We focus on long-term effects of low social status (social subordination -SUB-) as a form of chronic social stress on adult prefrontal cortex (PFC), amygdala (AMY) and hippocampal (HIPPO) structure and functional connectivity, circuits critical for stress and emotional regulation and vulnerable in aging-related disease.Structural and resting-state brain MRI scans were collected in 27 adult female rhesus monkeys living in social groups at the Emory National Primate Research Center (ENPRC) Field Station (13 dominant -DOM-, 14 subordinate -SUB-), at 7 years of age. Volumes and functional connectivity (FC) were assessed in brain subregions involved in stress responses, including dorsolateral PFC (dlPFC; Areas 9, 46), orbitofrontal cortex (OFC; Area 13), and medial PFC (mPFC; Areas 14, 24/ACC, 25). Stress reactivity was tested using the Human Intruder (HI) task. Effects of social status on MRI and behavioral measures were tested using ANOVA, and associations between MRI and HI outcomes were assessed with Spearman rank correlations.SUB animals had larger OFC (Area13: $F(1,23)=6.480$, $p=0.018$) and HIPP ($F(1,24)=5.043$, $p=0.034$), than DOM (particularly in the rostral right HIPP) and exhibited more freezing during the HI task. Larger HIPP volume was associated with elevated levels of cortisol ($rho=0.452$, $p=0.04$). DOM subjects showed more negative FC between left AMY-mPFC compared to SUBs ($F(1,11)=5.604$, $p=0.037$), while more negative FC between these regions was associated with blunted stress reactivity and freezing responses ($rho=0.403$, $p=0.041$). Our findings suggest that social subordination stress leads to alterations in PFC-AMY-HIPP circuits underlying increased emotional responses in the animals. Ongoing longitudinal follow-up studies will determine whether cumulative social stress amplifies these neurobehavioral alterations with aging, and whether they are mediated by inflammation.

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Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.01/EE4

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R35 GM127102

Title: Flickering Light Disrupts Sleep in Drosophila through Frequency- and Color-Dependent Photoreceptor Pathways.

Authors: *X. LUO[1], M. ALI[2], D. D. AU[3], T. C. HOLMES[4];
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Abstract: Light is a critical environmental factor that influences sleep rhythms and sleep quality in Drosophila. While light intensity and spectra have been studied extensively for their impact on sleep, artificial light often exhibits flicker across a range of frequencies and little is known about the impact of flickering light on sleep in flies. We tested sleep patterns across a wide range of flickering frequencies and different colors of light using custom designed instrument we call FLASH (Flickering Light of Actuatable Spectral Hues). We find that slow frequency flickering white light almost completely abolishes daytime sleep and reduces nighttime sleep latency. Red flickering light has a more severe effects on sleep quantity and quality than blue flickering light. Using mutant analysis, we find that both external image-forming and internal non-image-forming photoreceptors contribute to sleep responses to slow flickering light, with Cryptochrome playing a surprisingly important role in modulating sleep responses to red flickering light. Together, these results show that slow flickering light as a form of non-invasive sensory stimulation is a potent environmental stimulus that severely disrupts sleep in *Drosophila*, and that flies are particularly sensitive to flickering red light through mechanisms involving both external and internal photoreceptors. This study reveals flicker frequency and color as important and previously underexplored parameters of light that strongly modulate sleep in Drosophila.

Disclosures: X. Luo: None. **M. Ali:** None. **D.D. Au:** None. **T.C. Holmes:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

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Topic: G.07. Biological Rhythms and Sleep

Support: JST SPRING Grant JPMJSP2130
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Title: Adaptive sleep like immobility state in Drosophila melanogaster under the presence of predators

Authors: *H. KATO, N. SHIMA, Y. UTSUMI, Y. SUZUKI, J. TOMITA, K. KUME; Nagoya city university, Nagoya, Japan

Abstract: Sleep is generally considered a vulnerable behavioral state because it reduces responsiveness to external stimuli. However, immobility, one of the most prominent behavioral features of sleep, may be beneficial in specific ecological contexts, particularly when predators rely on prey movement for detection. Here, we examined whether immobility can function as an adaptive behavioral response using *Drosophila melanogaster* and its natural predator, the jumping spider *Hasarius adansoni*. We first tested whether experimentally enhanced arousal affects predation risk. Using thermogenetic activation of arousal-promoting neurons, we found that forced-awake flies were more frequently preyed upon by jumping spiders than control flies. This result suggests that increased arousal and activity elevate predation risk, whereas reduced activity may be advantageous in the presence of visually hunting predators. We next investigated how flies alter their behavior in response to predator cues. Visual presentation of a spider markedly reduced daytime activity and increased prolonged immobility in flies. This response was abolished under constant darkness and in visual mutants, indicating that visual input is required. In addition, non-visual spider-associated cues also reduced activity and increased immobility, suggesting that flies can use multiple predator-related cues to regulate their behavioral state.We further characterized the predator-induced immobility. Spider exposure increased long immobility bouts and reduced responsiveness to mechanical stimulation, indicating that predator-induced immobility shares key behavioral features with a sleep-like state. Importantly, the increase in immobility partially persisted even after spiders were removed, suggesting that predator exposure induces a sustained behavioral state rather than a transient freezing response. Together, our findings indicate that predator-induced low-activity states may represent an adaptive defensive strategy. We are currently investigating how predator-related visual information is processed in higher-order visual circuits to induce this sustained immobility.

Disclosures: H. Kato: None. **N. Shima:** None. **Y. Utsumi:** None. **Y. Suzuki:** None. **J. Tomita:** None. **K. Kume:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.03/EE6

Topic: G.07. Biological Rhythms and Sleep

Support: University of Vienna
Vienna BioCenter

Title: Investigating the effects of conspecific interactions on sleep behaviours of Danionella cerebrum

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Abstract: Sociability in fish has been a well-researched topic of behavioral neuroscientists typically focusing on schooling and shoaling behaviours, in the wild or in controlled lab environments. Such studies revealed that fish school and shoal with conspecifics to evade predators, forage for food, and to mate, among other motivators. These behaviours are largely visually guided, which is why during darkness, schooling is typically absent; however, their ability to 'dark-shoal' prevails, mediated by the lateral line sensory system. However, such behaviours have not been extensively researched during the night, when fish have a heightened tendency to be in their sleep state. Zebrafish sleep studies have mainly focused on individual fish, hence, de-coupling the effects of conspecific interactions. In this project, we aim to bridge these concepts and investigate unique behavioural features that occur in groups of interacting *Danionella cerebrum* in the day and night-time, with a special focus on investigating circadian regulated sleep behaviours. We first aimed to develop a three-dimensional behavioral imaging and machine learning pipeline to seamlessly observe social dynamics of fish throughout the day and night and over several days. We observed that fish in groups display altered behaviours as opposed to isolated fish or fish without any sensory cues. Most notably, fish that interacted with conspecifics, exhibited coordinated swimming speeds, and they maintained a similar inter-fish distance throughout the day and night, behaving as a single unit. In contrast, isolated fish showed higher variance in swimming speeds across the day and night. Fish without sensory cues, in the night-time, exhibited intermediate behaviours, behaving similarly to isolated fish, in the absence of both vision and sensation. However, complete loss of group cohesion was not observed. We propose that factors such as lateral line mechanosensation, olfaction, and vocalizations might influence their ability to recognize conspecifics. Finally, we observe that grouped fish actively maintain close proximity in the night, without visual cues, which is lost in the case of fish without lateral line cells, indicating the role of mechanosensation in recognizing conspecifics during the night phase. Next, we will aim to leverage the small size and transparency of *Danionella cerebrum* to observe whole-brain neuronal activity in adult sleeping fish using 2-photon microscopy. In conclusion, we aim to investigate the effects of conspecific interactions on the overall sleeping behavior and underlying neuronal dynamics of *Danionella cerebrum*.

Disclosures: M. Bhattacharya: None. **P. pichler:** None. **W. li:** None. **M. Zimmer:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

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Title: Analysis of sleep and torpor phenotypes in polygenic mouse models of type 2 diabetes mellitus

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Abstract: The relationship between sleep, torpor, and metabolism has attracted increasing attention because these physiological states are closely linked to energy homeostasis and endocrine regulation. Sleep regulates energy metabolism and endocrine function. Lack of sleep can cause overeating, reduced stress tolerance, and impaired glucose metabolism. Furthermore, fragmented sleep has also been reported in diabetic patients, potentially creating a negative feedback loop where sleep disorders and metabolic abnormalities mutually worsen. Type 2 diabetes develops from genetic factors such as low insulin secretion or insulin resistance, while lifestyle factors including overeating, lack of exercise, smoking, stress, and lack of sleep. In diabetes research, db/db and ob/ob mice are widely used. However, these mice exhibit severe overeating due to congenital leptin system failure caused by a single-gene mutation. This differs from human type 2 diabetes, which is multifactorial and arises from interactions between genetic predispositions—such as numerous susceptibility gene polymorphisms (SNPs)—and environmental factors like obesity, lifestyle, and aging. From the perspective of sleep, torpor, and metabolism, this study focused on polygenic mouse models of type 2 diabetes, which develop obesity, insulin resistance, and hyperinsulinemia on a multifactorial genetic background. Reports on sleep in polygenic models are limited. These models exhibited altered sleep architecture, including changes in wakefulness, NREMS, REMS, REM ratio, REM latency, REM cycle, and NREMS duration. EEG power spectrum analyses also suggested altered brain oscillatory activity, particularly in the delta range. Mice typically enter torpor during fasting, but torpor is less likely to occur in obese mice. In contrast, leptin-deficient ob/ob mice, despite being obese, readily enter torpor during fasting, suggesting leptin may function as an anti-torpor hormone. Therefore, we examined fasting-induced thermoregulatory responses in polygenic mouse models of type 2 diabetes, which are associated with altered leptin sensitivity. The results suggested that these models exhibit characteristic changes in sleep and body temperature during fasting. Together, these findings provide new insights into the relationship between sleep, torpor, and metabolic regulation in polygenic models of type 2 diabetes.

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Poster

PSTR145: Sleep: Behavior in Animal Models

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Program #/Poster #: PSTR145.05/EE8

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01AG072513
NIH T32NS115667

Title: CLASS-Net: Chronic Longitudinal Adaptive Sleep Scoring Network for EEG

Authors: *T. RIVERA[1,2,3,4], K. NAYLOR[1,2,3], C. J. BOUCHER[1,2,3,4], Z. CHEHAB[1,3], B. J. GLUCKMAN[1,2,3,4,5];
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Abstract: Electrophysiological recordings provide a high-fidelity, high-resolution window into neural activity and are essential for characterizing sleep-wake states across development, aging, and neurological disease. Using chronic hippocampal and cortical EEG recordings combined with EMG and behavioral monitoring in freely behaving mice, we have collected more than 70 mouse-years of longitudinal EEG data. This scale creates a major analysis bottleneck: manual sleep scoring is no longer feasible, is difficult to standardize across animals and scorers, and is poorly suited for recordings in which signal quality, electrode properties, and electrophysiological features change across weeks to months. To address this challenge, we are developing an automated sleep-scoring pipeline for large-scale longitudinal rodent EEG/EMG datasets. The workflow begins by extracting interpretable EEG/EMG features that capture spectral power, muscle activity, and state-dependent electrophysiological structure. These features are projected into a low-dimensional state space, allowing wake, NREM1, NREM2, and REM to be visualized, separated, and evaluated across animals and recording time. Because chronic recordings are affected by signal drift, changing electrode quality, evolving animal physiology, and recording variability, the feature space is stabilized through a normalization step designed to preserve state structure across recordings. These normalized sequential features are then passed into a machine-learning temporal segmentation model to classify sleep-wake states while preserving the temporal organization of sleep and transitions between states. The resulting classifications are incorporated into an adaptive framework that refines state representations over time, allowing the model to account for within-animal changes while maintaining consistent state definitions across animals and cohorts. Ongoing validation focuses on determining how accurately the model performs within individual animals, how well it generalizes across animals, and whether adaptive scoring improves robustness across chronic recordings. This work provides a scalable foundation for automated analysis of sleep architecture, state transitions, and neural state dynamics across the lifespan and in models of neurological disease.

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Poster

PSTR145: Sleep: Behavior in Animal Models

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.06/EE9

Topic: G.07. Biological Rhythms and Sleep

Title: Mechanism of Memory Consolidation during Sleep

Authors: *X. WANG[1,2], P. TIAN[2], P. YUAN[3], Z. ZHANG[2];
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Abstract: Associative learning is a fundamental cognitive process that requires the integration of distinct information modules. While sleep-dependent plasticity is known to be critical for memory consolidation, but the mechanisms that bridge these disparate neural representations remain poorly understood. This study aims to investigate whether and how engram coordinate the functional integration of contextual and fear memory during post-learning sleep. We trained mice using a CFC paradigm, where they learned to associate a specific context with a brief foot shock. To study the underlying mechanisms, we used fiber photometry to record the activity of engram cells in the dentate gyrus (DG). Combined with closed-loop optogenetics, we inhibited these engram cells during specific sleep stages (NREM or REM) in the hours following the CFC training. We also recorded LFP, EEG, and EMG signals to monitor brain oscillations and sleep states. Memory was assessed by measuring freezing behavior in subsequent memory tests. Our data showed that during the sleep period following CFC training, the activities of neurons representing the context and the fear experience began to show a coordinated pattern. The closed-loop experiments revealed that inhibiting these specific neural activities during sleep led to a significant reduction in freezing behavior during the memory test. This indicates that these sleep activity patterns are essential for the successful consolidation of the associative fear memory. Our research has revealed a mechanism for associative learning, which organizes and integrates different memory information through sleep.

Disclosures: X. Wang: None. **P. Tian:** None. **P. Yuan:** None. **Z. Zhang:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

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Topic: G.07. Biological Rhythms and Sleep

Support: CONAHCYT Grant CBF2023-2024-337
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Title: M_4muscarinic Acetylcholine receptors stimulation effect in the regulation of memory in rats during chronic REM sleep restriction and in recovery period

Authors: F. CASTANEDA-SOLIZ[1], L. ACOSTA-SALDANA[1], ***A. JIMENEZ-ANGUIANO**[2];
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Abstract: Sleep is a fundamental physiological state in several animal species, regulates various cognitive processes. Several studies have demonstrated that Acetylcholine (ACh) is involved in the modulation of sleep and memory. However, it is still unknown the selective participation of muscarinic Acetylcholine receptors (mAChR) in both processes. Therefore, the objective of this study was to evaluate the effect of M_4 mAChR on episodic memory, as well as during the chronic REM sleep restriction (REMSR) and during the recovery period of REMSR through the Novel Object Recognition test (NOR test). Thirty male Wistar rats were anesthetized and implanted with a cannula in the dorsal hippocampus (P=3.8, L=2.2, V=3.2). After one week the animals were randomly placed in the following groups (n=6): 1. Control-vehicle DMSO 0.2 ul, 2. LY2033298 (agonist M_4 mAChR)-0.2 ug/0.2 ml, 3. LY2033298-0.4 ug/0.2 ml, 4. REMSR x 21 days, 5. REMSR x 21 days + LY2033298-0.2 ug/0.2. REMSR was performed using the multi-platform technique. After 7, 14 and 21 days of REMSR, and during the first two weeks of sleep recovery, the animals were evaluated by the NOR test. The results obtained showed that sleep deficit produced a decrease in NOR test performance. The microinjection of M_4 mAChR at a dose of 0.2 ug reduced the negative effects on memory in animals with 7 and 14 days of REMSR; and during sleep recovery of the animals, this dose was insufficient to adequately restore the adverse effects of sleep loss generated by the REMSR. From the results obtained, we suggest that differential sleep loss and M_4 mAChR have an impact in the correct learning and produces degradation in declarative memory.

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Poster

PSTR145: Sleep: Behavior in Animal Models

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Topic: G.07. Biological Rhythms and Sleep

Support: I01 BX006105
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Title: Selective Knockdown of Connexin36 in the Thalamic Reticulate Nucleus Impairs Task-evoked EEG Activity

Authors: *S. CAREY[1,2], V. LOMBARDI[4], D. S. UYGUN[3], J. M. MCNALLY[5], R. BASHEER[6];
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Abstract: Introduction: The thalamic reticulate nucleus (TRN) plays an important role in the regulation of thalamo-cortical dynamics, gating of sensory processing, as well as in the regulation of sleep and consists entirely of inhibitory GABAergic neurons. These GABAergic neurons are largely coupled via electrical synapses, or gap-junctions, consisting of Connexin 36 (Cx36) protein hexamers. Utilizing targeted, TRN-specific localized CRISPR-Cas-mediated Cx36 gene knockdown (KD), we interrogate the specific role of Cx36 within the TRN and how its depletion affects thalamo-cortical dynamics and processing of sensory information. **Methods:** We examined spontaneous sensory task-evoked EEG activity via the auditory steady-state response (ASSR) and social interaction behavioral assay in PV-Cre-Cas9 mice before and after localized Cx36 gene KD. **Results:** Preliminary results from localized CRISPR KD of TRN-Cx36 KD showed a trending reduction of -36.5% in evoked cortical gamma power during ASSR (N=6) when compared to pre-AAV-injection condition in the same mice. Similarly, in our social interaction assay (N=3), a trending reduction in the cortical gamma power during the 0-2s time period of social novelty interaction was observed. The observed increase in cortical gamma power under pre-injection was reduced by a percent change of -23.9% post-injection under Cx36KD conditions. **Conclusion:** Our data suggest that Cx36 is involved in regulating thalamocortical network activity. Impairments in Cx36 KD mice are consistent with abnormalities observed in neuropsychiatric disorders, including schizophrenia, suggesting Cx36 containing gap junctions as a novel therapeutic target.

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Poster

PSTR145: Sleep: Behavior in Animal Models

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Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01NS073613

Title: Parallel supramammillary nucleus circuits organize the architecture of wake

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Abstract: Wakefulness is not a unitary brain state but rather an organized forebrain network configuration that supports vigilance, environmental engagement, and sustained arousal. The hypothalamic supramammillary nucleus (SuM) has emerged as a candidate organizer of arousal-related network states; however, the downstream circuit architecture through which SuM coordinates arousal-related network states remains unresolved. Here, we combine projection- and cell-type-specific gain- and loss-of-function approaches, closed-loop optogenetics, and in vivo recordings to dissect the circuit logic by which SuM glutamatergic (SuM^{Vglut2}) neurons organize wakefulness. Using retrograde targeting strategies, we find that chemogenetic activation of basal forebrain (BF)-projecting SuM^{Vglut2} neurons increases wakefulness, confirming the SuM^{Vglut2}→BF projection as a potent wake-promoting route. Complementing these findings, closed-loop optogenetic stimulation of SuM^{Vglut2} neurons triggers arousal from both NREM and REM sleep, demonstrating that SuM^{Vglut2} neurons can directly gate transitions into wakefulness. In contrast, optogenetic stimulation of SuM^{Vglut2} terminals in the BF robustly induces arousal from NREM sleep but is comparatively ineffective from REM sleep, indicating that SuM somatic stimulation recruits additional output routes, local circuitry, or both, required for REM-to-wake transitions. Intersectional targeting of projection-defined SuM^{Vglut2} neurons confirms this dichotomy: activation of SuM^{Vglut2}→BF projection neurons rapidly elicits arousal primarily from NREM, supporting pathway-specific constraints on state transitions. We next identify a parallel SuM output pathway to the medial septum (MS). Chemogenetic activation of MS-projecting SuM neurons increases wakefulness, and intersectional optogenetic stimulation of SuM^{Vglut2}→MS projection neurons robustly triggers arousal, implicating the SuM^{Vglut2}→MS pathway as a major wake-promoting branch. Consistent with this circuit organization, anatomical and functional mapping indicates that SuM^{Vglut2}neurons preferentially recruit wake-promoting BF GABAergic neurons as downstream effectors, positioning the SuM^{Vglut2}→BF projection as a pathway that can rapidly engage basal forebrain output to sustain forebrain activation. Collectively, these findings reveal that parallel SuM^{Vglut2}→BF and SuM^{Vglut2}→MS circuits differentially gate state transitions and sustain wake, and support a model in which SuM functions not simply as a wake trigger but as a forebrain network organizer that coordinates arousal architecture and associated oscillatory dynamics.

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Poster

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Topic: G.07. Biological Rhythms and Sleep

Support: CIHR 212055

Title: Social familiarity affects sleep-wake patterns in Octodon degus

Authors: *B. HENRIKSEN CARTMELL[1], V. NAGARWALA[1], A. PEJOUYAN[1], S. PEETUSH[1], A. LEBEL[1], A. THATCHER[3], N. INSEL[2];
[2]Dept. of Psychology, [1]Wilfrid Laurier Univ., Waterloo, ON, Canada; [3]Univ. of Montana, Missoula, MT

Abstract: Sleep is essential for survival, yet social mammals often sacrifice sleep quality for social contact. Field research in baboons has shown not only that this trade-off can be influenced by social relationships, but also, conversely, that social sleeping can change social relationships by promoting bonding. Measuring sleep patterns in social settings may therefore offer a naturalistic and ethologically relevant window into both the functions and management of social relationships. Degus (Octodon degus) are small, diurnal rodents native to South America, and female members are known to live and cooperate with unrelated peers. To test how kinship and social familiarity affect sleep architecture in this species, we measured behavioral and physiological signatures of sleep across 48-hour sessions while degus were paired with a long-term cagemate or an unrelated stranger. Sleep states were classified using human rating of video data and, independently, using machine learning classifiers (random forest and U-Net) on cortical field potential, EMG, and accelerometry data. Initial data suggest that sleep is highly coordinated between co-housed individuals. In female degus, co-housing with a stranger reduced variability in both timing and amount of sleep relative to cagemate pairings. In males, the presence of a stranger decreased sleep levels. The observation of decreased inter-individual variability in females housed with strangers can be considered alongside prior research in our lab showing that re-exposures to new individuals involves less, across-session variability than encounters with familiar cagemates; i.e., it may be that females cope with social uncertainty through behavioral consistency and reliability. Ongoing analyses are examining how more nuanced differences in social context impact the cycle of sleep stages throughout a night.

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Poster

PSTR145: Sleep: Behavior in Animal Models

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World Premier International Research Center Initiative (WPI)

Title: The Dreamy gene, identified by forward genetics screening, regulates quantity and quality of rapid eye movement sleep in mice

Authors: *K. MIYANISHI[1,2], C. MIYOSHI[2], T. FUJIYAMA[2], Y. HAYAKAWA[1], S. KANNO[2], N. HOTTA[2], M. KAKIZAKI[2], A. IKKYU[2], H. OZAKI[1], H. FUNATO[3,2], M. YANAGISAWA[2];
[1]AI biology research team, RIKEN BDR, Kobe, Japan; [2]IIIS / TIAR / Univ. of Tsukuba, Tsukuba, Japan; [3]Toho Univ. Sch. of Med., Tokyo, Japan

Abstract: Rapid eye-movement (REM) sleep in mice is characterized by the loss of muscle tone and theta-dominant electroencephalogram (EEG) signals. While optogenetic and chemogenetic approaches have delineated neuronal circuits controling REM sleep, the molecular and cellular mechanisms remain largely unknown. To address this, we have performed a large-scale, phenotype-driven forward genetic screening in mice and established a novel pedigree, *Dreamy* (*Dmy*) with markedly increased REM sleep. Quantitative trait loci analysis and whole-exome sequencing pinpointed a nonsense mutation in the *Dreamy* gene which is responsible for the REM sleep phenotype of *Dmy* pedigree. Genome-edited mice carrying the *Dmy*-mimic point mutation recapitulated the increase in total REM sleep time with elevated EEG theta power during REM sleep. To dissect functional role of Dreamy, we used AAV-based genetic manipulations targeting the *Dreamy* gene. Brain-wide AAV-B10-driven knockdown of the *Dreamy* gene induced the increased total REM sleep time with higher EEG theta power during REM sleep. By contrast, local knockdown of the *Dreamy* gene within the hippocampus, which is well-known as an essential source of theta oscillations, enhanced EEG theta power during REM sleep without altering REM sleep time. To further identify downstream molecular pathways, we performed single-nucleus RNA sequencing (snRNA-seq) on the hippocampus collected from the AAV-mediated Dreamy knockdown mice. snRNA-seq identified differentially expressed genes in response to the silencing of the *Dreamy* gene among the neuronal subclusters, highlighting molecular network of cation channel regulation which is potentially crucial for theta oscillation. Collectively, our study demonstrates that Dreamy regulates both quantity and quality of REM sleep and provides novel insights into unexplored molecular mechanisms regulating REM sleep.

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Poster

PSTR145: Sleep: Behavior in Animal Models

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Topic: G.07. Biological Rhythms and Sleep

Support: NIH R21MH131527

Title: Daytime light intensity modulates sleep architecture in diurnal grass rats

Authors: *J. HARTNER[1], D. BEREZHNOI[2], D. ZUTSHI[3], L. YAN[5], B. O. WATSON[4]; [1]Univ. of Michigan Molec & Behav Neurosci Inst. (MBNI), Ann Arbor, MI; [2]Dept. of Neurodegenerative science, [4]Dept. of Psychiatry, [3]Univ. of Michigan, Ann Arbor, MI; [5]Psychology, Michigan State Univ., East Lansing, MI

Abstract: Sleep is a fundamental biological process essential to daily physiological and cognitive function. Disruptions to sleep architecture are implicated in the onset and progression of a wide range of neuropsychiatric diseases, including Major Depressive Disorder (MDD) and Seasonal Affective Disorder (SAD), as well as anxiety disorders and schizophrenia. Understanding the neurobiological mechanisms underlying sleep and its disruption is therefore critical to advancing our understanding of mental health and disease.

The Nile grass rat (Arvicanthis niloticus; NGR) is an established diurnal rodent model well-suited for studying the relationship between light, circadian rhythms, and sleep. Our previous work demonstrated that NGRs exposed to brighter daytime lighting over multiple weeks exhibit increased daytime locomotor activity with little to no change in nighttime activity, suggesting that daytime light intensity modulates diurnal behavioral patterns in a circadian-dependent manner. However, very few studies have characterized sleep behavior in NGRs, and none have performed chronic long-term electrophysiological recordings using high-density electrodes to systematically examine sleep architecture in response to altered lighting conditions.

This project aims to reveal the electrophysiological signatures of sleep across lighting conditions in a diurnal animal model by utilizing high-density chronic recordings to characterize how light intensity shapes sleep quality and architecture. Preliminary evidence from our ongoing work indicates that animals undergoing chronic electrophysiological recordings via cable tether similarly exhibit increased daytime movement patterns, consistent with our prior findings under bright light conditions. Furthermore, NGRs exposed to brighter daytime lighting may exhibit markers of improved sleep quality, including an increase in nighttime NREM and REM bout durations with fewer disruptions, potentially reflecting a relationship between increased daytime activity and enhanced sleep architecture. This work will establish a critical neurophysiological foundation for understanding how light-driven improvements in sleep may modulate mood-relevant brain circuits, with important translational implications for light-based therapies in neuropsychiatric disease.

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Poster

PSTR145: Sleep: Behavior in Animal Models

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Program #/Poster #: PSTR145.13/EE16

Topic: G.07. Biological Rhythms and Sleep

Title: Home Cage Analysis Enables Scalable and Cost-Effective Wakefulness Assessment for Preclinical Screening of Sleep Therapeutics

Authors: *L. C. PARK, J. LEE, S. LEE, K. PARK, P. J. SWEENEY;
Naason Sci., Cheongju-si, Korea, Republic of

Abstract: Sleep disorders, including insomnia and narcolepsy driven by both psychological factors and genetic mutations, impose significant neurological and societal burdens. Preclinical evaluation of sleep wake regulation traditionally relies on electroencephalography/electromyography (EEG/EMG), the gold standard for quantifying vigilance states. However, these approaches are low-throughput, resource-intensive, and associated with high operational costs, limiting their utility for efficacy screening of diverse candidate compounds.
Here, we assessed a high-content analysis (HCA)-based behavioral platform as a scalable and cost-efficient alternative for quantifying wakefulness across multiple translational models. In wild-type (WT) mice, EEG/EMG recordings confirmed that administration of a reference compound (Modafinil) significantly increased wakefulness compared to baseline. Notably, HCA-based measurements robustly recapitulated these EEG/EMG findings, demonstrating a comparable and statistically significant elevation in wakefulness following Modafinil treatment.
To further evaluate assay sensitivity, we employed a caffeine-induced arousal model. HCA detected an approximately 20% increase in wakefulness, particularly during the light phase, consistent with the known pharmacological effects of caffeine on sleep suppression.
We next applied this platform to a disease-relevant narcolepsy transgenic model (Orexin/Ataxin-3). In these mice, characterized by impaired wake maintenance, HCA reliably detected a significant increase in wakefulness following Modafinil administration, indicating sensitivity to pharmacological modulation in a pathological context.
While HCA does not capture cataplexy, a key feature of narcolepsy, these findings support HCA-based wakefulness quantification as a robust, translatable, and cost-effective alternative to EEG/EMG. This approach provides an efficient and scalable solution for early-stage efficacy screening of candidate therapeutics targeting sleep and arousal mechanisms.

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Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.14/EE17

Topic: G.07. Biological Rhythms and Sleep

Support: FAPESP Grant: 2025/05513-3 and 2022/16417-7

Title: Anxiolytic-Like Responses and Hyperlocomotion in Chronically Sleep-Deprived Rats: Statins Modulate Molecular Pathways Without Altering Single Genes or Behavior

Authors: *G. DA SILVA[1], M. DOURADO[1], A. KAIZELER[3], S. DA SILVA ALVES[1], K. SILVA MULLER[4], A. GASPARINDO-MOREIRA[2], P. RIBOLLA[2], D. ALONSO[2], Y. MANATA JACOBINA[1], H. H. DIAS[1], A. M. SEBASTIAO[5], J. D. HORTA JUNIOR[1]; [1]Structural and functional biology, [2]São Paulo State Univ. - Unesp, Botucatu, Brazil; [3]New Univ. of Lisbon, Lisboa, Portugal; [4]Univ. of Campinas, Campinas, Brazil; [5]Inst. of Pharmacol. and Neurosciences, Sch. of Med. and Inst. of Mol. Medi, Lisboa, Portugal

Abstract: Statins are widely prescribed for treating dyslipidemias and exhibit pleiotropic neuroprotective effects, including anti-inflammatory and modulation in the nervous system. Given that chronic sleep deprivation impairs cognitive function, this study investigated the effects of statins on behavior and hippocampal gene expression in chronically sleep-deprived rats. Male Wistar rats were distributed into eight groups (behavior: N=15; transcriptome: N=6): control (C); sleep deprivation (SD); deprivation with rosuvastatin (2.1 or 20 mg/kg); atorvastatin (4.2 or 20 mg/kg); and simvastatin (4.2 or 20 mg/kg). SD was induced over 45 days using an adapted multiple platform method with concomitant daily drug administration. In the open field, light-dark box, and elevated plus maze (EPM), the SD group exhibited a robust hyperlocomotive and anxiolytic-like phenotype. Statins generally failed to reverse these changes, except for low-dose rosuvastatin, which counteracted this pattern in the EPM. No significant differences were detected in the novel object recognition test and object location test. In the social recognition test, SD animals showed preserved recognition memory, with increased interaction frequency toward a novel conspecific. In the radial arm maze, SD impaired spatial working memory, increasing errors despite shorter completion time, and statins failed to reverse. Analysis of differentially expressed genes revealed increased expression of Cdkn1b, Zng1a, and Ptger3, and reduced expression of Fbxl6 and Crym in the SD group, whereas no significant differences were detected with statin treatment. Gene set enrichment analysis indicated downregulation of adipogenesis, glycolysis, and oxidative phosphorylation in SD. Atorvastatin and rosuvastatin showed enrichment of all three metabolic pathways alongside modulation of inflammatory gene sets, whereas simvastatin showed more modest effects, acting in phosphorylation, however, given the absence of differentially expressed genes in the statin groups, these pathway-level signals should be interpreted cautiously, as GSEA can return significant enrichment scores in the absence of individual gene-level evidence, particularly in small datasets. These findings demonstrate that chronic sleep deprivation induces a hyperlocomotor, anxiolytic-like phenotype with spatial memory impairment but preserved recognition memory. At the molecular level, sleep loss reduced the metabolic pathway activity with moderate single-gene alterations. Although statins did not reverse behavioral deficits, they potentially attenuated the mild bioenergetic decline through pathway-level modulation.

Disclosures: G. da Silva: None. **M. Dourado:** None. **A. Kaizeler:** None. **S. da Silva Alves:** None. **K. Silva Muller:** None. **A. Gasparindo-Moreira:** None. **P. Ribolla:** None. **D. Alonso:** None. **Y. Manata Jacobina:** None. **H.H. Dias:** None. **A.M. Sebastiao:** None. **J.D. Horta Junior:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.15/EE18

Topic: G.07. Biological Rhythms and Sleep

Support: 5R01AG062398
Roy J. Carver Directorship

Title: Effects of chronic sleep restriction on hippocampal function

Authors: *T. JORGENSEN-KEIMIG[1], A. PETRUCCI[1], L. C. LYONS[2], T. ABEL[1];
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Abstract: Chronic sleep disorders and insomnia affect more than 50 million Americans. While even one night of sleep deprivation can disrupt memory and increase emotional reactivity, chronic sleep loss can lead to prolonged cognitive impairments. The hippocampus is particularly impacted by the effects of sleep loss, including disruption in memory, altered molecular signaling, and a decrease in synaptic plasticity. Studies have shown that REM sleep deprivation alters human brain connectivity and suppression of REM theta waves impairs hippocampus-dependent memory. Given the prevalence of long-term sleep disturbances in the general population, we chose to investigate the molecular impacts of chronic sleep restriction in the hippocampus using a primarily REM sleep deprivation paradigm. In the present study, we utilize the platform over water method of chronic REM sleep restriction (CSR). Through activity monitoring, we find that this method of REM sleep deprivation does not induce a circadian phase shift. More in depth studies of sleep states are ongoing for CSR and recovery using EEG/EMG recordings and spectral analysis. To test the effect of CSR on hippocampus-dependent memory, we utilized the spatial object recognition (SOR) task. Compared to homecage controls, CSR animals did not show any differences in exploration during the three training trials. During SOR testing 24 hours after training, we found that CSR animals displayed impaired spatial memory, whereas the control animals showed a preference for exploring the displaced object. Future work will assess the transcriptomic profiles of CSR and control animals after SOR training to identify the molecular mechanisms underlying this cognitive impairment. Together, our findings show that five days of REM sleep deprivation is sufficient to impact hippocampus-dependent memory without disrupting circadian rhythms, and lay the groundwork for further investigation into the molecular underpinnings of chronic sleep loss.

Disclosures: T. Jorgensen-Keimig: None. **A. Petrucci:** None. **L.C. Lyons:** None. **T. Abel:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.16/EE19

Topic: G.07. Biological Rhythms and Sleep

Title: Effects of circadian timing of weekly semaglutide injections on body weight, feeding, and behavior in male TallyHo/JngJ mice

Authors: L. G. ROTH, *J. A. SEGGIO;
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Abstract: Glucagon-like peptide-1 receptor agonists such as semaglutide are administered at varying times of day, yet whether dosing time influences the metabolic or behavioral effects of this long-acting weekly drug remains unknown. We tested whether circadian timing of weekly semaglutide modulates body weight, food intake, sucrose preference, anxiety-like behavior, and motor function in male TallyHo/JngJ mice, a polygenic model of type 2 diabetes. In two cohorts spanning the light:dark cycle, mice received weekly semaglutide injections (0.42 mg/kg) or vehicle at ZT0 or ZT6 (rest/light phase) or ZT12 or ZT18 (active/dark phase), forming a 2 (drug) × 4 (ZT) design (n = 7/group; N = 56). Body weight and food intake were recorded weekly for 9-10 weeks; sucrose preference, elevated plus maze (EPM), and rotarod were assessed terminally. Because dosing time was confounded with cohort and season, drug and drug-by-time effects are treated as primary, and phase effects as descriptive. Independent of drug, circadian phase strongly shaped metabolic and hedonic measures: active-phase animals showed higher sucrose preference, lower and more uniform food intake, and greater weight gain, although these findings should be interpreted cautiously due to cohort/season confounding. Semaglutide reduced food intake only at ZT6 (mid-rest phase), with no effect at other times (drug-by-time interaction). It increased sucrose preference across all dosing times without interaction, indicating a dosing-time-independent hedonic effect. Semaglutide did not reduce overall body weight, although a trend suggested attenuated weight gain at ZT12. Rotarod performance improved with training but was unaffected by drug or timing, indicating no motor impairment. EPM revealed no reproducible effect of semaglutide on anxiety-like behavior. Together, these findings indicate that anorectic effects of weekly semaglutide are time-of-day dependent, whereas effects on sucrose preference are not, with no evidence for changes in anxiety-like behavior or motor function.

Disclosures: L.G. Roth: None. **J.A. Seggio:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.17/Web Only

Topic: G.07. Biological Rhythms and Sleep

Support: ZIC ES103330

Title: Diphenhydramine disrupts sleep architecture in 5XFAD and wild-type mice

Authors: *M. H. COPELAND[1], D. YOUNGSTROM[1], K. S. KONRAD[2], A. LETSINGER[1], L. R. WILSON[1], J. D. CUSHMAN[1], J. L. YAKEL[1];
[1]Neurobio. Lab., Natl. Inst. of Envrn. Hlth. Sciences, Natl. Inst. of Hlth., Research Triangle Park, NC; [2]Publ. Hlth. and Scientific Res., DLH, LLC., Bethesda, MD

Abstract: Sleep disruption is common in Alzheimer's disease (AD). Diphenhydramine (DPH), a first-generation antihistamine with anticholinergic properties, is widely used as an over-the-counter sleep aid. We tested whether chronic DPH treatment alters sleep architecture in 5XFAD and wild-type mice. Female 5XFAD (n=15) and wild-type (WT) littermates (n=13) were implanted with wireless telemetry recording devices to measure electroencephalography (EEG), electromyography (EMG), temperature, and activity continuously. After a 24h baseline recording at 5 months of age, mice received oral DPH (10 mg/kg) or vehicle at ZT0 for 28 days. After 21 days, sleep was recorded continuously for 48h during ongoing dosing. Sleep was scored as rapid eye movement (REM), non-rapid eye movement (NREM) 1, NREM2, or wake. A survival curve analysis was used to investigate the microarchitecture of sleep phases after chronic diphenhydramine treatment. At baseline, 5XFAD mice had more time in NREM1 than WT controls and had shorter REM and NREM2 bouts. Chronic DPH treatment fragmented NREM2 in both genotypes, reducing long NREM2 bouts. DPH increased total duration of NREM1 and REM during the active phase, which is analogous to daytime drowsiness in humans. DPH did not rescue 5XFAD sleep deficits; instead, DPH treatment exacerbated NREM2 fragmentation. Overall, chronic DPH use degrades sleep quality and increases fragmentation in both WT and AD-model mice, which questions the use of sedating anticholinergics as sleep aids, especially in AD.

Disclosures: M.H. Copeland: None. **D. Youngstrom:** None. **K.S. Konrad:** None. **A. Letsinger:** None. **L.R. Wilson:** None. **J.D. Cushman:** None. **J.L. Yakel:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.18/EE20

Topic: G.07. Biological Rhythms and Sleep

Support: NIH R01AA028175
VA Merit Award I01BX006240

Title: Chronic Voluntary Fentanyl Consumption Escalates Intake, Blunts DRN Serotonergic Activity, and Disrupts Sleep Architecture in Mice

Authors: *R. SHARMA, M. M. THAKKAR;
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Abstract: Opioid use disorder (OUD) affects over 3 million Americans and is the leading cause of drug overdose mortality. OUD is characterized by escalating consumption and progressive sleep disruption, yet the relationship between mesolimbic neuroadaptation and sleep-wake dysregulation across chronic exposure remains poorly defined. Fentanyl — a synthetic full μ-opioid receptor agonist responsible for over 70,000 overdose deaths in 2021 — was used due to its clinical dominance and rapid neuroadaptive properties. Dorsal raphe nucleus (DRN) serotonin (5-HT) neurons are Wake-On/REM-Off neurons critical for sleep-wake regulation; fentanyl-induced serotonin toxicity — manifesting clinically as Serotonin Syndrome in overdose — reflects μOR-mediated DRN 5-HT hyperactivation and provides a compelling rationale for investigating serotonergic neuroadaptation in chronic OUD. We hypothesized that chronic fentanyl produces progressive serotonergic neuroadaptation in the DRN that is coupled to worsening sleep-wake disruption across the 21-day drinking period. To test this hypothesis, we used a voluntary oral fentanyl DID protocol (10 μg/ml, ZT15-ZT19, 4h/day) and characterized fentanyl consumption, DRN 5-HT activity via GCaMP6s fiber photometry during the drinking period (ZT15-ZT19) in mice, and sleep-wake architecture via continuous EEG/EMG. Fentanyl intake escalated across Days 1, 7, and 15 ($R^2 \geq 0.80$). DRN 5-HT ΔF/F was elevated on Day 1 but markedly blunted by Day 15 despite escalating intake — a tolerance dissociation indicating serotonergic neuroadaptation. EEG/EMG revealed progressive wakefulness and suppression of NREM and REM sleep persisting beyond drug clearance, indicating homeostatic sleep rebound failure. These findings suggest serotonergic neuroadaptation contributes to both compulsive fentanyl use and chronic insomnia in OUD.

Disclosures: R. Sharma: None. **M.M. Thakkar:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.19/EE21

Topic: G.07. Biological Rhythms and Sleep

Title: A Dynamic Stability Landscape Governs Sleep-Wake Transitions and Fragmentation

Authors: *O. C. GONZALEZ[1], G. S. MANNINO[2], A. LUGO[1], R. K. ROWE[1];
[1]Univ. of Colorado Boulder, Boulder, CO; [2]Stanford Univ., Stanford, CA

Abstract: Sleep-wake behavior emerges from interactions between homeostatic and circadian processes, yet the dynamical principles governing state stability and fragmentation remain poorly understood. Existing models accurately capture sleep timing and duration, but provide limited insight into how physiological perturbations alter the stability of sleep and wake states. Here, we developed a dynamic landscape framework that conceptualizes sleep-wake regulation as

movement through a time-varying stability landscape shaped by homeostatic sleep pressure, circadian drive, and stochastic neural fluctuations. Within this framework, sleep and wake emerge as stable attractor states separated by a dynamic barrier whose geometry continuously evolves over time. Homeostatic sleep pressure progressively biases the landscape toward sleep during prolonged wakefulness and dissipates during sleep, while circadian signals modulate landscape structure across the day. This approach provides a quantitative description of state stability, transition probabilities, and fragmentation dynamics. Simulations reproduced key features of mammalian sleep architecture, including realistic state occupancies, transition frequencies, and circadian organization of sleep-wake behavior. Systematic perturbations of model parameters revealed that distinct forms of landscape destabilization produce characteristic signatures of sleep instability. Increased stochastic fluctuations elevated transition rates and fragmented sleep without substantially altering total sleep time, demonstrating that sleep quantity and sleep stability can be dissociable dimensions of sleep regulation. In contrast, reductions in barrier height decreased state persistence and increased bidirectional transitions, whereas circadian modulation primarily influenced state occupancy and the temporal organization of transitions across the day. Together, these findings establish a quantitative dynamical systems framework linking sleep architecture to the stability properties of neural state space. More broadly, the results suggest that sleep-wake fragmentation can arise through multiple mechanistically distinct forms of landscape destabilization, providing a unifying framework for understanding how physiological and pathological perturbations alter brain-state dynamics.

Disclosures: O.C. Gonzalez: None. **G.S. Mannino:** None. **A. Lugo:** None. **R.K. Rowe:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR145.20/EE22

Topic: G.07. Biological Rhythms and Sleep

Support: VA Merit Research Award; I01BX002661

Title: Predator odor-induced trauma model of PTSD exhibits enhanced pain sensitivity. hypersensitivity

Authors: M. PARIKH[1], R. SHARMA[2], ***M. M. THAKKAR**[3];
[1]Neurol., Univ. of Missouri, Columbia, Columbia, MO; [2]Neurol., Univ. of Missouri, Columbia, MO; [3]Neurol., HSTMV Hospital/University of Missouri, Columbia, MO

Abstract: Background:
Post-traumatic stress disorder (PTSD) is frequently associated with chronic pain syndromes, including heightened pain sensitivity and phantom pain-like symptoms that occur in the absence of ongoing tissue injury. Clinical studies suggest that traumatic stress can alter central pain-processing pathways; however, the mechanisms linking trauma exposure to pain hypersensitivity

remain poorly understood. We hypothesized that exposure to predator odor trauma (POT) would mimic pain sensitivity and anxiety-like behavior in mice, modelling trauma-associated pain phenotypes observed in PTSD patients.
Methods: Adult C57/bl6j mice were exposed to a predator odor trauma (POT) paradigm using soiled cat litter as the traumatic stimulus. On Day 1, mice underwent a 15-minute trauma acquisition session in a new context, followed by 45 minutes of exposure to soiled kitty litter. Anxiety-like behavior was assessed on Day 2 using the Elevated Plus Maze (EPM). On Day 3, pain sensitivity was evaluated using behavioural nociceptive testing. POT-exposed animals were compared with non-trauma control (NOC).Day-4, animals were exposed to the same cage as previously presented for traumatic memory recall.
Results: Mice exposed to predator odor trauma will exhibit increased anxiety-like behavior in the EPM, characterized by reduced open-arm exploration, together with enhanced pain sensitivity (Acetone test) compared with control animals. These behavioural changes would be consistent with stress-induced alterations in central pain-processing pathways and may resemble phantom pain-like symptoms reported in individuals with PTSD.
Conclusions: The predator odor trauma paradigm may provide a translational model for investigating the relationship between traumatic stress and altered pain processing. Demonstrating increased pain sensitivity following trauma exposure would support the hypothesis that PTSD-related neural adaptations contribute to chronic pain vulnerability and may help identify therapeutic targets for trauma-associated pain disorders.

Disclosures: M. Parikh: None. **R. Sharma:** None. **M.M. Thakkar:** None.

Poster

PSTR145: Sleep: Behavior in Animal Models

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: G.07. Biological Rhythms and Sleep

Support: G20251001-14500; Sigma Xi, The Scientific Research Honor Society
The Veterans Administration (through the Merit Research Award; I01BX002661 and I01BX006240-0

Title: Closed Loop Optogenetic Activation Of The Preoptic Area after Memory Reactivation Improves Extinction Memory Recall

Authors: *M. PARIKH[1], R. SHARMA[2], M. M. THAKKAR[3];
[1]Univ. of Missouri, Columbia, Columbia, MO; [2]Neurol., Univ. of Missouri, Columbia, MO; [3]Neurol., HSTMV Hospital/University of Missouri, Columbia, MO

Abstract: Introduction: Sleep plays a critical role in the consolidation and modification of emotional memories. Memory reactivation can destabilize previously acquired traumatic memories, creating a reconsolidation window during which memories become susceptible to

updating. The preoptic area (POA) is a major sleep-promoting brain region that regulates sleep stability and supports memory consolidation. However, whether targeted enhancement of POA activity during post-reactivation sleep facilitates extinction memory formation remains unclear. We hypothesized that closed-loop optogenetic activation of POA neurons during NREM sleep following memory reactivation would enhance extinction memory recall. **Methods: Adult** male C57BL/6J mice underwent predator odor trauma conditioning (Day 1), extinction training (Day 2), memory reactivation (Day 3), and extinction recall testing (Day 4). A stimulatory opsin was expressed in POA neurons using stereotaxic delivery of an AAV-hSyn viral vector. Mice were implanted with EEG and EMG electrodes for real-time sleep-state detection and local field potential (LFP) electrodes targeting the BLA and PFC. Following memory reactivation, closed-loop optogenetic stimulation was delivered selectively during NREM sleep. Simultaneous EEG, EMG, and LFP recordings were collected throughout the experiment. Theta (4-12 Hz) and gamma (30-80 Hz) oscillatory activity within the BLA and PFC were analyzed during memory reactivation, post-reactivation sleep, and extinction recall. Extinction memory recall was assessed by quantifying freezing behavior. **Results: Memory** reactivation increased theta activity within the BLA, consistent with the retrieval of traumatic memory traces. Closed-loop activation of POA neurons during post-reactivation NREM sleep significantly enhanced extinction memory recall, resulting in reduced theta power during retrieval testing. POA activation increased extinction-associated theta and gamma oscillatory activity within the PFC and enhanced coordinated BLA-PFC network dynamics during the post-reactivation consolidation period. These neural changes were associated with improved extinction memory performance. **Conclusions: Closed-loop** activation of sleep-promoting POA circuits during NREM sleep following memory reactivation enhances extinction memory recall and strengthens extinction-related theta and gamma activity within the BLA-PFC network.

Disclosures: M. Parikh: A. Employment/Salary (full or part-time):; Rutgers, The state university of New Jersey. **R. Sharma:** None. **M.M. Thakkar:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.01/EE24

Topic: H.03. Motivation

Support: College of Liberal Arts
CSULB BUILD Program in the Office of Undergraduate Research Services

Title: Functional consequences of early life amphetamine exposure on adolescent fentanyl sensitization and cross-sensitization to morphine

Authors: *T. E. FALCON[1], E. N. SIU[1], A. E. FELIX[1], J. L. DIAZ[1], N. MABINI[1], C. A. CRAWFORD[2], A. R. ZAVALA[1];

[1]California State Univ., Long Beach, CA; [2]Col. of Hlth. and Human Sci., North Carolina A&T State Univ., Greensboro, NC

Abstract: Attention-deficit hyperactivity disorder (ADHD) is a relatively common disorder in children and adolescents that has nearly doubled in prevalence across the last two decades. Several factors indicate that children aged 6-10 years are misdiagnosed with ADHD and improperly treated with stimulant medications such as Adderall® (amphetamine; AMPH). Exposure to stimulants during this period is problematic, given the rapid brain development that occurs and the neuroadaptations that AMPH can cause in brain reward regions. The latter may alter vulnerability to drugs of abuse in adolescence and adulthood. Thus, the present study examined the effects of juvenile AMPH exposure on behavioral sensitization in adolescent rats. Specifically, we examined whether AMPH exposure early in life affects the development and expression of fentanyl (FENT) sensitization, given that the use of FENT, a synthetic opioid, has increased among adolescents over the past decade. Beginning on postnatal day (PD) 16, rats were administered 0 or 5 mg/kg AMPH twice daily (6 hours apart). They continued this treatment until PD 25, a period of rat development similar to that of children aged 6-10 years. Following AMPH pretreatment, animals underwent a washout period until PD 40. From PD 40-49, rats were injected daily with 0, 50, or 100 µg/kg FENT and immediately placed into locomotor activity chambers, where distance traveled (m) was recorded over 60 min. On PD 52, rats received a challenge dose of 25 or 50 µg/kg FENT, and distance traveled was assessed over a 180 min session. Lastly, on PD 54, rats received 3 mg/kg morphine to assess locomotor cross-sensitization in a 120 min challenge session. Results indicate that repeated FENT exposure during adolescence elicits a sensitized locomotor response in a dose-dependent manner, which was not potentiated by juvenile AMPH exposure. Additionally, cross-sensitization to morphine was not seen, nor was it affected by early exposure to AMPH. These findings suggest that developmental AMPH exposure does not lastingly affect the development and expression of behavioral sensitization later in life.

Disclosures: T.E. Falcon: None. **E.N. Siu:** None. **A.E. Felix:** None. **J.L. Diaz:** None. **N. Mabini:** None. **C.A. Crawford:** None. **A.R. Zavala:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.02/EE25

Topic: H.03. Motivation

Support: NIH Grant R16GM154678

Title: Impact of juvenile methylphenidate on sleep/wake patterns and attention in Wistar Kyoto and Spontaneous Hypertensive rats

Authors: L. GONZALEZ[1], C. MORENO[1], S. GOMEZ[1], A. MARTINEZ[1], P. GUERRERO[1], K. GUERRERO LEON[2], A. MORA[1], E. MOSQUEDA[1], *L. R. AMODEO[3];
[1]Psychology, California State Univ. San Bernardino, San Bernardino, CA; [2]Psychology, Univ. of Nebraska, Lincoln, CA; [3]CSU San Bernardino, San Bernardino, CA

Abstract: Children with attention-deficit/hyperactivity disorder (ADHD) experience significantly more sleep problems than their typically developing peers, regardless of stimulant medication use. Despite clinical awareness of this association for over 60 years, research on the intersection of ADHD and sleep remains limited. While methylphenidate (MPH) improves core ADHD symptoms, it has also been linked to sleep disturbances, though findings remain inconsistent, and causality is difficult to establish through human studies alone. Spontaneously hypertensive rats (SHR) are a validated animal model of ADHD that also display aberrant EEG activity similar to those seen in ADHD individuals. To our knowledge, there are limited preclinical studies investigating the role that sleep may play in ADHD-related behaviors in SHR and control rat models. This study examines the effects of MPH on sleep/wake activity in juvenile SHR, an established ADHD model, compared to the Wistar-Kyoto (WKY) background strain. Male and female juvenile rats were administered MPH (1, 2 mg/kg) or control twice daily for 20 days (PD 20-39). Non-invasive activity monitors were used to assess circadian rhythms and detailed activity patterns over a 24-hour reverse light/dark cycle. Microanalysis of activity patterns were assessed on the last day of MPH treatment and after 1, 10, 20, and 30 days of discontinuation. On the final day of adolescent treatment, MPH increased both activity and rest fragmentation relative to controls. After 10 days of withdrawal, rats treated with MPH continued to exhibit shorter rest episodes and increased rest fragmentation, consistent with effects observed in our published findings. Adolescent SHR rats exhibit significantly longer active episodes during the dark period compared to the WKY strain. Additionally, MPH-treated rats displayed reduced anxiety-like behavior, spending more time in the center of the open field. In adulthood, SHR rats continue to display significantly greater overall activity, along with shorter rest episodes and increased rest fragmentation during the light period. SHR rats also show significantly higher rhythm-adjusted mean (MESOR) and circadian amplitude relative to WKY controls. Adult rats were also evaluated using a sustained attention task. Preliminary results suggest that SHR rats perform significantly worse, making fewer correct responses. Together, these data will clarify how 24-hour sleep/wake patterns change across development and how the interplay between ADHD-related phenotypic behaviors and stimulant treatment modulates these patterns.

Disclosures: L. Gonzalez: None. **C. Moreno:** None. **S. Gomez:** None. **A. Martinez:** None. **P. Guerrero:** None. **K. Guerrero Leon:** None. **A. Mora:** None. **E. Mosqueda:** None. **L.R. Amodeo:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

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Program #/Poster #: PSTR146.03/EE26

Topic: H.03. Motivation

Support: NIH Grant R01AA006059
NIH Grant R16GM154678

Title: Impact of GLP-1 agonist on alcohol motivation and sleep/wake patterns in adulthood after adolescentintermittent alcohol consumption

Authors: *A. MORA[1], C. CUETO[3], L. FELEMA[2], A. ISBAEL[2], D. O. LEMUS[2], S. GOMEZ[2], L. GONZALEZ[2], P. BOM[2], C. MORENO[2], L. R. AMODEO[4];
[1]Psychology, California State Univ. San Bernardino, Santa Clarita, CA; [2]Psychology, California State Univ. San Bernardino, San Bernardino, CA; [3]Neurosci., Virginia Commonwealth Univ., Richmond, VA; [4]Psychology, CSU San Bernardino, San Bernardino, CA

Abstract: Glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as promising pharmacological agents for reducing reward-related behaviors, including alcohol consumption. Preclinical studies demonstrate that semaglutide (Ozempic®) dose-dependently decreases both binge-like and dependence-induced alcohol drinking in rats, highlighting its potential as a treatment for alcohol use disorder (AUD). However, little is known about its effects on sleep and circadian regulation, particularly following adolescent alcohol exposure. This gap is important given the bidirectional relationship between alcohol use and sleep disruption. Understanding how GLP-1 signaling affects both alcohol motivation and sleep-wake behavior may provide insight into the therapeutic potential of GLP-1-based treatments. Male and female Wistar rats received intermittent 24-hour access to 20% ethanol for five weeks beginning on postnatal day 26. Rats were categorized as high or low adolescent ethanol consumers using a median split, while control rats received no ethanol. Rest/wake activity and circadian measures were assessed during adolescent drinking, acute withdrawal, and prolonged withdrawal. In adulthood, rats were tested on fixed-ratio (FR3-15) and progressive-ratio operant paradigms in which responses earned temporary access to 20% ethanol. High adolescent ethanol consumers completed more fixed-ratio trials and exhibited higher progressive-ratio breakpoints in adulthood than controls, indicating greater motivation for alcohol. Semaglutide (0.01 or 0.1 mg/kg) was then evaluated for its effects on alcohol motivation and sleep-wake activity. One hour after administration, GLP-1 agonist reduced progressive-ratio breakpoints in rats exposed to adolescent ethanol but not controls. Twenty-four hours later, both doses reduced alcohol motivation regardless of adolescent exposure, an effect that was no longer evident after 48 hours. Semaglutide also reduced activity during the light phase and the subsequent dark phase immediately following treatment. Notably, the higher dose (0.1 mg/kg) increased rest episode duration and reduced rest fragmentation in rats with high levels of adolescent ethanol consumption. These preliminary findings suggest that GLP-1 receptor agonists may reduce alcohol motivation while improving sleep quality, although they may also produce daytime sedation.

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Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.04/EE27

Topic: H.03. Motivation

Title: Effects of adolescent ketamine on AKT-mTOR protein expression in the adult hippocampus

Authors: *J. GARCIA[1], C. A. FRAUSTO[1], J. REYES[2], A. THEMANN[1], M. RODRIGUEZ[3], S. D. INIGUEZ[2];
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Abstract: Ketamine is increasingly used to treat mood-related disorders in adolescents; however, its long-term neurobiological effects remain poorly understood. Thus, we examined whether adolescent exposure to ketamine, social defeat stress (SDS), or their combination, induces lasting alterations in hippocampal *protein-kinase b* (AKT)-*mammalian target of rapamycin* (mTOR)-related protein expression, a pathway implicated in the antidepressant actions of ketamine. Male C57BL/6 mice were exposed to a 10-day SDS paradigm during adolescence (postnatal day [PD] 35-44) and received ketamine (20 mg/kg/day; PD35-44) or vehicle treatment after each episode. In adulthood (PD70), mice were euthanized for hippocampal tissue collection and protein expression of AKT-mTOR-related signaling molecules. Adolescent exposure to ketamine resulted in long-lasting reductions in hippocampal AKT-mTOR-Raptor protein expression, whereas individual exposure to SDS did not alter this pathway later in life. Collectively, ketamine exposure alone induces persistent dysregulation of hippocampal AKT-mTOR-Raptor signaling. Thus, the data suggest that the long-term molecular consequences of adolescent ketamine exposure depend on the environmental/social context in which the drug is experienced.

Disclosures: J. Garcia: None. **C.A. Frausto:** None. **J. Reyes:** None. **A. Themann:** None. **M. Rodriguez:** None. **S.D. Iniguez:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.05/EE28

Topic: H.03. Motivation

Support: College of Liberal Arts
CSULB BUILD Program in the Office of Undergraduate Research Services

Title: Persistence of nicotine-seeking behavior in an aversive environment in adolescent male and female rats

Authors: *M. L. ROACH, C. YEAP, R. H. CHIANG, A. R. ZAVALA;
California State Univ., Long Beach, CA

Abstract: OOne defining characteristic of substance use disorder (SUD), as defined by the DSM-5, is the use of a substance despite adverse consequences. Animal models commonly assess the extent to which animals continue to self-administer the drug despite being associated with an aversive stimulus (e.g., shock) to characterize this behavioral phenotype. However, this method is costly, time-consuming to establish, and has not been demonstrated for nicotine-seeking. While cigarette use has decreased, the rise in popularity of e-cigarettes, particularly among adolescents, has seen a rapid increase in nicotine use in the past decade. Thus, this study establishes nicotine-seeking in an aversive environment using the conditioned place preference (CPP) paradigm in adolescent rats. A two-chamber CPP apparatus with distinct environments (one with white/circular pattern walls and one with black walls) was modified to allow turning white LED lights (600 lux) on and off in the white/circular chamber and red LED lights (30 lux) on and off in the black chamber. The white LED lights were used because preliminary tests showed that rats consistently avoided the compartment, allowing us to examine the persistence of nicotine-seeking in an aversive environment. During conditioning, rats received a subcutaneous injection of saline, nicotine (0.05, 0.2, or 0.6 mg/kg), ascending nicotine (0.05-0.6 mg/kg), or the same doses in a random order, before being confined to the white/circular chamber for 15 min for 10 consecutive days. During conditioning, both LED lights were turned off. Nicotine-seeking behavior was then assessed in the presence of both LED lights by allowing rats free access in a drug-free state to both chambers of the apparatus for 60 min. The LED lights remained on for the remainder of the experiment. Rats then underwent 9 extinction sessions, during which they had free access to both chambers for 30 minutes in a drug-free state. Finally, reinstatement of nicotine-seeking behavior was assessed by administering all rats 0.2 mg/kg nicotine. Results show that chronic nicotine exposure results in a sex- and dose-dependent effect on nicotine-seeking behavior, with the females given 0.6 mg/kg of nicotine exhibiting an increase in time spent in the nicotine-paired environment on the test day, as well as during the extinction and reinstatement phases. Overall, we demonstrate that nicotine-seeking behavior persists in an aversive environment in adolescent female rats, and this approach captures a hallmark behavioral phenotype of SUD and provides a better means to study its neurobiology.

Disclosures: M.L. Roach: None. **C. Yeap:** None. **R.H. Chiang:** None. **A.R. Zavala:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.06/EE29

Topic: H.03. Motivation

Support: College of Liberal Arts, California State University, Long Beach
CSULB BUILD Program

Title: Methamphetamine-seeking behavior and its persistence in an aversive environment in adolescent male and female Sprague-Dawley rats

Authors: *A. G. SEDILLO, C. H. NGUYEN, H. G. PANAMENO, A. R. ZAVALA; California State University, Long Beach, Long Beach, CA

Abstract: The transition from recreational use of drugs like methamphetamine (METH) to more problematic use and inability to regulate use despite adverse consequences is a characteristic of substance use disorder (SUD) in humans. In rodents, this behavioral phenotype can be assessed by measuring the extent to which animals continue to self-administer the drug despite being shocked. However, this approach is costly, invasive, and time-consuming to establish, with the latter making it difficult to study this effect in adolescence, which has a short developmental window in rodents (20-30 days). In the present study, we used a modified conditioned place preference procedure to examine whether rats would exhibit METH-seeking behavior in a brightly lit environment, which rats naturally find aversive. Adolescent male and female Sprague-Dawley rats were randomly assigned to receive daily injections of METH (0.0, 0.2, 0.6, or 1.0 mg/kg, intraperitoneally), or these doses were administered in an ascending or random order for 10 consecutive days without the presence of any lights. Rats were then tested for METH-seeking behavior in a drug-free state by allowing them free access to explore the METH-paired environment illuminated with bright white LEDs (600 lux) or a novel environment illuminated with red LEDs (30 lux). Rats then underwent 9 extinction sessions, during which they were allowed free access to both LED-lit chambers during daily 30 min sessions. Finally, rats underwent a reinstatement test, during which all rats received a priming injection of METH (0.6 mg/kg, intraperitoneally) before being allowed to explore both LED-lit chambers. Results show that chronic METH exposure results in a dose-dependent effect on METH-seeking behavior, with the 1.0 METH dose exhibiting an increase in time spent in the METH-paired environment on the test day, as well as higher time spent in this environment during the extinction and reinstatement phases. Overall, this novel approach enables the study of the persistence of METH-seeking behavior in an aversive environment during adolescence, which can be used to study the neurobiology of SUD in human adolescents.

Disclosures: A.G. Sedillo: None. **C.H. Nguyen:** None. **H.G. Panameno:** None. **A.R. Zavala:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.07/EE30

Topic: H.03. Motivation

Title: Behavioral, Epigenetic, and Molecular Correlates of Cocaine Exposure in Two Rodent Models of Substance Use Disorder

Authors: *A. GRAVES[1], P. A. VIEIRA[2], K. E. CONNER[3];
[1]Biol., California State Univ. Dominguez Hills, Santa Monica, CA; [2]Psychology, California State University, Dominguez Hills, Carson, CA; [3]Psychology, CSU Dominguez Hills, Carson, CA

Abstract: Although a large amount of addiction literature focuses on male model organisms, it is established that women become addicted more readily and show larger escalation and withdrawal symptoms from cocaine use compared to men (Becker, 2016). Due to there being limited research outlining sex differences in addiction, the present study investigates the molecular and behavioral facets of sex differences in addiction using two rodent models. Brain-derived neurotrophic factor (BDNF) is a protein associated with neural genesis, learning and memory, and addiction behavior. During cocaine exposure, BDNF increases in reward regions of the brain, including the nucleus accumbens, ventral tegmental area, and prefrontal cortex. BDNF is also shown to mediate drug seeking and craving, as it is elevated during withdrawal conditions compared to acute intoxication. Quantitative polymerase chain reaction (qPCR) was used to compare BDNF levels between naive, acute cocaine intoxicated, cocaine withdrawal, and cocaine abstinence rat models delivered via operant conditioning in reward-associated regions of the brain. Regional BDNF levels were also compared between male and female rats. We expect female rats to have higher levels of BDNF compared to males in reward-associated regions of the brain, and BDNF to be expressed more in withdrawal mice compared to acute intoxication.
Methyl CpG-binding protein-2 (MECP2) regulates transcription by binding to methylated DNA, and in addiction studies, is shown to be associated with cocaine sensitization and interacts with other known molecular components of addiction (Feng & Nestler, 2010). In a wider scope, knocking out MECP2, which is used to model Rett's syndrome (an autism spectrum disorder), has been shown to cause social deficits and heightened anxiety behavior (Gemelli et al., 2006). When comparing these two fields, cocaine MECP2 literature exclusively uses male rodents, while autism MECP2 literature exclusively uses female rodents. Given this, the current study used immunohistochemistry and immunoblotting to investigate whether MECP2 is differentially expressed in male and female mice prenatally exposed to cocaine, and whether this leads to increased anxiety, social deficits, and drug sensitization measured using elevated plus maze, three-chambered sociability, and conditioned place preference paradigms. Understanding more about the molecular effects of addiction could help us work towards developing more substantial and effective treatments for substance use disorder.

Disclosures: A. Graves: None. **P.A. Vieira:** None. **K.E. Conner:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.08/EE31

Topic: H.03. Motivation

Title: Morphine Withdrawal and Kappa Opioid Receptor Activation Convergently Disrupt Pavlovian Motivation in Adaptive Reward Seeking

Authors: *R. M. BULEY[1], S. CASTILLO RIVAS[2], A. ESSLING[3], T. NGUYEN[4], A. THOMAS-BOWMAN[6], J. HILL[6], B. HALBOUT[5];
[1]Psychology, MAPR, California State University, Long Beach, Long Beach, CA; [2]Psychology, [3]Mol. Cell Biol. and Physiol., [4]Chem. - Biochem., [5]Biol. Psychology, California State University, Long Beach, Long Beach, CA; [6]Psychology, California State Univ. Long Beach, Long Beach, CA

Abstract: Opioid use disorder (OUD) is a chronic relapsing disorder characterized by persistent drug use despite adverse consequences. Withdrawal is associated with reduced engagement in adaptive natural rewards, with drugs becoming more salient, increasing the risk of relapse. This reduced engagement suggests that there may be a disruption in motivational processes during withdrawal. Activational motivation, defined as the energy, effort, and persistence required to engage in adaptive reward-seeking behavior may be particularly vulnerable to these withdrawal-related changes. Although withdrawal-related physical symptoms are well characterized, less is known about the psychological and neurobiological mechanisms underlying motivational deficits that persist during withdrawal. Because dynorphin/kappa opioid receptor (KOR) signaling is altered during opioid withdrawal and plays a key role in regulating reward processing and motivation, we examined its potential contribution to withdrawal-related motivational deficits. The present study examined whether morphine withdrawal and pharmacological KOR activation produce similar impairments in cue-elicited activational motivation measured using general Pavlovian-to-instrumental transfer (PIT) for food reward. Methods: Adult Female and Male Sprague Dawley Rats (70f, 70m) were tested using general PIT. Rats underwent Pavlovian conditioning of an auditory cue with a food reward, and instrumental training (i.e., lever pressing for food reward). In our first experiment, morphine- or saline- exposed rats received naloxone to precipitate withdrawal prior to PIT testing. In the second experiment, morphine-naïve rats were treated with a selective KOR agonist (U50,488) before PIT testing. Results: Naloxone precipitated morphine withdrawal reduced cue-elicited invigoration of reward seeking. Similarly, U50,488 treatment (high dose) reduced cue-elicited lever pressing relative to vehicle controls, indicating a dose dependent reduction in cue-elicited activational motivation. Conclusions: Morphine withdrawal and pharmacological KOR activation convergently disrupted cue-elicited activational motivation responding, suggesting dynorphin/KOR signaling may contribute to withdrawal-associated disruptions in cue-elicited motivational processes that support adaptive reward seeking.

Disclosures: R.M. Buley: None. **S. Castillo Rivas:** None. **A. Essling:** None. **T. Nguyen:** None. **A. Thomas-Bowman:** None. **J. Hill:** None. **B. Halbout:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.09/EE32

Topic: H.03. Motivation

Title: Kappa Opioid Receptor Activation Alters Goal-Directed Choice: Relevance to Morphine Withdrawal

Authors: *I. MONTEROSSO, C. FANELLI, A. LUNDIN, A. THOMAS-BOWMAN, A. ESSLING, J. HILL, N. REIMER, S. CASTILLO RIVAS, B. HALBOUT;
Psychology, California State University, Long Beach, Long Beach, CA

Abstract: Opioid withdrawal is characterized by emotional and cognitive deficits that may result in maladaptive decision-making, which hinders recovery from opioid use disorder (OUD) by promoting relapse. Recent work has shown that spontaneous acute morphine withdrawal causes impaired decision-making. Other studies have shown that upregulation of kappa opioid receptor (KOR)/dynorphin transmission mediates withdrawal-associated behaviors, including cognitive impairments. The present study further examined the nature of withdrawal-related, reward-seeking deficits and the contribution of KOR activity in adaptive decision-making behavior. We tested the hypothesis that naloxone-induced morphine withdrawal following limited morphine exposure would cause deficits in goal-directed decision making, and KOR agonism would induce goal-directed choice deficits like those caused by morphine withdrawal. Adult male and female Sprague Dawley rats learned to perform two instrumental actions, each for a unique food reward (e.g. left lever sucrose, right lever grain pellets). Subsequently, rats underwent an outcome-specific devaluation test. Specific satiety reduced the value of a single reward before an extinction test measured goal-directed choice via lever pressing. In one group of rats, we examined the effect of systemic administration (i.p.) of the KOR agonist U50,488 (U50) before the devaluation test. In a second group, we studied the effect of pre-test naloxone-induced (s.c) morphine withdrawal after a brief 5-day morphine treatment regimen. Results show a significantly altered lever pressing and diminished choice following U50 treatment. However, following both U50 and vehicle treatments, rats performed the action associated with the non-devalued outcome more than the one paired with the devalued outcome, suggesting that U50 did not fully disrupt the ability to select actions based on outcome value. Preliminary results show that naloxone-precipitated morphine withdrawal inflicts minimal motivational or cognitive impairments, as rats exposed to morphine treatment-maintained goal-directed reward-seeking behavior. Results will be discussed in the context of potential U50-induced locomotor impairments and parameter-dependent morphine effects. Together, these findings suggest that KOR activation may reduce reward-seeking without fully impairing the cognitive processes required for flexible decision-making. The behavioral profile and relevance of KOR signaling to withdrawal is to be further defined and explored in future projects.

Disclosures: I. Monterosso: None. **C. Fanelli:** None. **A. Lundin:** None. **A. Thomas-Bowman:** None. **A. Essling:** None. **J. Hill:** None. **N. Reimer:** None. **S. Castillo Rivas:** None. **B. Halbout:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.10/FF1

Topic: H.03. Motivation

Support: NIH NIDA Grant R01DA056602

Title: Fentanyl dependence modulates homeostatic and hedonic regulation of feeding behavior

Authors: *L. LIAW[1,2], S. DESFOR[3], A. M. LIBSTER[4], M. WILLIAMS[5], C. LITIF[4], F. TELESE[4];
[1]Psychiatry, UC San Diego, San Diego, CA; [2]Sch. of Biol. Sci., [3]Biol., [4]Psychiatry, [5]Biomed. Sci., UCSD, La Jolla, CA

Abstract: As of 2024, fentanyl use has driven approximately 80,000 overdose deaths annually in the U.S. Opioid exposure is associated with disruptions in feeding behavior and reward processing, but it remains unclear whether withdrawal-related changes in consumption reflect compensatory homeostatic responses or altered hedonic valuation.
Male C57BL/6 mice underwent fentanyl (n=10) or saline (n=10) administration using a 4-day escalating dose paradigm. Behavioral assessments were performed during three defined phases: pre-treatment (1 day of training and 2 days of baseline assessment), early withdrawal (1 day post-treatment), and abstinence (7 days post-treatment). Feeding behavior and body weight were assessed across all phases using home-cage intake measures. Sucrose preference testing (SPT) was conducted in fentanyl- (n=7), saline- (n=14), and weight-matched food-restricted control mice (n=7). All behavioral analyses were performed under blinded conditions. Amygdala RNA sequencing and Allen Brain Cell Atlas analyses were used to identify candidate molecular and circuit-level substrates.
Fentanyl treatment reduced food intake and body weight relative to controls, with partial recovery during withdrawal. Early withdrawal was associated with increased pellet consumption normalized to body mass, consistent with compensatory feeding. Pellet intake varied significantly across treatment and phase (repeated-measures ANOVA, $p<0.05$). During abstinence, fentanyl-treated mice uniquely exhibited sucrose preference ratios below 0.5, whereas food-restricted controls showed elevated preference, indicating divergent reward valuation despite similar or greater metabolic deficit. Fentanyl-treated mice also exhibited prolonged impairment in weight recovery relative to food-restricted controls. Transcriptomic analysis identified GPR88 as among the most differentially expressed genes in the amygdala following fentanyl exposure. OPRM1-GPR88 co-expression was enriched in ventral striatal and amygdalar cell populations implicated in motivated behavior and reward processing.
These findings demonstrate that fentanyl dependence produces persistent disruptions in feeding behavior and reward valuation extending beyond caloric need. Withdrawal-associated compensatory feeding and altered sucrose preference suggest dissociable influence of homeostatic and hedonic mechanisms that are consistent with opioid-driven modulation of reward circuitry and motivational state.

Disclosures: L. Liaw: None. **S. Desfor:** None. **A.M. Libster:** None. **M. Williams:** None. **C. Litif:** None. **F. Telese:** None.

Poster

PSTR146: Substance Exposure, Withdrawal, and Motivated Behavior

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR146.11/FF2

Topic: A.06. Developmental Disorders

Support: Jim and Betty Ann Rodgers Chair Fund
FSU Council on Creativity and Research
Florida Department of Health

Title: Early-life nicotine exposure produces persistent deficits in motivated behavior via striatal circuit disruption

Authors: M. X. TRUPIANO, J. M. TRAINOR, E. D. WASSON, *D. M. MC CARTHY, P. G. BHIDE;
Florida State Univ. Col. of Med., Tallahassee, FL

Abstract: Early-life nicotine exposure remains a critical public health concern due to its long-term neurodevelopmental consequences, yet the specific behavioral domains and neural circuits most vulnerable to nicotine during development are not fully defined. Using a mouse model of early-life nicotine exposure, we identified persistent impairments in motivated behavior, including reduced nest-building performance and increased latency in novelty-suppressed feeding. These behavioral deficits were accompanied by a marked reduction in striatal parvalbumin (PV) interneuron density, a key inhibitory population that regulates medium spiny neuron output and supports cognitive, emotional, and motivational processes. Whether these alterations reflect a direct developmental disruption of PV interneuron maturation or a long-lasting consequence of early circuit perturbation remains unknown. To test the functional relevance of PV interneuron loss, we selectively activated the remaining PV interneurons using chemogenetic approaches. This manipulation influenced motivational deficits, demonstrating that impaired striatal inhibitory signaling is a mechanistic driver of the long-term behavioral outcomes. Transcriptomic profiling across motivation- and reward-related brain regions revealed the most robust nicotine-induced molecular changes in the striatum, further highlighting this region's selective vulnerability. Together, these findings identify motivation as a previously underappreciated behavioral domain affected by early-life nicotine exposure and establish striatal GABAergic circuit disruption as a key mediator of its enduring effects. These results reinforce the need for stronger public-health guidance regarding nicotine use during pregnancy.

Disclosures: M.X. Trupiano: None. **J.M. Trainor:** None. **E.D. Wasson:** None. **D.M. Mc Carthy:** None. **P.G. Bhide:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.01/FF3

Topic: H.04. Emotion

Title: Behavioral state gates respiratory coding in the Central Amygdala

Authors: *K.-L. HSIEH[1,2], J. P. JOHANSEN[1,3,2];
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Abstract: Interoceptive signals influence emotion, cognition, and behavior, but their neural representations and behavioral consequences are strongly state-dependent. How interoceptive information is integrated with behavioral state in emotional control centers remains unclear. To address this, we simultaneously recorded respiration and central amygdala (CeA) neural activity in 12 male Long-Evans rats performing an ethologically relevant reward-aversive conflict task across 22 sessions (450 single units). Using 3D pose tracking, behavioral classification, and hidden Markov modeling, we identified six overt behavioral classes and inferred three latent behavioral states corresponding to reward seeking, exploration, and immobility. CeA population activity robustly decoded latent states even after controlling neural activity related to overt behaviors, respiration, and locomotion, indicating that CeA state representations were not explained solely by ongoing movements or physiological variables. We identified two complementary forms of respiratory coding in the CeA. Respiratory rate coding tracked breathing frequency, whereas temporal coding synchronized CeA activity to the respiratory cycle through respiration-gamma phase-amplitude coupling and spike-respiration phase locking. These coding modes showed distinct overt-behavioral and state dependencies. Respiratory rate coding was strongest during reward-seeking states, whereas respiratory temporal coding was strongest during rearing and scanning behaviors. Respiration-gamma coupling was further enhanced when rearing and scanning occurred during reward-seeking and exploration states, despite minimal differences in overall breathing frequency across states. In contrast, spike-respiration phase locking was largely state-invariant. This result demonstrate that respiratory synchronization of CeA activity is organized by higher-order behavioral state rather than uniformly reflecting respiratory dynamics or overt behaviors. The same overt behavior can engage distinct respiratory coding regimes depending on the latent state, indicating that respiratory information is selectively encoded according to the adaptive significance of ongoing behaviors in specific states.

Disclosures: K. Hsieh: None. **J.P. Johansen:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.02/FF4

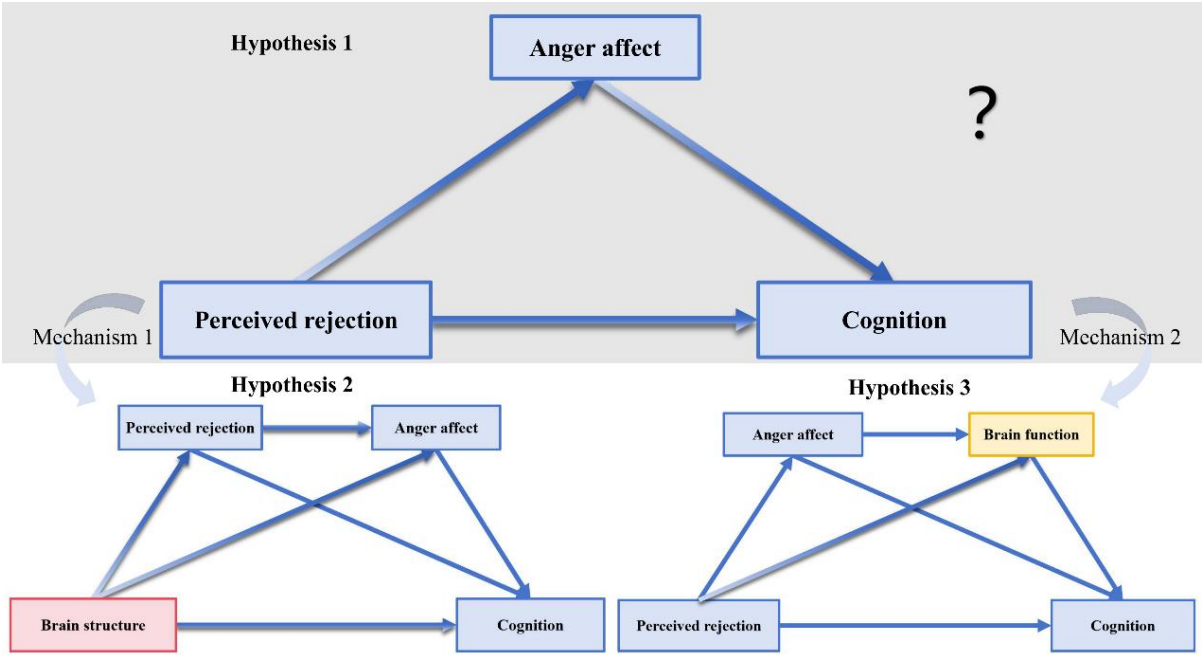
Topic: H.04. Emotion

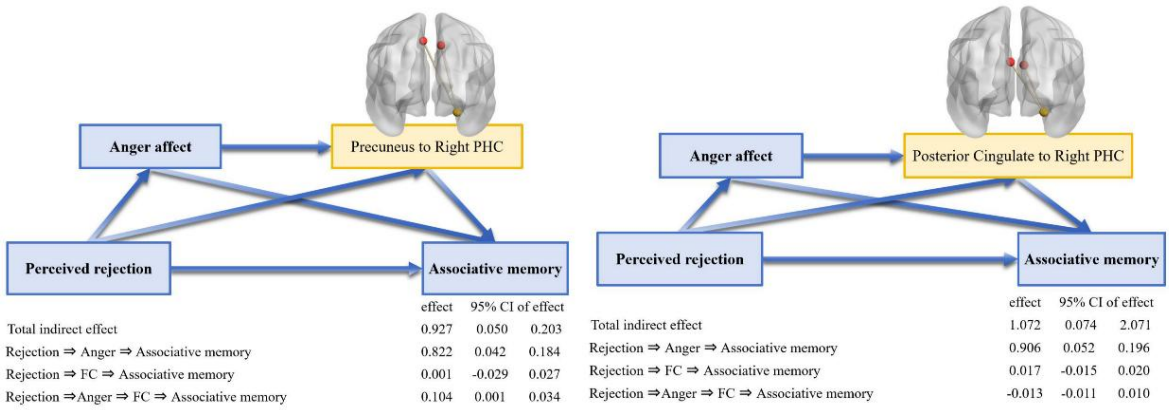
Support: National Natural Science Foundation of China (32400914)
Multi-Year Research Grant (MYRG-GRG2025-00228-FSS)

Title: Perceived social rejection, anger, associative memory, and neural correlates across adulthood

Authors: ***R. HUANG**, L. LIU;
Univ. of Macau, Macau, Macao

Abstract: This study investigated the neurocognitive processes through which perceived social rejection influences associative memory performance via anger across adulthood. Behavioral assessments in 274 adults (aged 18-89) and neuroimaging data (structural and resting-state fMRI) from a subsample ($N = 189$) supported a sequential pathway in which anger mediates the effect of perceived rejection and enhanced associative memory. Structural analyses revealed that gray matter volumes of the left inferior parietal gyrus (angular gyrus), precuneus, and superior temporal regions were associated with sensitivity to social evaluation and perceived rejection, consistent with an antecedent role of structural features in shaping emotional responses. Functional connectivity analyses demonstrated that coupling between emotion-related regions (e.g., amygdala, precuneus) and memory-related regions (e.g., parahippocampal cortex, cingulate cortex) mediates the link between anger and memory, indicating that the cognitive benefit arises through anger-driven neural reorganization. Together, these findings provide mechanistic evidence that negative social experiences can facilitate adaptive cognitive engagement when appraised through anger, highlighting a multilevel pathway from social perception to emotional response and neural network dynamics that support associative memory.





	effect	95% CI of effect	
Total indirect effect	0.927	0.050	0.203
Rejection ⇒ Anger ⇒ Associative memory	0.822	0.042	0.184
Rejection ⇒ FC ⇒ Associative memory	0.001	-0.029	0.027
Rejection ⇒Anger ⇒ FC ⇒ Associative memory	0.104	0.001	0.034

	effect	95% CI of effect	
Total indirect effect	1.072	0.074	2.071
Rejection ⇒ Anger ⇒ Associative memory	0.906	0.052	0.196
Rejection ⇒ FC ⇒ Associative memory	0.017	-0.015	0.020
Rejection ⇒Anger ⇒ FC ⇒ Associative memory	-0.013	-0.011	0.010

Disclosures: R. Huang: None. **L. Liu:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.03/FF5

Topic: H.04. Emotion

Support: Leibniz Best Minds Grant

Title: Whole brain SPECT imaging reveals sex-specific neural architectures and learning trajectories of rescue behavior in mice

Authors: *E. TAFANI[1], A. M. OELSCHLEGEL[1], J. GOLDSCHMIDT[2], S. BAUER MIKULOVIC[3];
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Abstract: Rescue behavior is a complex form of prosocial action requiring detection of distress, evaluation of social information, and motivated responding. Although male and female rodents exhibit comparable rescue behavior, the neural circuits underlying helper and nonhelper phenotypes and their reorganization during learning remain poorly understood. We combined longitudinal behavioral assessment with whole brain single photon emission computed tomography (SPECT) imaging to characterize neural activity associated with rescue behavior in male and female mice.
Male and female mice (12-14 weeks) were tested in a rescue paradigm in which an observer mouse learned across six days to open a door and release a conspecific trapped in cold water. Animals were classified as helpers or nonhelpers based on task performance. During task engagement, mice were intravenously injected with the cerebral blood flow tracer 99mTc-HMPAO, and voxel wise statistical parametric maps were generated from SPECT images of tracer distribution ($p<0.01$). Analyses included female helpers (n=10), female nonhelpers (n=14),

male helpers (n=14), male nonhelpers (n=9), and early- versus late-phase helpers (females n=5/group; males early n=9, late n=5).
Despite comparable acquisition of rescue behavior across sexes, helping was associated with distinct neural networks in each sex. Female helpers preferentially recruited orbitofrontal-insular-hippocampal networks, whereas female nonhelpers showed greater sensorimotor and striatal engagement. Male helpers preferentially recruited olfactory-amygdalar-entorhinal networks, while male nonhelpers exhibited broader activation of sensorimotor, hippocampal, septal, and thalamic circuits. Longitudinal analyses revealed sex-specific learning trajectories. Female helping shifted from cingulate and septal-striatal recruitment during early learning toward amygdalar, olfactory, and cerebellar engagement during later stages. In contrast, male helping shifted from somatosensory-limbic recruitment toward insular-somatosensory and cerebellar networks.
Together, these findings show that comparable rescue behavior can arise through sex-specific patterns of neural recruitment, indicating that males and females engage distinct circuit configurations to achieve a similar behavioral outcome. By revealing distinct circuit mechanisms underlying comparable behavioral outcomes, this work provides a framework for identifying sex-specific neural targets relevant to disorders marked by altered social motivation and prosociality.

Disclosures: E. Tafani: None. **A.M. Oelschlegel:** None. **J. Goldschmidt:** None. **S. Bauer Mikulovic:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.04/FF6

Topic: H.04. Emotion

Support: NIMH IRP ZIAMH002887

Title: Effects of unseen threat-related stimuli on macaque autonomic arousal

Authors: G. CASTRO[1], *P. KUSMIEREK[1], E. A. MURRAY[2];
[2]Lab. of Neuropsychology, [1]NIMH, NIH, Bethesda, MD

Abstract: The primate brain possesses circuits to rapidly process threats, especially visually perceived social threats. In macaques, neurons in several subcortical structures including the superior colliculus (SC), the pulvinar (PUL), and the amygdala (AMY) exhibit short-latency and robust responses specific to face images (Maior et al., Behav Brain Res 2010, Nguyen et al., Front Neurosci 2014, Inagaki et al., Cereb Cortex 2022). Because anatomical pathways connect SC to PUL and, in turn, PUL to AMY (e.g., Inagaki et al. 2022, Tamietto et al., Cur Biol 2012), a SC to PUL to AMY pathway has been hypothesized to underlie the short-latency responses to faces in AMY. This hypothesis is supported by studies in patients with visual cortex damage who

exhibited affective blindsight: their behavior was altered when images of fearful faces were presented within the scotoma (thus inaccessible to the visual cortex)—but not if their PUL was damaged (Bertini et al., Front Psychol 2018). We aim to identify anatomical substrates involved in threat-biased processing using a nonhuman primate blindsight model. Here, we studied autonomic and behavioral effects of affective stimuli presented in the scotoma using a paradigm similar to that used by Bertini et al. (2018). Three rhesus monkeys were trained to perform a visual discrimination task while maintaining central fixation. Next, they underwent unilateral V1 aspiration lesions. Affective and control test stimuli were presented in the resulting scotoma and were presumably 'unseen', while discrimination cues (horizontal and vertical Gabor patches) appeared in the intact visual field. Test stimuli included fearful, threatening, and neutral monkey face images and videos, snake and scrambled snake images, and images of staring or profile-oriented human faces (human intruder paradigm). We assessed reaction times (RT), heart rate, and pupil diameter in trials with affective vs. control stimuli presented in the scotoma. Unlike Bertini et al. (2018), we observed virtually no effects of unseen stimuli on RT. In contrast, significant modulation of pupil diameter by unseen threat-related stimuli was observed in some stimulus presentation conditions in all three monkeys, mainly by affective monkey faces, and more rarely by snakes. Heart rate was less sensitive to unseen images but it was occasionally modulated by monkey faces and human intruder stimuli. Though the effects were not consistent across animals and stimulus types, our findings suggest that unseen biologically relevant stimuli influence the autonomic states of monkeys. The results support continued investigation of subcortical pathways for visual threat processing.

Disclosures: G. Castro: None. **P. Kusmierek:** None. **E.A. Murray:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.05/FF7

Topic: H.04. Emotion

Support: NIH grant R01NS118197

Title: Context-dependent prefrontal hypoactivity in Rett syndrome reflects selective disruption of state-encoding ensembles

Authors: P. XU[1], X. SUN[1], ***H. LU**[2];
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Abstract: How neural circuits generate flexible behavioral states across contexts, and how disease-related perturbations disrupt these representations, remains a central question in systems neuroscience. Rett syndrome, caused by loss-of-function mutations in MECP2, provides a powerful model to test whether circuit dysfunction reflects uniform hypoactivity or selective disruption of state-encoding ensembles. We addressed this question in the medial prefrontal

cortex (mPFC), a region important for social, affective, and exploratory behaviors. Using in vivo calcium imaging with head-mounted miniature microscopy, we recorded mPFC pyramidal neurons in freely behaving female Mecp2+/- and wild-type mice across open-field exploration, social and nonsocial stimulus interaction, and anxiety-related contexts. In wild-type mice, mPFC activity was organized into distinct state-related ensembles. Center-ON neurons were preferentially recruited during exposed or stimulus-interaction states, whereas Corner-ON neurons were associated with exploration in protected locations. In Mecp2+/- mice, mPFC hypoactivity was not uniform. Activity was relatively preserved during some exploratory states but reduced during stimulus interaction and anxiety-provoking environments. Ensemble-level analysis showed that this deficit primarily reflected impaired recruitment, reduced activity, and weaker cross-context generalization of Center-ON neurons. In contrast, Corner-ON exploration-related ensembles remained largely preserved. Thus, MeCP2 deficiency shifts the balance of prefrontal state coding rather than globally silencing mPFC pyramidal neurons. Consistent with this model, mPFC circuits normally use pattern decorrelation to distinguish social from nonsocial cues, and restoration of social preference required restoration of this representational separation. These findings identify context-dependent, ensemble-specific hypoactivity as a core prefrontal circuit phenotype in Rett syndrome and suggest that therapeutic strategies should restore the precision and balance of prefrontal state representations rather than simply increase overall circuit activity.

Disclosures: P. Xu: None. **X. Sun:** None. **H. Lu:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

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Title: Orexin-driven theta oscillations in the anterior cingulate cortex link affective empathy and prosocial behavior

Authors: *J. KIM, G. O. CRON, M. KIM, A. HOSSAIN, J. LEE;
Stanford Univ., Stanford, CA

Abstract: Prosocial helping is essential to strengthen group cohesion across many species. Such prosocial behavior can be driven by affective empathy - the capacity to perceive and share the emotional states of others. Observational fear, measured by vicarious freezing responses to distressed conspecifics, is a well-established paradigm for studying affective empathy. During

such vicarious freezing, theta oscillations (5-7 Hz) in the anterior cingulate cortex (ACC) are known to be enhanced. However, whether ACC theta oscillations contribute to prosocial behavior, and if so, how affective states are translated into prosocial action, remains unclear. Here, we combined observational fear and consolation assays, further classifying vicarious freezing into gazing during observational fear and allogrooming - a consoling behavior defined by repeated licking toward distressed demonstrators - during the consolation assay. In fear-experienced observers, ACC theta power was significantly enhanced during both freezing with gazing and allogrooming. Furthermore, using a genetically encoded orexin sensor (OxLight1), ACC-projecting orexinergic neurons from the lateral hypothalamus (LHA) were selectively recruited during both behaviors in these observers. Real-time, gaze-dependent optogenetic inhibition of the ACC-projecting orexinergic neurons significantly reduced both behaviors, accompanied by suppression of ACC theta power. Together, these findings identify an orexinergic mechanism by which LHA inputs drive ACC theta oscillations to link affective empathy to prosocial behavior, suggesting a neural substrate for translating affective states into prosocial action.

Disclosures: J. Kim: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Department of Neurology and Neurological Sciences, Stanford University. **G.O. Cron:** None. **M. Kim:** None. **A. Hossain:** None. **J. Lee:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Department of Neurology and Neurological Sciences, Stanford University, Department of Bioengineering, Stanford University; Stanford, Department of Neurosurgery, Stanford University, Department of Electrical Engineering.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.07/FF9

Topic: H.04. Emotion

Support: NIH Grant R01NS118197
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Title: Functional specialization of mPFC-BLA and mPFC-NAc pathways in affective state representation

Authors: *C.-H. LAI[1], G. PARK[3], J. LIN[5], S. WANG[6], A. LI[7], J. DU[4], H. LU[2];
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for Sci. and Technol., McLean, VA; [6]McLean High Sch., Fairfax, VA; [7]James Madison High Sch., Vienna, VA

Abstract: Adaptive behavior requires the medial prefrontal cortex (mPFC) to integrate internal state with context and select appropriate responses. The mPFC sends major projections to both the basolateral amygdala (BLA) and nucleus accumbens (NAc), but whether these output pathways carry overlapping or specialized representations of behavioral state remains unclear. We combined projection-specific in vivo calcium imaging with a sequence of behavioral assays that sampled threat-avoidant, exploratory, social, and social-rank-related states. Although average activity patterns were broadly comparable across conditions, pathway- and ensemble-level analyses revealed clear functional specialization. In open-field testing, mPFC-BLA neurons, particularly center-ON cells, were preferentially recruited during exposed or threat-avoidant behavioral epochs, whereas mPFC-NAc neurons were more active during exploratory and approach-related behavior. During social interaction, mPFC-NAc ensembles showed robust pattern decorrelation between social and object conditions, consistent with a prominent role in social preference processing. Longer-lasting behavioral states also biased these circuits in opposite directions: positively valenced contexts enhanced mPFC-NAc activity, while negatively valenced conditions preferentially increased mPFC-BLA activity. In repeated tube-test competitions, winning was associated with elevated mPFC-NAc pathway engagement, whereas losing was associated with elevated mPFC-BLA pathway engagement. Together, these findings indicate that mPFC outputs to BLA and NAc do not simply relay a common prefrontal state signal. Instead, they form functionally specialized channels that differentially encode threat-avoidant, exploratory/social, and social-outcome-associated behavioral states. This pathway-specific framework provides a circuit basis for understanding how prefrontal dysfunction may contribute to maladaptive emotional and social behavior in neuropsychiatric disorders.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Title: Reweighting reward preference during naturalistic foraging: The role of amygdala-prelimbic coding under predatory threat

Authors: *E. KIM[1], J. JEONG[3], J.-S. CHOI[3], J. J. KIM[1,2];
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Abstract: Foraging presents a canonical reward-threat conflict: as predation risk increases, animals must shift from high-yield, exposed resource patches to safer, lower-return alternatives. Although behavioral ecology has formalized these adaptive decision rules, the neural circuit mechanisms that continuously integrate reward value with environmental threat to guide flexible action selection remain poorly understood. To address this, male Long-Evans rats underwent a real-world predator-prey encounter scenario where they emerged from a safe nest to forage in a large open arena. Rats chose between highly preferred (chocolate) and standard (grain) pellets at opposite ends while facing surges from a robotic predator upon approach to the preferred option. We simultaneously recorded single-unit activity from the basolateral amygdala (BLA; n = 379 cells) and prelimbic cortex (PL; n = 514 cells) across pre-robot and robot sessions. Rats reliably shifted preference from the high-value to the low-value option under threat. BLA neurons responded predominantly to the predator, whereas PL neurons encoded multiple task variables with choice-predictive activity. Using population decoding, mutual information, transfer entropy, and cross-correlation analyses, we have characterized how information is shared between these regions across behavioral contexts. Linear SVM classifiers trained on population activity revealed that BLA decoding was predominantly reactive, rising after robot activation, and failed to predict behavioral choice. In contrast, PL maintained proactive, multi-variable decoding across the full peri-event window, predicting behavioral choices before they occurred. Mutual information between BLA and PL peaked following robot activation, with transfer entropy confirming preferential BLA-to-PL information flow after threat onset. Cross-correlation analyses showed that BLA-PL spike synchrony increased before threat-induced preference shifts. Critically, robot-biased BLA cells and multi-event PL cells were selectively recruited into synchrony during safe choices, whereas this specificity was absent during risky choices. Together, these findings reveal a functionally dissociable BLA-PL circuit architecture in which threat-selective BLA input modulates PL's multi-variable representations to guide adaptive decision-making under ecological risk.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Simons Foundation Bridge to Independence Award
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Aligning Research to Impact Autism (ARIA)

Title: Lateral septum serotonin dynamics mediate aggression following sleep disruption

Authors: *J. CHOI, M. WANG, C. EGEBJERG, T. HARRIS, O. C. GONZALEZ, L. DE LECEA, N. ESHEL;
Stanford Univ., Stanford, CA

Abstract: Sleep problems are highly prevalent in autism spectrum disorder (ASD) and are often associated with increased irritability and aggression, yet the neural mechanisms linking disrupted sleep to aggression remain unclear. Here, we show that repeated mild sleep disruption selectively increases aggression without broadly altering social preference, anxiety-like behavior, locomotion, or corticosterone levels. This behavioral effect is transient and is accompanied by sustained hyperactivity in the ventral lateral septum (LSv). Inhibition of the LSv attenuates sleep disruption-induced aggression, suggesting that LSv activity is required for this effect. We identify median raphe serotonergic neurons as a major input to the LSv. Activation of MRN^{SERT}-LSv projections reduces sleep disruption-induced aggression and suppresses LSv activity, supporting an inhibitory role for raphe serotonergic input in this circuit. In vivo $GRAB_{5\text{-}HT}$ recordings further reveal that intruder entry evokes dynamic serotonin responses in the LSv, and that sleep disruption attenuates prolonged LSv serotonin suppression during social challenge. Importantly, $Shank3^{+/-}$ mice recapitulate key sleep disruption-associated phenotypes, including elevated aggression, LSv hyperactivity, altered MRN^{SERT} activity dynamics, disrupted LSv serotonin signaling, and altered sleep architecture. Circuit manipulations and almorexant treatment reduce aggression in $Shank3^{+/-}$ mice. Together, we uncover a median raphe serotonin to lateral septum circuit that provides a neurobiological link between sleep disruption and aggression, suggesting a conserved sleep-sensitive pathway that may contribute to aggression in neurodevelopmental disorders.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.10/FF12

Topic: H.04. Emotion

Title: Hippocampal Stem and Granule Cells in Affective Behavior and Cognition

Authors: ***F. LI**[1], C.-Y. PENG[2], J. A. KESSLER[2];
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Abstract: The hippocampal dentate gyrus (DG) plays a critical role in emotion regulation, learning, and memory, and DG granule cells (GCs) dysfunction contributes to many neurological and psychiatric disorders. DG GCs form a heterogeneous population that differs in maturation stage and functional properties. A common feature across these populations is the expression of bone morphogenetic protein (BMP) receptors. While BMP signaling is well known for its essential roles in early development and in regulating adult hippocampal neurogenesis, its effects on different existing GC populations and their behavioral consequences remain poorly understood.Previously, we demonstrated that BMP signaling levels throughout the DG correlate with hippocampus-dependent behavior: elevated BMP signaling impairs, whereas reduced signaling improves hippocampal function. Building on this work, we found that activation of newborn GCs suppresses depression- and anxiety-like behaviors, and many classes of antidepressants act through this mechanism. One such example is ketamine. We found that ketamine's rapid and sustained antidepressant effects arise through distinct mechanisms. A single subanesthetic dose of ketamine rapidly improves affective behavior by increasing activity of existing immature neurons in the DG without altering neurogenesis. In contrast, repeated low-dose ketamine administration produces longer-lasting behavioral effects that require decreased BMP signaling, leading to increased numbers of immature GCs.Current work investigates how cell-autonomous BMP signaling in different GC populations regulates the structural and functional properties, influencing both affective and cognitive behaviors. Together, these studies will elucidate cell-type-specific mechanisms underlying hippocampus-dependent behavior and highlight BMP signaling as a potential therapeutic target for neurological and psychiatric disorders.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: H.04. Emotion

Support: TCU Honors College
TCU SERC grant

Title: Role of the mPFC on recovery from reward downshift: Frustration or exploration?

Authors: A. DRICKAMER, J. A. SUAREZ, ***M. R. PAPINI**;
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Abstract: Frustrative nonreward is induced by unexpected reward reductions. In a consummatory task, licking 2% sucrose is suppressed after ten 5-min sessions of access to 32%

sucrose, but it recovers over subsequent sessions. The neural mechanisms of this behavioral recovery remain incompletely understood. Previous research shows that inhibition of the pathway connecting the basolateral amygdala and nucleus accumbens (BLA-NAc) interferes with behavioral recovery from reward loss. Do cortical regions also contribute to the recovery process? This study examined whether inhibition of the medial prefrontal cortex (mPFC) influences behavioral recovery following a 32-to-2% sucrose downshift. Male Wistar rats (n=24) received mPFC infusions of the hM4Di inhibitory DREADD. Inhibitory DREADDs were activated with CNO (clozapine N-oxide) 30 min before each downshift session in a random half of the animals, whereas the rest were treated with the vehicle. CNO/vehicle injections were also administered 30 min before an open field test (OF). Approximately 60% of the infralimbic region (40% of the prelimbic) showed fluorescence indicating the presence of neurons expressing inhibitory DREADDs. mPFC inhibition had no effect on the first downshift session, but it enhanced licking and suppressed locomotion in subsequent downshift sessions. Thus, neural activity in the mPFC may normally enhance suppression after unexpected reward downshifts perhaps by its excitatory input into the central amygdala, thus playing a function opposite to that of the BLA-NAc pathway in behavioral recovery following frustrative nonreward. However, CNO also led to higher locomotion in the periphery of the OF (but not in the center), suggesting that mPFC neurons may have interfered with exploratory behavior thus releasing licking from competition. Whether chemogenetic inhibition of mPFC neurons reduced frustrative nonreward after an unexpected reward downshift or enhanced exploratory behavior remains to be established.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

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Title: Social isolation duration orchestrates mPFC population dynamics and valence encoding in a sex-specific manner

Authors: *C. R. LEE[1,2,3], G. P. SCHNEIDER[1,2], T. B. TUAZON[1,3], A. GARCIA[1,3], T. TSIN[1,3], N. MOUSSA[1,3], M. G. CHAN[1,2], A. RUIZ D'ARGENCE[1,3], K. BATRA[1,3], A. BAKHTI-SUROOSH[1,3], F. MILLS[1,4], B. JOO[1,2], R. L. MIRANDA[1,3], J. CRESSY[1,3], A. C. BASTUBA[1], L. KEYES[1,2], B. NIELSEN[1], R. WICHMANN[1,2], Y. LI[5], T. D. PEREIRA[1], K. M. TYE[1,2,3,6];
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Abstract: Reports of prosocial responses to acute social isolation and aggression following chronic social isolation led to a conceptual framework for social homeostasis (Lee et al., 2021), but behavioral and neural dynamics across social isolation remain unexplored. Previously, we found dorsal raphe dopamine (DA) neurons mediate a loneliness-like state (Matthews et al., 2016) and innervate the medial prefrontal cortex (mPFC) (Lee et al., 2025).
To explore how social isolation alters mPFC encoding of social and valence information, we used cellular resolution calcium imaging, DA sensors, ultrasonic vocalizations, and computer vision. Across durations (2 hours to 28 days), adult male and female mice underwent a juvenile intruder task. Using DiscoPose, a custom SLEAP (social LEAP estimates animal poses)-based pipeline, we extracted pose features and applied unsupervised clustering to discover behavioral motifs. In males, isolation duration negatively correlated with interaction time (N=80 mice, r=-0.384, p=0.004), and 2 and 6 hours of isolation promoted social interaction (N=107 mice, F6,100=5.875, p<0.0001; GH vs 2hr: p<0.0001; GH vs 6hr: p=0.03). In contrast, isolation duration in female mice positively correlated with interaction time (N=54 mice, r=0.425, p=0.001), with increases after 14 and 28 days (N=63 mice, $F_{6,56}$=6.152, p<0.0001; GH vs 14d: p=0.022; GH vs 28d: p<0.0001). Unsupervised clustering revealed changes in male social behavior, promoting face sniffing and reducing chasing in 7 and 28 day isolated mice (N=107 mice, $F_{18,400}$=3.705, p<0.0001), an effect not seen in females. mPFC calcium imaging revealed isolation increases responsiveness of mPFC neurons to social contact (N=25 mice, n=5681 cells, GH vs 24hr: χ^2=9.09, p=0.0106; GH vs 7d: χ^2=30.28, p<0.0001) in males, but not females. mPFC population trajectory length increased following isolation versus prior group housing, reversible after re-housing (N=6 mice, $F_{2,6}$=16.60, p=0.004; GH_{D1} vs 24hr: p=0.011; 24hr vs GH_{D2}: p=0.006). To assess how social isolation alters valence processing, we trained mice on a Pavlovian discrimination task (N=16 isolated mice, N=8 grouped mice), enabling us to test the hypothesis that isolation-induced mPFC encoding shifts co-occur with changes in valence processing. Trajectory analysis revealed growing population dynamics across timepoints in group-housed but not isolated mice, consistent with the hypothesis that isolation attenuates representational drift. Together, these findings reveal sex-specific mPFC adaptations underlying social and valence processing following isolation.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR147.13/Web Only

Topic: H.04. Emotion

Title: The Role of Beta Network in Emotion Regulation and Cognitive Inhibition: Evidence from Source-Localized Resting-State EEG Network Analysis

Authors: *K. KANANI[1,2], H. SHAHI[2], A. GHADERI[3,2];
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Abstract: A growing body of literature implicates beta-band oscillations (~13-30 Hz) in cognitive control; causal manipulation of fronto-central beta activity modulates motor inhibition, and positive affect is predicted by theta and beta power, with an indirect effect via reappraisal. Specific emotional states, such as fear, grief, and jealousy, exhibit enhanced beta band activity. Rumination and self-blame can be considered a failure of cognitive inhibition against recurring negative thoughts. This study aims to understand neural mechanisms underlying maladaptive emotion regulation styles—rumination and self-blame—reflecting an inability to inhibit persistent negative thought cycles. We re-analyzed resting-state EEG data from the mind-body-brain dataset (Max Planck institute Leipzig) in right-handed adults aged 20-30 with no history of substance abuse or psychiatric disorders (N = 52; 38 males). EEG was recorded from 61 scalp electrodes during eyes-open (8 min) and eyes-closed (8 min) conditions. Source localization was estimated using sLORETA, and whole-brain connectivity matrices were computed for eight frequency bands using lagged nonlinear and lagged coherence metrics. four topological and dynamical network measures(i.e., clustering coefficient (CC), global efficiency (GE), energy (H), and entropy (S)) were calculated and normalized against null models. Then the associations between these network measures and cognitive emotion regulation questionnaire scores were assessed using Spearman correlation with FDR correction. During the eyes-open state, the results showed a negative correlation between the tendency for self-blame and rumination and GE ($r = -0.46$, $q < 0.001$/$r = -0.46$, $q < 0.001$) and H ($r = -0.29$, $q < 0.05$ /$r = -0.43$, $q < 0.001$) and positive correlation between these traits and CC ($r = 0.30$, $q < 0.05$ /$r = 0.48$, $q < 0.001$) in the beta-3 band (???-??? Hz) for lagged-coherence metrics. GE in beta-3 frequency for nonlinear connectivity was negatively correlated with self-blame trait ($r = -0.35$, $q < 0.05$). These results suggest that rumination and self-blame specifically correlate with topology and dynamics of beta-3network and extends existing literature on the role of beta oscillations in inhibition and emotions. This network profile may reflect a neural substrate of rigid, repetitive thought patterns characteristic of maladaptive cognitive emotion regulation.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

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Howard Hughes Medical Institute
Salk Institute for Biological Studies

Title: Stress reverts the effects of VTA dopamine on social behavior in female mice

Authors: *A. PALLE[1], R. WICHMANN[3,2], C. R. LEE[2], C. VANDER WEELE[3], A. YOSAFAT[3], S. TANG[2], F. ALGHAMDI[2], E. H. SCHUT[4], J. VERHAREN[3], S. SUBRAMANIAM[3], T. TUAZON[2], B. DURUBEH[5], M. CHAN[2], J. CRESSY[2], F. ALOBOUDI[2], F. MASSA[2], C. SICILIANO[3], K. M. TYE[2,3,6,7];
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Abstract: Stress-induced mood disorders are enriched in women, yet the mechanisms of female vulnerability are relatively understudied. The mesolimbic dopaminergic system regulates social reward, is altered by stress, and shows sex-specific signaling, making it a candidate mediator of stress-induced social withdrawal. We tested stress effects on dopamine (DA) modulation in social interaction in females by optogenetically manipulating ventral tegmental area (VTA) DA neurons in mice that underwent a 5-day forced swim stress at postnatal day P28 (remote-stress), P86 (recent-stress), or non-stress controls, with behavioral testing at P97. We used a counterbalanced 2-day juvenile intruder task, with one day serving as baseline (OFF) and the other involving either VTA dopamine activation or inhibition (ON), to assess the effects of VTA dopamine modulation on social behavior. Photoinhibition of VTA DA neurons reduced social interaction in controls with no effect in stressed groups (N= 15 Ctrl, 15 recent-stress, 19 remote-stress; Sidak's post-hoc test p=*0.033). Strikingly, VTA DA activation induced an anti-social behavior in stressed females but not in control mice (N= 20 Ctrl, 10 recent-stress, 11 remote-stress; Sidak's post-hoc test *p=0.012 recent-stress, **p=0.008 remote-stress). Blocking DA receptors in the Nucleus Accumbens (NAc) attenuated this effect (N=11 Ctrl, 12 recent-stress, 4 remote-stress; ON-OFF vehicle **p=0.003 vs antagonists p=0.362). Finally, we used SLEAP (Social LEAP Estimates Animal Poses) pose estimation data to extract animal keypoints and

constructed a 33-feature behavioral parameter space on which we performed Principal Component Analysis (PCA). By analyzing the feature contribution and magnitude of the OFF→ON vector shift in 2D PC space, we found that VTA dopamine activation reversed the opsin-induced behavioral profile in stressed animals compared to controls, with features such as touching and sniffing driving the magnitude of this change, reflecting an enrichment of social proximity features in control animals and a suppression of these same features in stressed groups. Performing PCA on a shuffled ON/OFF session labels dataset eliminated this effect, validating the photostimulation-driven nature of our findings. A parallel but shifted effect was observed for VTA photoinhibition, confirming that photoactivation and photoinhibition drive similar behavioral effects in control and stressed animals but in opposite direction. Together, our data reveal a novel role for VTA dopamine in mediating the effects of stress-induced social withdrawal in female mice.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

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Program #/Poster #: PSTR147.15/FF16

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Title: Internal state shifts valence biases while maintaining population differences in basolateral amygdala projection circuits

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Abstract: Not all internal states are created equal: Hunger induces a negative emotional affect, while voluntary exercise elicits a positive emotional state in humans and animals. While both are caloric stressors, these opposing emotional outcomes draw the question: How do these internal states differently affect valence-encoding circuits in the brain? The basolateral amygdala (BLA) encodes emotional associations with projections targeting the centromedial amygdala (CeM) and the nucleus accumbens (NAc), which preferentially encode negative and positive valence, respectively. We trained mice on a head-fixed Pavlovian discrimination task to associate two tones with a positive (ensure) or negative (air puff) outcome, and imaged BLA-NAc and BLA-CeM populations under sated, food-deprived, idle, and exercise-access conditions. Mice learned to distinguish the two tones, as demonstrated by changes in anticipatory licking (paired t-test, N=34, $p<0.0001$) and eye width (paired t-test, N=15, $p=0.013$). Following food deprivation (FD), licking behavior acutely increased, (1-way ANOVA, $p=0.006$); licking behavior increased 24 hours after exercise (1-way ANOVA, $p=0.013$). Facial expressions demonstrate that exercise mellows reactions to air puff trials (Kruskal-Wallis test, $p<0.0001$), whereas food deprivation intensifies reactions to air puff trials (Kruskal-Wallis test, $p=0.0021$), suggesting changes in discomfort thresholding following internal state change. Analysis of neural data demonstrate stated BLA-CeM and BLA-NAc populations have negative and positive biases in responsive neurons, respectively (X^2. $p=0.0059$). Following food deprivation, populations shift negatively (X^2, $p=0.065$); populations shift positively after exercise (X^2, $p=0.055$). Both populations shift bias to air puff trials following food deprivation, while maintaining different means (Mann-Whitney test, $p=0.0006$). Both populations also shift bias to ensure trials following exercise, while maintaining population differences (Mann-Whitney test, $p=0.015$). Population means demonstrate that BLA-NAc populations were affected by food deprivation in ensure and air puff trials (1-way ANOVA, $p<0.0001$), but were not affected by exercise. Alternatively, BLA-CeM populations were affected by exercise during ensure and air puff trials (1-way ANOVA, $p<0.0001$). Taken together, our findings show that food deprivation and exercise distinctly alters BLA projection-specific valence encoding, and that facial expression is sufficient to decode internal state.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

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Topic: H.04. Emotion

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T32NS115705

Title: Temporal cortical inputs to basal nucleus subdivisions: a general ventral to dorsal topography predicted by cortical granularity

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Abstract: The primate temporal cortex (TC) is an important source of auditory, visual, and polysensory input to the amygdala. The basal nucleus of the amygdala receives this information via intrinsic connections from the lateral nucleus, and also direct TC inputs. We previously found that the topography of prefrontal cortex (PFC) to basal nucleus paths can be predicted by cortical granularity. In that system, least differentiated PFC regions project broadly throughout the basal nucleus, and more differentiated regions contribute overlapping inputs topographically, moving from the parvicellular subdivision (Bpc) to the intermediate (Bi) and magnocellular (Bmc) subdivisions. Here, we examined whether TC inputs to the basal nucleus exhibit similar principles. We placed retrograde tracer injections throughout the Bpc, Bi, and Bmc in 7 Old World macaques, then mapped and quantified labeled neurons in TC areas to which we assigned a 'granularity index'. The least differentiated regions of the TC are found rostrally, with progressive patterns of lamination, and presence of layer IV, in caudal and lateral cortex. Entorhinal (ER) and perirhinal (PR) cortices are side-by-side regions, extending caudally from the temporal pole. Within the ER and PR, rostral regions are the least differentiated, with progressively greater laminar organization caudally. Sensory association regions, including the superior temporal gyrus (STG), superior temporal sulcus (STS), and inferotemporal cortex (TE), are situated lateral to the ER and PR, and are more differentiated 'isocortical' regions. Following all injections, 62% of labeled cells were found in the PR, 21% in the ER. Comparatively, the TE, STS, and STG together constituted just 11% of total basal nucleus inputs, and the parahippocampal region 6%. Labeled cells in ER and PR were found after all injections but were densest for Bpc (ER: 46% of labeled cells, PR: 70%) and Bi (ER: 41%, PR: 17%) sites (Bmc: ER 13%, PR 14%). In contrast, sensory association areas TE, STS, and STG favored the Bmc (TE: 42%, STS: 24%, STG: 44%), Bi (TE: 20%, STS: 23%, STG: 28%), and a dorsal transitional Bpc site (TE: 35%, STS: 42%, STG: 28%). The two ventral Bpc sites constituted 3%, 11%, and 1% of TE, STS, and STG inputs. In conclusion, ER and PR provide a "foundational" input of the basal nucleus, and more differentiated association cortical inputs are added dorsally, resembling the organizational rule of PFC-amygdala circuits. The ventral Bpc/Bi receive the most ER/PR inputs, while sensory association inputs add to these in the Bi/Bmc. The Bi is a key connectional bridge from the Bpc to the Bmc as ER/PR inputs taper and sensory association inputs increase.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

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Title: Evaluating ultrasonic vocalizations as a behavioral assay of psilocybin-induced changes in socioemotional processing

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Abstract: Psilocybin has demonstrated therapeutic potential across a range of psychiatric disorders, including treatment-resistant depression, post-traumatic stress disorder, and anxiety disorders. However, many commonly used preclinical behavioral assays provide only indirect measures of affective state and may be limited in their ability to detect psychedelic-induced changes in socioemotional processing. Ultrasonic vocalizations (USVs), which reflect affective and social communication in rodents, may offer a complementary, noninvasive approach for examining these behavioral effects. Current literature categorizes USVs into 22-kHz and 50-kHz call types, which are generally associated with negative and positive affective states, respectively. Additionally, these calls can be categorized by rate of call production and acoustic profile. The present study examines whether USVs detect changes in socioemotional behavior following psilocybin administration. In order to test this, twenty adult rats (10 males, 10 females) housed as pairs of socially familiar peers were assigned, using a within-subject experimental design to four USV acquisition conditions: social USVs following vehicle administration, social USV following psilocybin administration (i.p.,1 mg/kg), isolated USVs following vehicle administration, and isolated USVs following psilocybin administration (i.p., 1 mg/kg). Social USVs were recorded in the presence of a familiar peer with both rats receiving vehicle or psilocybin in an open field arena. Isolated USVs were recorded from single rats in the same open field arena. Social and isolated vocalizations were analyzed for total call number, acoustic frequency, and vocalization syllable composition. Our analyses indicate social experience and psilocybin-related differences. Rats tested in social conditions produce a greater number of USVs than rats tested in isolation, reflecting increased socioemotional processing and communication. Psilocybin administration reduces the overall vocalization production and alters vocalization frequencies (Hz) relative to vehicle-treated conditions. Additional analyses aim to dissect vocalization syllables unique to isolated and social psilocybin experience. The study forms the foundation for isolating USV signatures of psilocybin-induced changes in socioemotional behavior and emotional valence.

Disclosures: E. Ludwig: A. Employment/Salary (full or part-time):; University of Kentucky, Department of Neuroscience. **P.I. Ortinski:** A. Employment/Salary (full or part-time):; University of Kentucky, Department of Neuroscience. **N. Tavakoli:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

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Title: Bonded by Adversity: Neural and Endocrine Signatures of Stress-Induced Partner Preferences

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Abstract: Social support profoundly shapes human health, reducing all-cause mortality by up to 45% (Wang et al., 2024). This effect is mediated by social buffering, a mechanism conserved across species where the presence of a social agent attenuates the stress response (Davitz & Mason 1955; Coe et al. 1978). While stress in humans often occurs in social contexts, most preclinical models isolate animals during stress exposure (Godoy et al. 2018), limiting insight into how co-experienced stress influences future social behavior. To address this gap, we developed the Comparative Sociability assay. Here, mice in the Stressed Together (ST) group co-experience inescapable footshocks. Changes in social preference are determined in a modified 3-chamber assay, where mice choose between interacting with their co-stressed partner or another cagemate. We simultaneously performed the behavioral assay, episcope imaging of GCaMP8m-expressing neurons in the medial prefrontal cortex (mPFC), and peripheral hormone sampling within the same subjects. We compared the ST group to three control groups: Stressed Alone (SA), Unstressed Alone (UA), and Unstressed Together (UT), which controlled for individual stress exposure and social context. Our results reveal a robust sex difference in post-stress social preference (N = 36 mice, $p = 0.0005$). A linear mixed-effects model confirmed that male, but not female, ST mice developed a preference for their co-stressed partner. Both sex ($\beta = -77.58$, SE = 19.40, $t(68) = -4.00$, $p = 0.00016$) and social stimulus ($\beta = -83.99$, SE = 18.29, $t(68) = -4.59$, $p = 1.94e-05$) significantly predicted changes in social preference. Next, we investigated the neurophysiological correlates of this sex-specific behavioral phenotype in male mice only. In vivo calcium imaging showed that co-experienced stress increased medial prefrontal cortex (mPFC) responsiveness to social interactions with the co-stress partner (N = 4 mice, n = 432 cells, $p = 0.00013$). This prosocial effect holds in a classic sociability assay where ST males develop a preference for their co-stressed partner compared to a novel object. During stress exposure, ST mice showed increased peri-shock social approach, consistent with consolation-like

behavior reported in rodents (Burkett et al., 2016) (N(ST)= 14 mice, N(UT)= 8 mice , p= 0.013). Lastly, we use venous access buttons to collect blood across the behavioral time course and quantify levels of corticosterone, testosterone, and progesterone via LC-MS (N = 4 mice). Together, this work introduces a novel method for studying co-experienced stress and uncovers sex-specific effects on social behavior, neural activity, and hormone regulation.

Disclosures: J. Cressy: A. Employment/Salary (full or part-time):; UCSD. 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.; NIMH F31. **A.C. Bastuba:** None. **F. Aloboudi:** None. **M. Arinel:** A. Employment/Salary (full or part-time):; Salk Institute for Biological Studies. **S. McGriff:** A. Employment/Salary (full or part-time):; UCSD. **K. Bilokur:** A. Employment/Salary (full or part-time):; Salk Institute for Biological Studies. **S. Flores:** None. **S. Mohanta:** A. Employment/Salary (full or part-time):; Salk Institute for Biological Studies. **C. Jia:** A. Employment/Salary (full or part-time):; UCSD. **C. Parker:** None. **A. Shah:** None. **C.R. Lee:** None. **R.L. Miranda:** None. **L. Keyes:** None. **D.O. LeDuke:** None. **R. Wichmann:** None. **K.M. Tye:** None.

Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

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Title: Electrical Stimulation of the Periaqueductal Gray in Non-Human Primates Evokes Facial Expressions and Increases in Heart Rate

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Abstract: Facial expressions communicate the emotional state of an animal to social partners. While facial expressions are produced in many mammals, they are particularly well developed and stereotyped in social primates. Little is known, however, about how the brain orchestrates the playout of these socio-emotional actions. The production of other innate behaviors - such as social vocalizations, defensive responses, freezing, escape, courtship, and maternal behaviors - have all been linked to the periaqueductal gray (PAG). The PAG receives rich inputs from the amygdala - a central hub of a distributed brain network coordinating social-emotional behaviors. The PAG, in turn, sends projections to several brainstem nuclei modulating cardiovascular, respiratory, and pain responses to exteroceptive stimuli. We hypothesized, that distinct sites in the PAG might concurrently coordinate the playout of facial expressions and drive autonomic

responses associated with emotionally salient situations. To test this idea, we stimulated small regions within the rostral PAG in an awake rhesus macaque while recording facial responses and heart rate. Stimuli were 4-s trains of biphasic (200 µs/phase) pulses that incremented from 50 - 500 µA. Stimuli were delivered separately to each of 32 contacts (200 µm apart) of a microelectrode array that spanned 6 mm along the dorsoventral axis. At a few contiguous sites in the lateral PAG (span of ~ 800 µm), stimulation evoked asymmetric, threat-like expressions in the contralateral face. These evoked facial expressions appeared tightly coupled to autonomic adjustments, as evidenced by near simultaneous increases in heart rate (up to 60 bpm). Upon cessation of stimulation, heart rate directly (within 1 - 2 beats) returned to baseline levels. Little change in heart rate was observed when stimulating at sites that did not produce facial actions. These results indicate that the PAG in macaques could be an important node involved in coordinating somatic and autonomic responses in the production of aggressive expressions.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

Location: WCC Halls A-C

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Program #/Poster #: PSTR147.20/FF21

Topic: H.04. Emotion

Title: Region-Specific Oxytocin Modulation of Emotion Discrimination

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Abstract: Social cognition deficits, particularly in emotion recognition, contribute to impaired social behavior and functional outcomes in autism spectrum disorder. Impaired emotion processing is associated with peer rejection, victimization, internalizing symptoms such as anxiety and depression, and poorer social adaptation. While broad emotion recognition may remain intact, deficits emerge when subtle emotional cues are presented. Oxytocin has been proposed to enhance emotional processing by increasing attention toward socially salient cues, though clinical trials have yielded inconsistent results. Rodent models have begun to address these inconsistencies, with evidence that oxytocin influences emotion discrimination via the central amygdala. Given oxytocin's interactions with dopaminergic reward circuitry, the nucleus accumbens may further modulate motivated social behavior toward emotionally salient conspecifics. The current study aimed to investigate the relationship between central administration of exogenous oxytocin and affective discrimination behavior. Female and male C57BL/6J mice received bilateral cannulations targeting either the central amygdala (CeA) or nucleus accumbens (NAc) followed by oxytocin administration after recovery. Behavioral assays included an affective preference test and a social conditioned place preference test to assess emotion discrimination, alongside free dyadic interaction, effort-based social tasks, and anxiety

measures. Current results suggest that CeA and NAc oxytocin administration, as compared to saline administration, reduces investigation of stressed conspecifics without altering investigation of neutral conspecifics, implicating enhanced emotional state discrimination. These findings may improve our understanding of oxytocin's role in social cognition and further inform the development of new treatments for psychiatric disorders.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

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Title: Lateral hypothalamus encodes social and spatial state to drive perception-to-action transformations during competitive hunting

Authors: *S. MOHANTA[1], C. R. LEE[2], A. C. BASTUBA[3], Y. BILANIUK[5], B. CHEN[5], C. THEIS[6], M. DU[5], J. CRESSY[1], B. JOO[7], K. M. TYE[4];
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Abstract: Social decision-making requires not only reacting to the world around us, but anticipating each other - reading intentions, predicting actions, adjusting in real time - the breakdown of which underlies social deficits in autism, schizophrenia, and bipolar disorder (Soderstrom et al. 2002). This requires neural circuits that integrate internal goals, social information, and environmental context in real time. Yet the neural circuits that perform this integration remain poorly understood, in part because existing paradigms lack the naturalistic complexity needed to engage them. The Lateral Hypothalamus (LH) receives dense input from prefrontal and insular cortex that encode social variables (Razenberg et al. 2024), and previous work from our lab (Padilla-Coreano et al. 2022) showed that medial prefrontal cortex to LH projections are preferentially engaged during group behavior compared to solitary contexts,

positioning the LH as a key site through which inferred social information can modulate motivated behavior. To test this, we developed an ethological behavioral assay in which two mice (self and partner) pursue a live cricket (prey) in an open arena, preserving the full computational richness of naturalistic social decision-making. Cagemates were trained to hunt together. We then recorded LH calcium activity from both animals as dyads hunted 10 crickets per session (N=6 mice, n=533 cells). We extracted pose features and applied unsupervised clustering to discover behavioral motifs: self-chase (self pursues prey); partner-chase (partner pursues prey); co-chase (both animals pursue prey together); and social interaction (self and partner interact; prey pursuit absent). LH neurons encoded egocentric position of both prey and partner: 15.8% were tuned to prey, 22.6% to partner, and 14.9% to both (circular mean vector length compared to null distribution, $p<0.0001$). To quantify the moment-by-moment probability of a successful chase given each agent's position, we calculated “expected chase” (xC). xC captures the likelihood of a successful chase given self, partner, and prey’s positions, speed, and direction of movement. LH neurons tracked xC moment-by-moment, predicting upcoming chases up to 3 seconds in advance (17.6% of neurons tuned to xC; binomial test, $p<0.001$). Finally, LH population activity encoded current action state - chasing alone, joining a partner, or aborting a chase (Wilcoxon test, $p=0.0002$). Together, these results demonstrate that the LH continuously integrates spatial and social signals to transform inferred social context into real-time behavior, revealing a hypothalamic mechanism for flexible social decision-making.

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Poster

PSTR147: Neural Circuits of Emotion: Amygdala, Prefrontal, and Socio-Affective Systems

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Program #/Poster #: PSTR147.22/FF23

Topic: H.04. Emotion

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Title: Anatomical and Electrophysiological Definitions of Basolateral Amygdala Projections to Dorsal Striatum Subdivisions

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Abstract: The balance between the dorsomedial striatum (DMS), which encodes flexible, goal-directed behavioral strategies and the dorsolateral striatum (DLS), encoding inflexible yet efficient behavioral strategies, is critical for optimal reward acquisition under changing environmental demands. A key component driving shifts between DMS and DLS-mediated behavior is affective state, where stress shifts behavior from DMS to DLS control. The

basolateral amygdala (BLA) encodes affective components of environmental cues and projects to the dorsal striatum. However, how this structure may differentially project to the DMS versus the DLS is poorly understood. Using retrograde viral tracing methods, we demonstrate that BLA neurons projecting to the DMS and DLS constitute anatomically distinct populations. Specifically, our data demonstrates that DMS-projecting neurons reside in the basolateral subdivision of the BLA, whereas DLS-projecting neurons reside in the basomedial subdivision of the BLA. Using whole-cell patch clamp electrophysiology, our data demonstrates that while DMS- and DLS-projecting BLA neurons are anatomically distinct, they are largely uniform in their passive and active membrane properties. These findings anatomically and functionally characterize dual BLA-dorsostriatal pathways and provide a node for future investigation of these circuits' involvement in behavior.

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Title: Postmortem mapping of the connectivity of the paralaminar nucleus in macaques reveals novel cortical and amygdala projections

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Abstract: The paralaminar nucleus of the amygdala (PLA) contains a reservoir of immature neurons that mature from infancy to adulthood and into old age. This prolonged period of maturation suggests that PLA cells could be a persistent source of plasticity throughout the lifetime. A significant number of cells within PLA mature during puberty, a time that coincides with the onset of socioemotional maturation and the appearance of some psychiatric disorders. An outstanding issue with respect to PLA function, and how it may contribute to changes in the brain during development, is a full understanding of PLA connectivity across the lifetime. Because PLA comprises a long, thin band of cells ventral to the basal nucleus of the amygdala and dorsal to the lateral ventricle, targeting this structure *in vivo* using stereotaxic approaches and traditional tract tracers is challenging. In the present study we used an alternative approach adapted from a protocol that allowed us to reveal connections ex vivo in as few as 10 days (Sivukhina and Jirikowski, J Chem Neuroanat, 2021). We studied four temporal lobes from adult rhesus monkeys (*Macaca mulatta*). First, tissue blocks were bisected through the amygdala to reveal PLA. Then, the bidirectional postmortem tracer, DiI, diluted in ethyl alcohol, was

precisely injected into PLA with the aid of a fluorescent macroscope. The progression of tracer transport was visualized and monitored along the surface of the tissue. Once transport times were reached, the tissue was sectioned on a vibratome at a thickness of 80 µm. Tissue was saved in two series; one series was used for tracer analysis and the second was processed for Nissl to reveal anatomical borders within the tissue blocks. We achieved successful postmortem transport of Dil within the medial temporal lobe. PLA injections resulted in retrogradely labeled cells and anterogradely labeled boutons within the basal nucleus of the amygdala, specifically within the parvocellular and intermediate divisions, similar to previous reports. In addition, we found anterogradely labeled boutons and retrogradely labeled cells in both the entorhinal and perirhinal cortex, reciprocal connections not reported previously. Because the entorhinal cortex has widespread connections with frontal, temporal, anterior insular, retrosplenial and cingulate cortex, these findings suggest that PLA can integrate information within several cortical networks. These findings provide new insights into how the PLA contributes to the broader amygdala and cortical networks in nonhuman primates; further, this method will enable examination of PLA connections across the lifetime in both human and nonhuman primates.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.01/FF25

Topic: H.04. Emotion

Support: NC3Rs NC/Y00082X/1
BBSRC BB/Y010981/1

Title: The 3Hs (Housing, Handling, Habituation) Initiative: a framework for improved animal welfare and more translational neuroscience

Authors: J. BARTLETT[1], J. K. HINCHCLIFFE[2], G. E. PORTLOCK[1], M. G. JACKSON[1], ***E. S. ROBINSON**[1];
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Abstract: Animal models remain crucial for both fundamental research and drug development. A major challenge when studying the brain in laboratory animals is the influence of stress. Repeated acute stress arises from experiences such as handling, cage changes, weaning and regulated procedures and chronic stress is associated with the artificial housing conditions. Reducing stress in laboratory animals can improve their welfare and benefit scientific objectives. The 3Hs initiative (www.3hs-initiative.co.uk) provides a framework considering lifetime experience and methods that improve welfare focusing on Housing, Handling and Habituation. The framework is based on two core principles, 1. To minimise the use of physical restraint and,

2. To use positive reinforcement. To benefit more normal development and provide animals with opportunities to express more natural behaviours the 3Hs also considers optimal species relevant enrichment strategies which are also compatible with scientific needs. A core component of the 3Hs initiative is to provide objective evidence of the welfare benefits achieved by adopting these approaches utilising behavioural readouts of affective state, stress and arousal, and ultrasonic vocalisation. Using these methods we have validated refined housing and handling methods which reduce stress in mice and rats. We show that habituating mice to cup handling with positive reinforcement and using refined methods for substances administration that minimise physical restraint, reduces overt signs of distress, reduces time to onset of anaesthesia and improves training and baseline stability in a tethered behavioural task. We also used our objective measure of affective state to show that sexually mature male mice are in a more positive affective state when housed individually. Similar results were seen for rats with habituation to handling and refined methods for substance administration shown to reduce physiological and behavioural signs of distress and generate a more positive affective state. We also provide evidence that measuring 50kHz vocalisations in rats provide a simple, graded measure of affective state. Replacing oral gavage with substance administration in a palatable solution avoids the use of physical restraint with protocols optimised for both species and a wide range of compounds. Stress associated with routine husbandry, welfare checks and regulated procedures can also be reduced by pairing the experience with positive reinforcement. These 3Hs approaches have been shown to improve animal welfare and support better scientific outcomes meeting the ethical requirements to refine the animal experience.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

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Title: Multiplex integration of emotional and task-performance signals in the primate dorsal raphe nucleus

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Abstract: Adaptive behavior requires appropriate response selection, yet real-world decision-making occurs under distinct emotional states such as stress, in which cognitive resilience is often compromised in neuropathological disorders. Neurons in the dorsal raphe nucleus (DRN), the major source of forebrain serotonin, encode appetitive and aversive information on distinct time scales, with relatively shorter time scales for appetitive information and longer time scales for aversive information, suggesting temporally differentiated processing of emotional context. DRN neurons also encode behavioral task progression, exhibiting activity that correlates with expected reward as animals approach future rewards. However, how emotional-context signals and task-performance signals are integrated within single DRN neurons remains unclear. To address this question, we first conditioned two monkeys (*Macaca fascicularis, male, n=1; Macaca mulatta, female, n=1)* in a Pavlovian conditioning task using gradually changing visual stimuli associated with either appetitive or aversive outcome. To examine how such signals contribute to adaptive behavior, we then developed a reversal-choice task in which monkeys were required to balance flexible and stable choice strategies under appetitive or aversive emotional context. The emotional contexts were induced by presenting the conditioned visual stimuli. Stimuli associated with a reward or an air-puff selectively altered behavioral and autonomic responses, indicating the induction of distinct emotional states. We found that a subset of DRN neurons was modulated by both emotional context and task performance in a multiplex manner. Neurons preferentially responsive to aversive conditioned stimuli during Pavlovian conditioning exhibited sustained enhancement of inter-trial interval activity in aversive contexts, and this sustained activity predicted subsequent task performance. However, these neurons' activity was weak in response to task-related events. In contrast, other neuronal populations, including neurons preferentially responsive to appetitive stimuli, showed task-related modulation without context-dependent modulation during the inter-trial interval. These findings suggest that distinct DRN neuronal populations differentially integrate emotional context and task-performance signals over time. Rather than directly controlling moment-to-moment choice selection, DRN neurons may contribute to adaptive behavior by regulating cognitive readiness and performance according to emotional context.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

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Program #/Poster #: PSTR148.03/FF27

Topic: H.04. Emotion

Support: IBS-R001-Y3-2026-a00

Title: A subcortical circuit controls positive empathy in reward-naive mice

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Abstract: Empathy for positive affect promotes social cohesion, yet how animals infer and internalize others' rewards vicariously remains unclear. Most paradigms confound this process with an animal's prior knowledge of the cue-reward causality, making it challenging to isolate true affective contagion from memory-dependent responses. Here, we establish a mouse paradigm in which reinforcer-naive observer mice develop real-time preference for conspecifics reveiving reward through medial forebrain bundle stimulation, which leads to vicarious reward evidenced by conditioned place preferences. Socially embedded sounds, but not visual inputs, drive the vicarious reward. Whole-brain activity mapping identified the inferior colliculus (IC) and paraventricular thalamus (PVT) as key nodes. Stepwise functional interrogation revealed the pathway from IC to the red nucleus (RN)-PVT-zona incerta (ZI) both necessary and sufficient for the vicarious reward, but not direct hedonic reward. These results delineate a subcortical circuit that enables auditory transmission of positive valence without direct perception of the reinforcer, supporting positive affective contagion in mice.

Disclosures: J. Byun: None. **J. Kim:** None. **M. Kim:** None. **H. Shin:** None.

Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

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Program #/Poster #: PSTR148.04/FF28

Topic: H.04. Emotion

Support: Rutgers Busch Biomedical Grant

Title: Neural Processing of Math Performance Feedback in Math Anxiety

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Abstract: Developing math skills is critical for achieving academic and financial success. However, one common impediment to math achievement is math anxiety (MA), which refers to feelings of tension when an individual anticipates or participates in math, often resulting in performance decrements. Previous fMRI research has found that neural activation during the anxious anticipation of math predicts math related deficits in MA. Furthermore, performance decrements in MA were mediated by activation of the ventral striatum (VS), a key region within the brain's reward system. Activation of the VS is known to correlate with stimulus value and with positive or negative affective states. One way that researchers can investigate affective states in MA is by leveraging performance feedback. Specifically, negative performance feedback can induce negative affect and is known to produce a "punishment" response signaled

by a decrease in VS activity. Here, we tested whether VS activity for the (1) anticipation of math and for (2) negative feedback differs between individuals with high and low MA. We hypothesized that because of math-related negative affect, high MA participants would demonstrate steeper, more negative responses in the VS during the (1) anxious anticipation of math and (2) receipt of negative feedback. 57 participants (30 high MA and 27 low MA) completed a math multiplication task, as well as a control task involving memory while undergoing fMRI scanning. For each trial, participants viewed an anticipatory cue signaling whether the upcoming trial was math or memory. Participants had 4 seconds to complete each trial, and afterwards were given performance-related feedback which indicated their accuracy. We found that VS activity to (1) the anticipatory cue decreased significantly more in high MA for math compared to memory, possibly reflecting negative affect during the anxious anticipation of math. However, this effect did not significantly differ between math anxiety groups. For (2) negative feedback, counter to our prediction we found that individuals with low MA, rather than high MA, had significantly larger decreases in the VS for the math condition compared to memory. A steeper punishment response in low MA may reflect more negative affect associated with being wrong in the math domain. This work demonstrates that task domain can influence neural signals generated by anticipation and feedback, in students with high and low MA, and provides insights into the neural mechanisms through which affect can influence the learning experience.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

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Program #/Poster #: PSTR148.05/FF29

Topic: H.04. Emotion

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2163200

Title: Prosocial behavior in female prairie voles as a neural activity marker of c-Fos expression

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Abstract: Prosocial behavior is modulated by neural circuits involved in reward, emotional regulation, and empathy. The prairie vole (*Microtus ochrogaster*) is a socially monogamous and

highly social rodent, making it an ideal model for studying prosocial behaviors. The present study aims to analyze, in both sexually naïve females and pair-bonded females, whether activity in the nucleus accumbens and anterior cingulate cortex increases following exposure to an individual experiencing pain, as assessed through c-Fos expression. Additionally, we aim to determine whether prosocial behavior induces oxytocin release.Sexually naïve females and females that had established a pair bond were used. Prosocial behavior was evaluated using a social approach test (15 min), in which approach toward a conspecific experiencing pain was quantified. The apparatus consisted of an arena composed of three interconnected cylinders; each contained a perforated transparent acrylic chamber housing a stimulus animal. Control females were tested in the absence of males. Experimental sexually naïve females interacted with a male experiencing pain induced by a plantar formalin injection and with two males not experiencing pain. For pair-bonded females, the stimuli consisted of their sexual partner experiencing pain and two unfamiliar males without nociception. Females were euthanized 75 min after the behavioral test, and their brains were processed for c-Fos and oxytocin detection using immunofluorescence.Preliminary data show that sexually naïve females tended to spend more time with the unfamiliar male treated with formalin, whereas pair-bonded females tended to remain in closer proximity to their sexual partner experiencing nociception. These findings suggest that female prairie voles display prosocial behaviors in response to the distress of a conspecific. Analysis of c-Fos expression and oxytocin will determine whether changes in neuronal activity and oxytocinergic signaling are associated with sexual experience and pair-bond formation.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.06/FF30

Topic: H.04. Emotion

Title: Multispectral Skin Sensing for Non-Invasive Detection of Psychological Stress

Authors: *V. BARYGINA[1], E. BARIA[2], F. S. PAVONE[3];
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Abstract: Skin contains multiple matrices, including tissue, interstitial fluid, blood-derived components and sweat, that can reflect physiological and psychological states. Current approaches to access the psychological stress are either invasive, time-consuming, costly, or limited to a restricted number of molecular targets. This study investigates the potential of a

high-throughput, multimodal optical sensor for the non-invasive detection of psychological stress through skin spectroscopy. Raman, reflectance, fluorescence and spectrally resolved fluorescence-lifetime signals were acquired from the palmar skin of healthy volunteers using a multimodal fibre-probe device. Psychological stress was induced through the Montreal Imaging Stress Task (MIST), which combines cognitive load, time pressure and social evaluative threat. Electrodermal activity, together with heart-rate-related physiological measures, was monitored using wearable biosensors to confirm stress induction. Spectral data were processed to correct instrumental artefacts and analysed using principal component analysis and supervised classifiers. The multimodal combination of optical techniques showed higher robustness than individual modalities in discriminating control and stress conditions. On palmar skin, after exclusion of one participant who did not show an electrodermal stress response, the multimodal classifier achieved 100% accuracy and 100% AUC in distinguishing “no-stress” from “stress” states. To move beyond binary stress detection and explore the molecular basis of the observed spectral changes, a reference database of stress-related biomolecules was initiated. Candidate biomarkers, including cortisol, interleukins, TNF-α, neuropeptide Y and sodium lactate, were measured in solid and diluted states using the same multimodal optical platform. Preliminary spectral unmixing analyses indicated stress-related variations in selected biomolecular signatures, including significant differences in several molecules' quantities. These preliminary results support the feasibility of multispectral optical skin sensing as a rapid, non-invasive approach for detecting psychological stress and exploring its molecular signatures. The technology may contribute to future portable or wearable systems for mental health monitoring, stress assessment in high-responsibility professions, and objective biomarker-based studies in clinical populations.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

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Program #/Poster #: PSTR148.07/FF31

Topic: H.04. Emotion

Title: Cholinergic Modulation of Approach-Avoidance Conflict Resolution in Mice

Authors: *O. TORRES-PINEDA[1], R. J. FLORES GARCIA[2];
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Abstract: Introduction: Approach-avoidance conflict resolution requires integrating information to guide behavior when rewards and risks are both present. This process is disrupted in psychiatric disorders, including anxiety, depression, and substance use disorders, which involve maladaptive approach and avoidance. Prior work links depression to dysregulated ACh, and preclinical studies implicate ACh in stress-related behavior. However, the role of cholinergic

signaling in approach-avoidance conflict remains unclear. **Methods:** We used the platform-mediated avoidance task to examine cholinergic contributions to conflict resolution. Mice learned to nosepoke for liquid Ensure during a reward-predictive light cue. During conflict training, the light cue was paired with an aversive 30-s tone that co-terminated with a mild 2-s footshock to generate five trial types: light-only, tone-only, full overlap, light-then-tone, and tone-then-light. Footshock was avoidable by stepping onto a platform opposite the reward port. In Experiment 1, adult male and female C57BL/6 mice completed five days of reward and conflict training, then were assigned to groups testing nicotinic blockade with mecamylamine [dose] or muscarinic blockade with scopolamine [dose]. Within each group, mice received vehicle and drug in a within-subjects Latin square crossover design, with off-drug sessions between tests. In Experiment 2, mice received a viral infusion of the GRAB-ACh3.0 sensor and optical fiber implantation targeting infralimbic cortex. Mice completed eight days of reward training, eight days of conflict training, three light-only sessions with higher-value Ensure and no tone-shock presentations, and eight additional conflict sessions with higher-value Ensure. **Results:** Mecamylamine did not affect conflict resolution. In contrast, scopolamine produced a trial-type-specific effect where mice failed to disengage from nosepoking when reward and threat cues were co-presented. During reward training, medial prefrontal ACh increased during inter-trial intervals and decreased after reward-cue presentation and reward-port engagement. During conflict training, ACh increased during footshock delivery and, after mice learned to avoid, during the shock-predictive tone. **Conclusions:** These findings suggest that muscarinic signaling may influence approach-avoidance conflict resolution under competing reward and threat. mPFC ACh dynamics were modulated by reward- and threat-related events, suggesting that prefrontal cholinergic activity tracks salient task features.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

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Title: Hormonal Contraceptives Alter Depression Symptoms and the Stress System in College Freshmen

Authors: *C. A. TURNER[1], H. KHALIL[3], A. ONICA[1], V. MURPHY-WEINBERG[1], F. LI[1], C. STACK[1], J. F. LOPEZ[4], S. J. WATSON, Jr.[2], H. AKIL[1];

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Abstract: Hormonal contraceptives (HCs) are widely used, yet their impact on depression symptoms remains unclear, especially during early adulthood. This study explores the relationship between HC use and future depression in relation to the Trier Social Stress Test (TSST) in a cohort of female college freshmen at the University of Michigan (N=365) from 2019-2024. We collected a number of self-report questionnaires at the start of the freshmen year on these subjects, including the PHQ-9 for depression symptoms. We performed the TSST during the school year on a subset of subjects and collected follow-up mood questionnaires quarterly, along with HC use. Overall, subjects on HCs had significantly higher depression scores at follow-up. Non-HC users experienced an increase in depression incidence during the freshman year, rising from 19.3% at baseline to 31.4% at follow-up, a 63% increase in incidence. In comparison, HC users rose from 19% at baseline to 39.4% at follow-up, a 107% increase in incidence. This divergence suggests that while college-related stressors affect all students, HC use may be associated with an amplified or altered mood response during this period. The neuroendocrine stress profile was notably different between the HC users and non-users. In particular, in the context of the TSST, females on HCs showed much higher CORT levels throughout the entire test period coupled with a significantly blunted ACTH response to the stressor. Interestingly, HC users also exhibited higher baseline fasting cortisol levels relative to non-HC users. More broadly, many of the typical stress related correlations fell apart on HCs, suggesting that HCs may be altering many aspects of the neuroendocrine stress response in these subjects. In summary, early adulthood represents a sensitive period for hormonal and stress regulation, and HC use during this time may interact with psychosocial stressors to influence emotional well-being. It will be important to better define the heterogeneity of the psychological response to HCs in this age group and to determine whether specific formulations of HCs are more or less conducive to the psychological and endocrine sequelae we observed.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

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The Hope for Depression Research Foundation
The Pritzker Neuropsychiatric Disorders Research Consortium Fund LLC

Title: Determinants of antidepressant usage and efficacy in college freshmen

Authors: C. STACK[1], ***H. KHALIL**[3], C. A. TURNER[2], V. MURPHY-WEINBERG[1], A. ONICA[1], F. LI[1], J. F. LOPEZ[4], S. J. WATSON[5], H. AKIL[1];
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Abstract: The Michigan Freshman Study aims to identify biomarkers of resilience and vulnerability to stress in college freshmen. Here, we investigate antidepressant (AD) usage in this sample of freshmen. We are looking to identify markers of AD usage and determine the efficacy of ADs in treating depression and anxiety in our cohort. Our sample consists of 749 University of Michigan freshmen (455 females, 294 males) between 2015-2024. At the start of the academic year the freshmen were genotyped, and a battery of self- report questionnaires were used to characterize subjects' psychological state, trait and family history. Subjects were surveyed quarterly on clinical rating scales (the PHQ-9 for depression and GAD-7 for anxiety) and their medication usage. In our combined cohort, 20% of females and 10% of males took ADs during their freshman year. Subjects with comorbid depression and anxiety were significantly more likely to be taking ADs. Moreover, ADs were by far the most prevalent psychiatric medication in this population, and AD usage increased significantly during the COVID-19 pandemic. Usage has been decreasing in females since its peak in academic year 2019-2020, while male usage continues to increase. Interestingly, about half the subjects taking ADs still met criteria for depression or anxiety during the freshman year leaving open the question of AD efficacy in these subjects. Several factors appear to contribute to treatment responsiveness in this cohort and will be discussed. Our analysis highlights the prevalence of depression and anxiety symptoms in this cohort of young adults and the impact of the pandemic on them. It identifies factors that contribute to AD efficacy and raises the question of whether AD usage is being optimized to combat mood and anxiety disorders in this population, and whether additional, complementary strategies may be needed.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

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Program #/Poster #: PSTR148.10/GG2

Topic: H.04. Emotion

Title: Emotion vector coding in the human anterior cingulate cortex

Authors: *S. GORDEEV[1], M. FRANCH[2], B. Y. HAYDEN[3];
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Abstract: Understanding how emotional context shapes meaning is a fundamental challenge in affective neuroscience. Recent work in artificial intelligence has demonstrated that large language models develop low-dimensional representations of emotional state, raising the possibility that biological neural systems may organize emotion in a similar manner. Here, we investigated how emotional affect influences neural representations in the human hippocampus and anterior cingulate cortex (ACC) during naturalistic speech comprehension. Single-neuron activity was recorded from epilepsy patients listening to engaging, long-form podcasts. To dynamically map the narrative's affective terrain, we leveraged automated speech emotion detection (audEERING) to assign continuous, signed valence and arousal markers to each spoken word, and semantic representations were extracted using GPT-2 embeddings. We first examined whether emotional affect predicted neural activity and then tested whether emotional state altered the neural representation of semantic information. Valence and arousal significantly predicted neural responses in both regions, with 45.2% of hippocampal neurons and 49.6% of ACC neurons significantly modulated by affective state. Our findings reveal that single neurons in both the hippocampus and ACC robustly encode valence and arousal. Crucially, rather than segregating these dimensions into separate anatomical streams or distinct neural populations, we show that valence and arousal jointly modulate the responses of individual neurons. At the population level, semantic representations differ across emotional contexts: representational similarity analyses revealed distinct neural semantic geometries under high and low affect conditions, and semantic tuning vectors exhibited reduced alignment across emotional states. These findings indicate that emotional affect does not merely modulate neural activity, but reshapes the representational structure through which meaning is encoded. By showing that single human neurons integrate V and A to represent continuous affective states, our results provide direct empirical alignment with the geometry of functional emotion concepts observed in deep artificial networks, suggesting a convergent computational principle for processing human emotional dynamics.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

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Department of Science and Technology-Promotion University Research and Scientific Excellence (DST-PURSE, SR/PURSE/2024/354)

Title: Central nucleus of amygdala regulates anger-like behavior in rats: Role of dopamine and serotonin

Authors: *D. K. SAHARE[1], B. B. DUDHABHATE[2], A. J. SAKHARKAR[3], N. K. SUBHEDAR[4], D. M. KOKARE[1];
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Abstract: Anger is a fundamental emotion characterized by feelings of hostility, frustration, social provocation and agitation that play an integral role in affective life. Studies on the neurobiology of anger, although scarce, hint at the role of serotonin (5-HT) in the framework of amygdala. Earlier studies suggests that the level of dopamine (DA) elevated and level of 5-HT reduced in the aggression. CeA innervates serotonergic inputs from dorsal raphe nuclei, dorsal subdivision (DRD) and dopaminergic inputs from ventral tegmental area (VTA). We test the hypothesis that serotonergic and dopaminergic inputs to the central nucleus of amygdala (CeA) may modulate the expression of anger-like phenotype in rats. Employed the protocol based on the principle that hungry rats, exposed to food but access denied, engage in intense biting (anger-like phenotype). The biting activity (number of bites and biting duration) was monitored. Food denied hungry rats (food on display), showed increase in biting activity, locomotor activity, heart rate and blood pressure as compared to control group rats. Moreover, level of serum corticosterone and nor-epinephrine increased during biting activity. Increase in population of tyrosine hydroxylase immunoreactive cells in the VTA. However, decrease in the population of 5-HT immunoreactive cells in DRD during biting activity task. Using microdialysis HPLC-ECD system assayed level of DA, DOPAC, 5-HT and 5-HIAA in the effluents collected from CeA. Increase in DA and DOAPC however, decrease in 5-HT and 5-HIAA during anger-like behavior. Increased level of DA D1 and D2 receptor gene expression and decreased level of 5-HT1A receptors gene in the CeA. Bilateral, intra-CeA administration of D2 agonist (quinpirole) or 5-HT1A antagonist (WAY100635) increased the biting behaviour, but D2 antagonist (sulpiride) reversed the effect. Intra-CeA administration of WAY100635 + quinpirole, both at sub-effective doses, potentiated the biting behaviour. Thus, suggesting that the inputs to the CeA from the dopaminergic neurons of the VTA elevates anger-like behaviour, while serotoninergic neurons from DRD may reduce the response.

Disclosures: D.K. Sahare: None. **B.B. Dudhabhate:** None. **A.J. Sakharkar:** None. **N.K. Subhedar:** None. **D.M. Kokare:** None.

Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.12/Web Only

Topic: H.04. Emotion

Title: Multi-scale functional network connectivity links to negative symptom assessments in psychosis spectrum disorders

Authors: *C. M. CORNELL[1], V. CALHOUN[2];
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Abstract: A lack of biological grounding in psychiatric disorder diagnosis reflects an artifact of the complex etiology of psychiatric disorders. Active research on generalizable neuroimaging-based biomarkers of psychiatric disorders continues to produce promising insights. Spatially constrained intrinsic connectivity networks (ICNs) enable refined individual-specific analysis of functional connectivity. We use the NeuroMark 2.2 ICN template to derive individual functional network connectivity (FNC) features and analyze the association with PANSS-Negative and PANSS-Positive scores in individuals with schizophrenia, schizoaffective disorder, and bipolar disorder. FNC features are derived for 1,239 subjects from the B-SNIP1 and B-SNIP2 datasets. Three significant ICN-to-ICN edges were identified in an edge-by-diagnosis interaction regression model of PANSS-Negative scores. Edge 1 includes the left medial occipitotemporal cortex and the inferior postcentral gyrus. Edge 2 includes the ventromedial occipitotemporal cortex and the right insula. Edge 3 includes the left medial occipitotemporal cortex and the right insula. For each of the three edges, linear regression showed that higher edge strength for individuals diagnosed with schizophrenia was associated with higher PANSS-Negative scores, whereas higher edge strength in individuals diagnosed with schizoaffective disorder is associated with lower PANSS-Negative scores. The right insula is implicated in abnormal modulation of central executive and gray matter volume reduction in the occipitotemporal cortex has been associated with negative symptoms for individuals with schizophrenia. These findings suggest a functional relationship among these regions and their association with PANSS-Negative scores. Overall results demonstrate the value of derived spatially constrained ICN features in investigating neuroimaging-based biomarkers for psychosis spectrum disorders.

Disclosures: C.M. Cornell: None. **V. Calhoun:** None.

Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.13/GG5

Topic: H.04. Emotion

Support: Philanthropic funding: Paul Margolis Charitable Trust

Title: Acute and Post-acute dose-dependent effects of psilocybin on behaviors and neurobiological markers

Authors: *P. TIWARI[1], B. W. JENKINS[3], C. F. MOORE[2], C. BERITELA[1], D. YADEN[1], E. M. WEERTS[1];
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Abstract: Background: Emerging evidence suggests that psychedelics show immense promise for treating a range of neuropsychiatric disorders through a spectrum of acute and post-acute behavioral modifications. Here we systematic characterize the behavioral effects of the psychedelic psilocybin on spontaneous behaviors acutely, and on task-dependent behaviors acutely and post acutely, and identify the change sin neuronal activation pattern and neural plasticity in brain regions associated with executive function, and anxiety- and compulsive-like behaviors. Methods: In the current study, male and female Sprague-Dawley rats were administered psilocybin (0.5, 1mg/kg, 1.5mg/kg, i.p.) or its vehicle (saline). In addition to the widely studied head-twitch response (HTR), five additional spontaneous behaviors that were modulated by psilocybin (immobility, rearing, grooming, sniffing/digging, and circling) were assessed immediately after psilocybin administration. Animals were also tested on context-dependent tasks to assess compulsive and anxiety-like behaviors, using marble burying test (MBT) 20 minutes and 4 hours post psilocybin administration to investigate acute and post-acute effects on compulsive-like response, and open field test (OFT) and acoustic startle for post-acute changes in anxiety-like behaviors. Brains were collected 2 hours and 48 hours post psilocybin intervention. Immunofluorescence assays were performed in target brain regions of prefrontal cortex (PFC) and basal ganglia (BG) to investigate acute and post-acute changes in neuronal activation pattern using c-Fos marker and change in neural plasticity using markers for perineuronal nets (PNNs) around the parvalbumin (PV) neurons. Results: There is a distinct dose-response profiles in both sexes for acutely measured spontaneous behaviors. Compulsive-like digging behavior decreased acutely, but not post-acutely, in a dose-dependent manner as measured on MBT. There was no post-acute effect of psilocybin on anxiety measures assessed using OFT and acoustic startle. Analysis is ongoing to investigate associations between change in c-Fos activation and PNN numbers with change in behaviors on psilocybin administration. Conclusion: Together, our findings highlight the actions of psilocybin in a dose-dependent manner on a broad range of behaviors with possible insights into neural markers in target brain regions, both acutely and post-acutely. This sstudy can provide a framework for investigating the neurobiological effects of psilocybin in Sprague-Dawley rats within a widely used physiologically relevant dose-range.

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Poster

PSTR148: Positive and Negative Affective States: Circuits and Correlates

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR148.14/GG6

Topic: H.04. Emotion

Title: Anticipating Good Things: Enhanced cognitive performance and hippocampal plasticity in positive emotion-trained male and female rats

Authors: ***K. G. LAMBERT**[1], S. HARTVIGSEN[2], E. M. BYRNES[4], M. H. KENT[5], K. BUDGE[6], I. DILANDRO[1], M. ZAMBROTTA[1], P. PFAFF[3], O. HARDING[2];
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Abstract: Positive emotions are increasingly recognized as important contributors to brain health and psychological resilience, yet their underlying neurobehavioral mechanisms remain understudied. Past research in our lab using the Unpredictable Positive Event Response (UPER) training paradigm has revealed evidence of enhanced positive affect, including increased optimism, exploration, and appetitive ultrasonic vocalizations. In the current studies, we investigated the influence of UPER training on cognitive performance in the Dry Land Maze (DLM), a foraging-strategy assessment. Consistent with previous studies, rats underwent 4-5 weeks of UPER training involving anticipation of rewarding experiences, including delayed sweet food rewards, access to an enriched environment (Rat Park), and consumption of sunflower seeds. The enriched controls (ENR) were exposed to the same stimuli and rewards at one time, thereby minimizing the anticipation interval. Additionally, the standard control (CNTL) rats were exposed to standard laboratory housing. In the initial study, the latency to successfully complete the first test trial in the DLM was significantly shorter than observed in the enriched control and standard control groups ($p=.02$/training effect); further, the UPERs had fewer errors on the last test trial ($p=.03$). Across the three test trials, only the UPER group exhibited the expected progressive reduction in latency, consistent with efficient learning of the task. In a follow-up study with a different cohort of animals, the brains were assessed following UPER or ENR training for the expression of BDNF mRNA in the dorsal hippocampus. UPER rats exhibited greater dorsal hippocampal BDNF mRNA expression than ENR animals ($p = .05$) despite equivalent exposure to rewards and enrichment, a finding that may contribute to the efficient learning strategies observed in the DLM. Together, these past and current findings suggest that repeated anticipation of positive experiences enhances affective expression, cognitive performance, and hippocampal plasticity. These convergent behavioral and neurobiological effects are potentially relevant for interventions designed to promote resilience and reduce vulnerability to mood and anxiety disorders.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.01/GG7

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant F32DA060662-01

Title: Temporal Dynamics of Cocaine-Elicited Dopamine Govern How Drug Cues Gain Value

Authors: *M. Z. LEONARD[1], T. CLARITY[1], A. KONOMI PILKATI[2], K. 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 of 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. Mice expressing the fluorescent dopamine sensor dLight1.2 or the calcium indicator GCaMP8 in the nucleus accumbens (NAc) received the same dose of intravenous cocaine (3.0 mg/kg) delivered over 3, 30, or 100 seconds. We quantified dopamine dynamics and single-cell activity across infusion conditions and assessed how cocaine delivery rate influenced cue-drug learning using conditioned reinforcement procedures. Cocaine had reproducible effects on cellular activity across all conditions; however, the time course and number of modulated cells varied as a function of injection speed. Rapid (3s) drug infusions elicited peak DA levels approximately 6-times faster than when the same dose was infused over 100s, while producing only a modest increase in maximal DA. Following repeated cue-drug pairings, stimuli associated with rapid cocaine delivery (3s-Cue) acquired substantially greater conditioned motivational value than cues paired with slower infusions (100s-Cue). Mice exhibited more vigorous instrumental responding to obtain the 3s-Cue in the absence of cocaine, demonstrating enhanced conditioned reinforcement. In parallel, 3s-Cues elicited larger phasic dopamine responses and recruited more stable cue-responsive neural ensembles than 100s-Cues, suggesting that rapid drug delivery strengthens both the neurochemical and population-level representations of drug-associated stimuli. Notably, delaying the onset of a 3s cocaine infusion was sufficient to attenuate the conditioned reinforcing effects normally produced by rapid drug delivery. Together, these findings demonstrate that cocaine pharmacokinetics strongly influence dopamine signaling, striatal ensemble dynamics, and the motivational properties acquired by drug-paired cues. Rapid drug delivery may enhance addiction liability by increasing the temporal contiguity between drug-evoked dopamine signals and predictive environmental stimuli, thereby promoting the formation of stronger and more persistent drug-cue associations.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.02/GG8

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA

Title: H2A.Z dysregulation during cocaine withdrawal modulates drug relapse behavior

Authors: *E. P. CHEN[1], M. ESTILL[1], Y. YIM[2], V. KONDEV[1], B. T. KIPP[1], E. KAHN[3], E. J. NESTLER[4];
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Abstract: Human and animal studies on drug addiction have demonstrated distinct behavioral and neuronal gene expression changes that occur during periods of prolonged abstinence, suggesting a role for stable epigenetic mechanisms that mediate long-lasting gene priming and desensitization that contribute to drug relapse. Recently, we demonstrated that H2A histone family member Z (H2A.Z), a variant of histone 2A, is dysregulated after prolonged cocaine withdrawal in the mouse nucleus accumbens (NAc) (Mews et al., *Sci Adv*, 2024). However, H2A.Z's mechanism of action and role in relapse behavior have yet to be elucidated. Here, we characterize H2A.Z dynamics in the NAc over the course of chronic cocaine exposure and withdrawal and further define the ways in which H2A.Z in the NAc affects cocaine action. We performed cleavage under targets and release using nuclease (CUT&RUN) to map H2A.Z enrichment across the genome at 24 hours or 4 weeks after chronic cocaine exposure. To investigate associated epigenetic regulation, we simultaneously performed CUT&RUN for histone H3 Lys 4 trimethylation (H3K4me3) and H3H27me3 to map how H2A.Z affects gene activation (H3k4me3-bound domains), gene repression (H3k27me3-bound domains), or gene priming (H3k4me3/H3k27me3 bivalent domains). To directly assess the causal role of H2A.Z in controlling cocaine reward, we virally manipulated H2A.Z in the mouse NAc and subjected H2A.Z-modified mice in a cocaine conditioned place preference (CPP) paradigm. We demonstrate that there is a depletion of chromatin-bound H2A.Z over the course of cocaine withdrawal. H3K27me3 is depleted over the course of withdrawal associated with H2A.Z depletion, whereas in contrast no change is seen in H3K4me3. In fact, we find that H3K27me3 depletion preferentially occur at H2A.Z/H3K4me3 bivalent domains, suggesting that H2A.Z binding at H3K4me3 sites is required for H3K27me3 deposition. Gene ontology analysis reveals that H3K27me3 sites predominately involve genes associated with synaptic plasticity, a finding that is unique to H3K27me3-bound regions. H2A.Z1- and H2A.Z2-KO CUT&RUN experiments confirm that H2A.Z is required for H3K27me3 at bivalent domains, and is predominantly an H2A.Z1-driven process after cocaine exposure. Direct cell-type-specific and variant-specific viral manipulation of H2A.Z in the NAc bidirectionally influences cocaine conditioning behavior, demonstrating H2A.Z's potential to modulate the rewarding effects of cocaine. Taken together, we demonstrate that dysregulation of H2A.Z during prolonged cocaine withdrawal influences the epigenetic landscape, gene priming mechanisms, and downstream relapse behavior.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.03/GG9

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH R01DA038613
UMSOM Bridge Funds
NIH/NIDA Grant F32DA066191

Title: The effects of ventral hippocampus Drp1 knockdown on cocaine reinforcement and cocaine seeking

Authors: *S. N. SCOTT, R. CHANDRA, M. LOBO;
Neurobio., Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Mitochondrial dynamics are critical regulators of neuronal function and have emerged as important contributors to substance use disorders. We have previously shown that dynamin-related protein 1 (Drp1), a key mediator of mitochondrial fission, contributes to cocaine-induced neuroadaptations in the nucleus accumbens (NAC\c). Specifically, mitochondrial fission promotes synaptic plasticity and drug-seeking behavior during acute abstinence. Furthermore, circuit-based studies uncovered altered plasticity at ventral hippocampus (vHippo)-NAc synapses. However, the role of mitochondrial fission within the vHippo, a region involved in contextual reward learning and relapse-related circuitry, remains unclear. To investigate the role of vHippo Drp1 signaling in cocaine use-disorder-related behaviors, male and female mice received bilateral intra-vHippo infusions of a viral vector expressing Drp1-targeting miRNA to knockdown Drp1 or control construct. Cocaine reward was then assessed using conditioned place preference, followed by intravenous cocaine self-administration (IVSA) and cocaine seeking after 24 hours of abstinence from IVSA. Following behavioral testing, brains will be collected for histological verification of viral expression and assessment of Drp1 knockdown efficacy. Additional analyses will examine mitochondrial morphology and neuronal activation within the vHippo. This experiment is currently ongoing. However, based on the established role of Drp1 in mitochondrial fission and cocaine-induced neuroplasticity, we expect that Drp1 knockdown within the vHippo will attenuate cocaine reward, reduce cocaine self-administration, and decrease cocaine seeking relative to controls. We further anticipate that these behavioral effects will be associated with reduced mitochondrial fragmentation and altered neuronal activation in reward-related brain regions. These studies will provide novel insight into the role of vHippo mitochondrial dynamics in cocaine-related behaviors and relapse-like vulnerability.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.04/GG10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R0DA038613

Title: Acute and Chronic Cocaine Exposure Differentially Alters Striatal Mitochondrial Respiration

Authors: *S. GANAPATHY-KANNIAPPAN[1], C. A. CALARCO[3], R. CHANDRA[4], A. KASHYAP[5], M. ROWELL[2], S. N. SCOTT[6], S. LIU[7], B. M. POLSTER[8], M. LOBO[9]; [2]Neurobio., [1]Univ. of Maryland Baltimore, Baltimore, MD; [3]Burnett Sch. of Biomed. Sci., Univ. of Central Florida, Orlando, FL; [4]Univ. of Maryland, Baltimore, Baltimore, MD; [5]USC, Ellicott City, MD; [6]Sch. of Life Sci., [7]Pharmacol. and Toxicology, Univ. of Maryland Sch. of Med., Baltimore, MD; [8]Anesthesiol., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [9]Anat. and Neurobio., Univ. of Maryland SOM, Baltimore, MD

Abstract: Multiple lines of evidence indicate that cocaine exposure disrupts brain energy metabolism, particularly glucose utilization. Our previous studies on brain mitochondria—central regulators of cellular bioenergetics—demonstrated that cocaine modulates mitochondrial function in a cell type-specific manner. Specifically, cocaine alters mitochondrial dynamics, morphology, and the transcriptional regulation of mitochondria-associated genes. However, its impact on mitochondrial metabolic capacity remains poorly understood. In the present study, we investigated the effects of cocaine on mitochondrial respiration. Using mouse models, including wild-type (C57BL/6) and transgenic D1-Cre line, we assessed the respiratory capacity of striatal mitochondria following both acute and chronic cocaine exposure. To examine cell subtype-specific effects, particularly in D1 receptor-expressing neurons, we employed a mitochondria-targeted tagging approach (Mito-Tag; 3×HA-EGFP) to isolate neuron-specific mitochondrial populations. Mitochondrial respiratory function was evaluated using the Seahorse XFe96 Extracellular Flux Analyzer, and ATP production capacity was quantified under both acute and chronic exposure paradigms. Our results reveal that cocaine exposure differentially alters mitochondrial oxygen consumption rates in a sex-dependent manner. Furthermore, both the abundance of metabolically active mitochondria and ATP production rates varied significantly between male and female mice. Ongoing studies aim to elucidate the molecular mechanisms driving these sex-specific bioenergetic alterations.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.05/GG11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Intramural Research Program

Title: Acute cocaine and abstinence drive opposing changes in prefrontal regulation of striatal dopamine

Authors: *A. CARR[1], R. RIMONDINI[2], J. SHIN[4], H. C. GOLDBACH[5], D. DIAZ-URBINA[3], R. BOCK[6], V. A. ALVAREZ[2];
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Abstract: Cocaine, a stimulant drug of abuse, is known for its highly reinforcing properties and capacity to impair cognitive control. It is well established that cocaine works as a monoamine transporter blocker, elevating striatal dopamine (DA) through midbrain reward circuitry and contributing to its rewarding effects. However, the involvement of the prefrontal cortex (PFC), a major cortical area implicated in cognitive control, is less understood and critical towards understanding the circuitry underlying the compulsive drug-seeking and relapse vulnerability observed in addicted individuals. In this study, we examine inputs to the striatum from the PFC and how the effects of cocaine lead to long-term adaptations that may drive the maladaptive components of addiction. We first examined the acute effects of cocaine and then extended our paradigm to study how repeated exposure and abstinence affect this corticostriatal circuit. Mice received daily injections of cocaine (15 mg/kg, i.p.) or saline for 5 days, and recordings were performed either immediately or following 14 days of abstinence. DA release in the dorsomedial striatum (DMS) was measured via fast-scan cyclic voltammetry (FSCV) in brain slices and fiber photometry in head-fixed mice. Both in vitro and in vivo recordings reveal that cocaine acutely suppresses striatal DA signals evoked by PFC stimulation. Previously cocaine-treated mice do not show changes in PFC-evoked DA release immediately following the injection paradigm. However, after the abstinence period, these mice exhibited enhanced PFC-evoked DA release compared to saline controls. Notably, longitudinal in vivo recordings reveal that this potentiation is not sustained. While saline-treated mice show progressive increases in PFC-evoked DA responses across days of stimulation, cocaine-treated mice exhibit a decline over the same period, suggesting blunted corticostriatal plasticity following abstinence. These findings collectively suggest that cocaine induces lasting and dynamic changes in PFC-striatal connectivity that evolve across abstinence. Lastly, ongoing work is utilizing intravenous self-administration (IVSA) paradigms, which allow for the differentiation of contingent versus non-contingent cocaine exposure and aim to determine whether the volitional nature of drug intake further shapes these corticostriatal adaptations and their relationship to addiction-like behaviors and relapse vulnerability.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant P30DA048472, Center for Neural Circuits in Addiction, University of Minnesota
Medical Discovery Team on Addiction, University of Minnesota

Title: Differential effects of cocaine experience on nucleus accumbens input-specific ICSS strategies

Authors: *F. A. IACOBUCCI[1], E. B. LIND[2], M. ESGUERRA[2], M. J. THOMAS[2];
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Abstract: The nucleus accumbens (NAc) integrates cortical and limbic inputs to regulate motivation, reward, and affective states. Repeated drug exposure disrupts this integration, biasing activity toward drug-seeking over natural rewards. Our lab has shown that chronic cocaine exposure potentiates glutamatergic projections to the NAc. This shift promotes relapse vulnerability, establishing the NAc as a key neural substrate for substance use disorders. To investigate how cocaine experience (abstinence or re-exposure) alters input-specific reinforcement strategies, C57BL/6J mice underwent an intracranial self-stimulation (ICSS) paradigm following 5 days of chronic cocaine exposure, followed by abstinence or cocaine re-exposure. Optogenetic stimulation was delivered to either medial prefrontal cortex (mPFC) or ventral hippocampal (vHPC) terminals in the NAc shell expressing channelrhodopsin (10 Hz, 465 nm, 5 ms pulse width). Animals freely explored an open-field arena containing four visually distinct quadrants, with stimulation triggered upon entry into a designated quadrant. Cocaine experience differentially altered ICSS-driven place preference depending on the stimulated input. Notably, differences in stimulation exposure arose from distinct behavioral strategies for obtaining reinforcement rather than overall preference alone. Prior to cocaine re-exposure, behavior was characterized by greater mPFC influence, consistent with flexible, action-guided control strategies. Following re-exposure, behavioral control shifted toward vHPC-dependent contextual strategies, resulting in context-biased reward seeking, and reduced mPFC influence. These findings suggest that cocaine experience shifts behavioral control in this task from PFC-mediated action strategies to vHPC-mediated contextual strategies, biasing reinforcement seeking in an input-specific manner and revealing dissociable contributions of cortical and hippocampal NAc inputs to relapse-relevant behavior.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

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Program #/Poster #: PSTR149.07/GG13

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000467
ZIA-DA000434

Title: Incubation of discriminative stimulus-controlled cocaine craving is associated with brain-wide neuronal activation in rats

Authors: *J. LEE[1], A. R. HOLMES[2], A. SOBUKUNOLA[3], Y. GERA[4], O. BERKO[5], D. PHAM[6], M. BRENNER[3], V. A. LENNON[7], O. R. DRAKE[8], J. H. CHOI[9], D. LEWIS[3], S. J. WEBER[10], L. E. KOMER[11], K. E. SAVELL[12], J. M. BOSSERT[14], Y. SHAHAM[15], B. T. HOPE[16], R. MADANGOPAL[13];
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Abstract: Background: Cues previously associated with drug self-administration can precipitate relapse long after the last drug-taking experience. We previously reported that rats' response to cocaine-associated discriminative stimuli (DSs) progressively increases (*or incubates*), during the first 60 abstinence days and persists to 300 days. Here we used the activity marker Fos to map brain-wide activation associated with DS-controlled cocaine seeking during early and late abstinence.
Methods: We trained rats to self-administer cocaine during DS+ trials (cocaine available upon lever press; 0.75 mg/kg/infusion; no drug-paired CSs) and but not DS− trials (cocaine unavailable) during the same session. Next, we tested rats for cocaine seeking under extinction conditions after 1 or 21 days of abstinence and extracted brains either immediately after the 90-min test (day 1 or day 21 test groups) or from the homecage (no-test group).
Results: We observed reliable DS-controlled cocaine self-administration and incubation of DS-controlled cocaine relapse during abstinence. Fos-based activity mapping identified multiple cortical, striatal, and thalamic regions showing (1) time-independent increased activation following DS-controlled relapse versus no-test controls, and (2) time-dependent increase in activation during the relapse tests on abstinence day 1 versus day 21.
Conclusions: Incubation of DS-controlled cocaine seeking is associated with widespread brain activation extending beyond regions previously implicated in incubation of food or drug craving.

In ongoing analyses, we are integrating region-wise activation with behavioral measures to test whether this widespread engagement reflects global activation or reorganization of specific co-activation networks during abstinence, and to identify candidate hub regions recruited during incubation of cocaine seeking.

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Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

Location: WCC Halls A-C

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Program #/Poster #: PSTR149.08/GG14

Topic: H.08. Drugs of Abuse and Addiction

Support: K99DA059608
NIDA IRP
NIH CCB
NIH SIP

Title: Transcriptional profiling of cocaine relapse ensembles in the rat medial prefrontal cortex to inform drug repurposing strategies

Authors: *K. E. SAVELL[1], R. MADANGOPAL[2], J. M. BOSSERT[3], J. LEE[1], A. R. HOLMES[1], A. SOBUKUNOLA[4], O. NURUDEEN[1], O. BERKO[1], D. THOMPSON[1], O. R. DRAKE[1], D. PHAM[1], M. BRENNER[1], Y. SHAHAM[1], B. T. HOPE[1];
[2]Neuronal Ensembles in Addiction Section, [3]Behavioral Neurosci., [1]NIH, NIDA IRP, Baltimore, MD; [4]NIH, NIDA IRP, Catonsville, MD

Abstract: Background: There are no effective treatments to prevent relapse to cocaine. Cues previously associated with cocaine taking can provoke relapse during abstinence. One strategy to decrease relapse in rodent models is to disrupt neuronal ensembles encoding drug-cue associative memories activated during relapse tests. However, the cell types comprising the relapse-associated ensembles and how they maintain this association at the molecular level are unknown. To answer this question, we recently developed Multiple**X**ed **Po**pulation **S**election and **E**nrichment single nucleus RNA-**seq**uencing pipeline (XPoSE-seq) to perform targeted snRNA-seq on cocaine relapse ensembles, providing an unbiased screen of ensemble-specific cell types and transcriptional changes during cocaine relapse at the individual animal level. **Methods:** Male and female Fos-mRFP rats were trained to self-administer cocaine (FR1 reinforcement schedule, 0.75 mg/kg/inf. Cocaine infusions paired with a 3.5-s light cue) during twice daily 3-h sessions. Following training and 21 days of abstinence, we tested rats for cocaine seeking (30 min, extinction conditions) and extracted their brains 3 h after test (peak Fos-driven mRFP

expression). **Results:** The rats showed reliable cocaine self-administration during training and relapse to cocaine seeking following abstinence. We applied the XPoSE-seq pipeline to identify which cell types comprise the cocaine-relapse ensemble and to characterize the associated cell-type specific transcriptional signatures. We identified distinct clusters corresponding to known cell types in the mPFC (excitatory and inhibitory neurons) that further subcluster into expected layer and interneuron sub-types within mPFC. We used drug repurposing analysis on the transcriptional signatures to identify drugs with compensatory molecular changes, which identified 35 FDA-approved candidates. We are currently testing a subset of these drugs for their effect on relapse to cocaine seeking.

Disclosures: K.E. Savell: None. **R. Madangopal:** None. **J.M. Bossert:** None. **J. Lee:** None. **A.R. Holmes:** None. **A. Sobukunola:** None. **O. Nurudeen:** None. **O. Berko:** None. **D. Thompson:** None. **O.R. Drake:** None. **D. Pham:** None. **M. Brenner:** None. **Y. Shaham:** None. **B.T. Hope:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: National Institute on Drug Abuse Intramural Research Program

Title: Structural memory-related signature in dendritic spines on Fos-positive ensemble neurons in rat nucleus accumbens following cue-induced cocaine seeking

Authors: *F. RUBIO[1], E. UKPONG[1], R. MADANGOPAL[1], D. OLIVARES[1], E. HILAIRE[1], A. KELLY[1], L. F. KANE[1], C. MEJIAS-APONTE[2], B. T. HOPE[1];
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Abstract: Learned associations between discrete cues (or contexts) and drug effects are thought to be encoded by sparsely distributed patterns of neurons called neuronal ensembles. Synaptic ensembles are specific patterns of synapses on the ensemble neurons where input-specific alterations were induced during learning to mediate long-lasting memories. Our hypothesis is that morphological changes in dendritic spines are unique in neurons that mediate long-lasting memories but not in neurons that are activated by a single novel exposure. We assessed morphological alterations of dendritic spines on medium spiny neurons in nucleus accumbens (NAc) following cue-induced cocaine craving. We trained all rats to lever press for cocaine infusions paired with a 3.5-s light cue. After training, all rats were injected in the NAc with a cocktail of AAVs encoding Cre recombinase and Cre-dependent GFP for sparse neuronal labeling. After 3-4 weeks in their home cages, rats were exposed for 30 min to either the cocaine-paired light cue (relapse test group) or a non-drug-related novel context control for

neural activation. Rats were sacrificed 60 min after cue exposure and their brains processed for Fos immunohistochemistry and cleared prior to confocal imaging. Morphological analysis of GFP-labeled spines of Fos-positive and Fos-negative neurons were performed using 3D reconstruction using Neurolucida.In distal dendritic segments, the inter-spine interval (ISI) and head diameters of mushroom spines were both decreased on Fos-positive vs Fos-negative neurons after cue-induced seeking but not after novel context exposure in rats with the same history of cocaine self-administration training. Other spine types were not altered. Thus, unique mushroom spine morphological changes were induced only on Fos-positive neuronal ensembles in the cue-induce relapse group and not induced on a different set of neurons simply by acute activation in the novel context exposure group. Our interpretation is that anatomical clusters (ISIs < 5 μm) of mushroom spines with smaller head diameters are likely physical memory traces or engrams encoded during self-administration training within the cocaine cue-induced neuronal ensembles.

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Poster

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Program #/Poster #: PSTR149.10/GG16

Topic: H.08. Drugs of Abuse and Addiction

Title: Real-time nucleus accumbens glutamate dynamics during cue- and cocaine-primed reinstatement of cocaine seeking

Authors: *M. GITS[1], H. BLOUNT[1], M. SCOFIELD[2], L. KNACKSTEDT[1];
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Abstract: Cocaine use disorder is a chronic, relapsing condition in which drug-associated cues and cocaine re-exposure trigger craving and relapse. Glutamate transmission in the nucleus accumbens (NA) is critical for relapse-like cocaine seeking behavior. Although glutamate release in the NA has been consistently observed during relapse-like cocaine seeking using microdialysis with temporal resolution at the minute-scale, sub-second dynamics of glutamate release during the reinstatement of cocaine seeking have not yet been characterized. Here we record glutamate dynamics in the NA using iGluSnFR fiber photometry. Male Sprague Dawley rats were implanted with jugular catheters and were infused with glutamate sensor iGluSnFR in either the NA core or medial shell, along with unilateral optic fiber implantation for in vivo fluorescence recordings. Rats then underwent 12 days of cocaine self-administration (2 h/day), where active lever presses resulted in intravenous cocaine infusions paired with light/tone cues. This was followed by 8-12 days of instrumental extinction training, during which lever presses had no

programmed consequence. Upon meeting extinction criteria (<20 presses), reinstatement of drug seeking was tested in a discrete trial cue-primed session, wherein lever presses produced drug-paired cues without cocaine delivery. After again meeting extinction criteria, a cocaine+cue-primed reinstatement test was performed. iGluSnFR signals were collected during both reinstatement tests and time-locked to active lever presses to quantify peri-event glutamate dynamics. The core and shell exhibited distinct glutamate signatures during cocaine seeking in reinstatement tests. NA core glutamate increased around active lever presses during cue-primed reinstatement, whereas NA shell glutamate decreased during cocaine+cue-primed reinstatement. These findings suggest that glutamate release in the NA core precedes lever presses and that cocaine exposure alters both the timing and magnitude of glutamate signaling within the NA. These data provide a foundation for future applications of machine learning techniques to identify latent neurochemical engagement states that organize relapse-like cocaine seeking.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: Pilot grants from the McKnight Brain Institute and the Center for Addiction Research and Education at the University of Florida.

Title: Investigating Female-Specific mGlu5-associated Neural Activity During Incubation of Cocaine Craving in rats

Authors: *V. GALBAVA, P. HAMOR, L. A. KNACKSTEDT, M. SCHWENDT;
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Abstract: Cocaine use disorder remains a public health concern marked by persistent drug seeking, high relapse and overdose risk, with no FDA-approved medications available. Clinical and preclinical evidence find that cocaine seeking behavior often increases during abstinence, a phenomenon termed ‘incubation of cocaine craving’. The neural mechanisms of craving incubation remain incompletely understood. Previous work by our lab and others found that glutamatergic maladaptations play a key role in cocaine seeking, and that inhibition of metabotropic glutamate receptor 5 (mGlu5) reduces incubated cocaine craving. However, mGlu5-expressing cell populations in the brain that contribute to incubated cocaine seeking have not been characterized. Fluorescence in situ hybridization (FISH) analysis of forebrain c-fos and mGlu5 co-localization in male rats identified several incubation 'hotspots' with increased activation during d45 vs. d1 relapse tests. These include - basolateral amygdala, orbitofrontal cortex, laterodorsal thalamus, and dorsal hippocampus, suggesting the presence of a distributed ‘incubation’ network. As sex differences in cocaine seeking, relapse vulnerability, and glutamate

neuroadaptations have been documented, here we extend this work to females. Female Sprague-Dawley rats (n = 47) were trained to self-administer cocaine on a fixed-ratio 1 schedule, over 6 daily short-access (1 hr) and 12 daily long-access (6 hr) sessions. Next, rats entered short-term (1-day) or long-term (45-day) abstinence, with a final (45 min) relapse test during which both the drug context and drug-associated cues were present. No test controls were also included. We found that, akin to male rats, female rats escalated cocaine intake during long access and displayed robust incubation of cocaine seeking (greater active nose poke responding on day 45 vs. day 1). We detected no effect of estrus on cocaine seeking. Immediately after relapse testing, brains were processed for multiplex FISH to co-localize c-fos and mGlu5 mRNA expression across forebrain regions. The ongoing analysis aims to map sex-specific relapse-related neural activity in mGlu5+ and mGlu5- cells, with network analysis used to identify circuits preferentially recruited during incubated cocaine seeking. This information will guide follow-up site- and circuit-specific mGlu5 interventions targeting incubated cocaine seeking using genetic and pharmacological tools to uncover where and how brain mGlu5 receptors regulate cocaine seeking.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA06364501A1
P20GM144041

Title: Breaking the Cycle: Ovarian Hormones, Cocaine Demand, and Oxytocin Therapy

Authors: A. COX[1], S. L. HUSKINSON[3], ***A. S. KOHTZ**[2];
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Abstract: There are substantial sex/gender differences that influence susceptibility to, subjective experience of, and relapse to cocaine. A key feature of cocaine use disorder is pathologically high demand (motivation) for cocaine. The behavioral economics (BE) procedure is a cross-species technique that measures individual differences in cocaine demand by determining consumption in a within-session paradigm and extracting key BE parameters that quantify demand elasticity (α, motivation) and free consumption (Q_0, hedonic setpoint). Our work demonstrates that female rats exhibit significantly greater motivation for cocaine than males, and that estrous cycle phase accounts for more than 70% of the variability in demand. Specifically, progesterone (P4) decreases demand, whereas estradiol (E2) increases free consumption at low

effort, indicating opposing roles for these ovarian hormones. Critically, cocaine itself disrupts ovarian hormone cyclicity. In rats, chronic cocaine self-administration reduces proestrus-to-estrus transitions, attenuates P4, and increases E2. Whereas in rhesus monkeys we and others have shown that cocaine lengthens menstrual cycles, produces luteal phase defects, and blunts P4 signaling. These endocrine disruptions may be directly linked to escalating cocaine demand, highlighting a bidirectional relationship between drug use and reproductive hormone function across species. As a potential therapeutic approach, we investigated oxytocin (OXT), a hypothalamic neuropeptide with emerging therapeutic relevance. In female rats, OXT dose-dependently reduced cocaine demand and restored normal estrous cyclicity, and the ovarian hormones P4 and E2, during active chronic cocaine exposure. Extending these findings to primates, OXT attenuated within-session demand in a female monkey, and restored menstruation to an anovulatory subject. These studies allow for direct alignment with human menstrual cycle dynamics and provide a critical bridge between rodent and human research. Together, our findings identify ovarian hormones as powerful modulators of cocaine motivation, reveal cocaine's endocrine-disrupting consequences as a mechanism contributing to persistent demand, and suggest OXT as a promising candidate therapy targeting both drug demand and the hormonal disruptions that drive relapse risk.

Disclosures: A.S. Kohtz: None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: COBRE - P20-GM144041-02
K99/R00 - R00DA045758

Title: Dorsal Hippocampal KCNT1 Promotes Cocaine Seeking During Early Abstinence in Female, but Not Male, Rats

Authors: *A. L. COX[1], S. JULIAN[4], J. WU[5], L. CHALLAGUNDLA[2], L. K. KACZMAREK[6], A. S. KOHTZ[3];
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Abstract: Inability to maintain abstinence is a hallmark of substance use disorders, with cravings during early abstinence strongly predicting relapse in both humans and rodents. Specifically, several measures of cocaine dependence are greater in women, and are similarly reflected in rodents. Maintaining successful abstinence may be particularly challenging in women, as

biological and psychological responses to drugs of abuse differ between sexes however, the mechanisms underlying these sex differences remain unclear. Extinction day 1 (ED1), the onset of abstinence when the expected drug is unavailable, represents a highly stressful period associated with increased cravings. We previously demonstrated that the dorsal hippocampus (dHPC) plays a significant role in mediating sex-specific cocaine-seeking behavior on ED1. To identify the molecular mechanisms underlying these effects we preformed RNA-Seq in the dHPC following exposure to the cocaine self-administration context on ED1 to reveal sex-specific transcriptional profile correlated with cocaine-seeking behavior. In females, 22 transcripts were differentially expressed between ED1 and withdraw day 1 (WD1) controls, with only 3 overlapping between sexes. Five female specific genes significantly correlated with cocaine-seeking behavior on ED1 ($R^2 \geq 0.70$), including KCNT1, a potassium channel that negatively predicted cocaine-seeking in females. To access its functional role, we infused PRX-2904, a KCNT1 antagonist, or an ASO targeting KCNT1 into the dHPC region CA1 via guide cannula 10 min prior to ED1 testing. Both compounds decreased cocaine-seeking behavior on ED1 in female rats, with effects persisting 2 weeks later and through subsequent extinction testing. To further evaluate the therapeutic potential of KCNT1 modulation we systemically administered a KCNT1 agonist, Niclosamide, or PRX-2904 in male and female rats. Systemic PRX-2904 decreased cocaine seeking behavior on ED1 persisting to ED2 whereas Niclosamide functioned to increase cocaine seeking behavior in females only. Together these findings identify that sex-specific transcriptomic adaptation in the dHPC, particularly involving KCNT1, may contribute to cocaine-seeking persistence during early abstinence thus highlighting KCNT1 as a potential therapeutic target for sex-specific treatment strategies in cocaine use disorder.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: COBRE - P20-GM144041-02
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Title: Dorsal Hippocampus to the Medial Prefrontal Cortex Projections Drive Sex Differences in Cocaine-Seeking Persistence.

Authors: *S. JULIAN[1], A. COX[2], A. S. KOHTZ[3];
[1]Psychiatry and Human Behavior, Univ. of Mississippi, Jackson, MS; [2]Psychiatry and Human Behavior, Univ. of Mississippi Med. Ctr., Brandon, MS; [3]Psychiatry and Human Behavior, Univ. of Mississippi Med. Ctr., Jackson, MS

Abstract: Maintaining abstinence remains one of the most difficult aspects of recovery from cocaine use disorder. Cravings during the initial abstinence period (e.g. extinction day 1, ED1 in rats), can predict long-term abstinence success. In rats, we find that females show greater cocaine-seeking on ED1 and greater cocaine seeking persistence. Our prior work indicates disrupting dorsal hippocampus (dHPC) memory formation can attenuate cocaine-seeking persistence in both sexes, however where these memories are stored downstream remains unknown. Herein we investigated the role of dHPC projections to the prelimbic (PL) and infralimbic (IL) regions of the medial prefrontal cortex (mPFC) in cocaine-seeking persistence. Using immunohistochemistry, we found that females have more Fos+ PL cortex neurons during ED1, while males have more Fos+ IL cortex neurons during ED1, that correlate to dHPC Fos. These results reflect the hypothesis that PL cortex projections are necessary for reconsolidation, or strengthening, of retrieved contextual memories, whereas IL cortex projections are necessary for extinction, or weakening, of retrieved contextual memories. Using designer receptors exclusively activated by designer drugs (DREADDs), we next investigated if projections from the dHPC to PL drive cocaine-seeking behavior on ED1 and following a 2-week period of forced abstinence, (ED2) and conversely if projections from the dHPC to IL promote extinction. Activating dHPC to PL using hM3Dq excitatory DREADDs increased cocaine seeking behavior in females during ED2, while inhibiting dHPC to PL using hM4Di inhibitory DREADDs decreased cocaine seeking behavior across both ED1 and ED2. Activating dHPC to IL using hM3Dq DREADDs decreased cocaine seeking behavior while inhibiting dHPC to IL using hM4Di DREADDs increased cocaine seeking behavior. These findings support our hypotheses that dHPC signaling to different regions of the mPFC has specific effects to promote or attenuate contextual cocaine seeking. Further studies will be conducted in males. Understanding the involvement of sex specific corticolimbic signaling is crucial to finding sex-specific therapies that promote abstinence success.

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Poster

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Support: DA054177
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R01DA054177
R01AA029023

Title: Self-Administration of Benzodiazepines in Drug-Naïve and Cocaine-Experienced Rhesus Monkeys: Role of $GABA_A$Receptor Subtypes

Authors: *M. D. STEMPKOVSKI[1], I. D. GILMORE[2], W. DOYLE[3], D. SHARMIN[4], J. M. COOK[4], J. K. ROWLETT[1,3], K. B. FREEMAN[1,3], S. L. HUSKINSON[1,3];
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Abstract: Self-administration of benzodiazepines in drug-naïve and cocaine-experienced rhesus monkeys: role of alpha subunit-containing GABAA receptors. *Rationale.* Benzodiazepine (BZ)-type compounds lacking efficacy at the α1 subunit-containing GABAA (α1GABAA) receptor appear to lack misuse potential, though their self-administration depends upon drug experience.*Objectives.* We used a choice procedure to evaluate whether positive allosteric modulators (PAM)with varying selectivity at α1GABAA vs. α2/3/5GABAA receptors would enhance food or cocaine choice when delivered as a mixture with food or cocaine over food or cocaine alone. We hypothesized that modulation at α1GABAA receptors would be required for enhancement of food or cocaine choice. *Methods.* Five female and four male rhesus monkeys chose between food vs. food + a BZ-type drug or food vs. cocaine + a BZ type drug. Drugs evaluated were all full-efficacy PAMs: zolpidem(0.0032-0.1 mg/kg/injection; α1GABAA), midazolam (0.0032-0.1 mg/kg/injection, nonselective),and MP-III-80 (0.032-0.18 mg/kg/injection; α2/3/5GABAA)*Results.* Zolpidem was the only compound that reliably enhanced cocaine choice, while zolpidem and midazolam reliably enhanced food choice, and MP-III-80 either had no effect or reduced food or cocaine choice compared with conditions in which food or cocaine were delivered alone. *Conclusion.* α1GABAA receptors are primarily involved in the reinforcing effects of BZs in drugnaïve or cocaine-experienced subjects. PAMs lacking efficacy at α1GABAA could be developed as anxiolytics with low misuse potential compared to nonselective, full-efficacy modulators in those without a substance use disorder or in those who use cocaine.

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Poster

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Title: Sex Differences in Fos Activated Perineuronal Networks in the Medial Prefrontal Cortex Following Pavlovian and Operant Cocaine Conditioning

Authors: *V. DIAZ[1], S. JULIAN[5], A. COX[2], M. BERRY[3], A. S. KOHTZ[4];
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Mississippi Med. Ctr., Brandon, MS; [3]Univ. of Mississippi Med. Ctr., jackson, MS; [4]Psychiatry and Human Behavior, Univ. of Mississippi Med. Ctr., Jackson, MS; [5]Univ. of Mississippi, Jackson, MS

Abstract: Women exhibit a greater susceptibility to cocaine use disorder (CUD) relapse than men, a phenomenon mirrored in rodent models. Prior studies show that some aspects of cocaine-seeking behavior are driven by contextual memory reinforcement and regulated by the prelimbic (PL) and infralimbic (IL) regions of the medial prefrontal cortex (mPFC). Specifically, PL neurons mediate the reconsolidation of retrieved contextual memories, while IL neurons are essential for their extinction. Here, we investigated perineuronal nets (PNNs) in the PL and IL cortex following the acquisition and expression of two forms of contextual cocaine memory: Pavlovian (conditioned place preference; CPP) and operant (self-administration with extinction). For CPP, male and female Sprague-Dawley rats underwent cocaine (10 mg/kg) or saline conditioning over 3 days following habituation and were tested for preference on day 5. Rats were either sacrificed immediately or retested 2 weeks later to assess memory retention. For operant memory, rats completed 10 days of cocaine self-administration followed by an extinction day 1 test (ED1) and a second extinction test 2 weeks later (ED2) to evaluate retention of extinction-associated cocaine memories. First, we found that male rats had a greater number of Fos+/WFA+ neurons in both the PL and IL during CPP retrieval, compared to females. When rats were retested 2 weeks later, these effects persisted, however Fos+ neurons, nor PNNs, predicted the magnitude of cocaine preference in either sex. Second, we observed sex- and region-specific activation of PNN-ensheathed neurons during cocaine extinction. Females exhibited greater Fos+/WFA+ expression in the PL, whereas males showed greater Fos+/WFA+ expression in the IL, on both ED1 and ED2. These findings indicate that there are significant sex differences in PNN activity in both the PL and IL, and this activity is influenced by the type of cocaine-conditioning environment the animal is seeking under. Thus, this data provides critical insight into the role the type of conditioning environment has on the circuitry underlying cocaine use disorder and how that same circuitry influences sex specific seeking behaviors.

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Poster

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R34DA061267

P30DA033934
Blick Scholar funds

Title: Transposable elements are transcribed in a time, dose, brain region, and cell type dependent manner following cocaine exposure in the mouse brain

Authors: *S. R. STRANDBERG[1], P. J. HAMILTON[2];
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Abstract: Background: Transposable elements (TEs) comprise about half of the mammalian genome and are commonly called 'jumping genes' for their ability to be transcribed and re-integrated at a novel location in the genome. This process, termed transposition, is retained by a notable fraction of mammalian TEs and can cause permanent disruptions to protein coding and regulatory regions of the genome. A growing body of literature, including publications from our lab, has observed alterations in brain TE transcript levels in various brain disorders, including substance use disorders. In particular, cocaine use is increasingly appreciated as able to alter brain TE transcript expression, but the exact time-course, brain region/cell type specificity, and transposition capacity of affected TEs remains under-explored. We investigated these points by creating a cocaine-induced brain TE transcript time-course from public RNA-sequencing (RNAseq) datasets from laboratory mice.
Methods: We identified transcriptomic studies of nucleus accumbens (NAc), dorsal striatum (DS), and prefrontal cortex (PFC) in cocaine exposed mice via self- or investigator-administered paradigms. We utilized both bulk RNAseq studies to resolve whole tissue dynamics and single-cell RNAseq or cell-sorted RNAseq to investigate cell-type-specific TE dynamics. Using the Python package TEtranscripts, we aligned gene and TE reads to mm10 and used an 5% FDR adjusted p-value cutoff.
Results: Across brain regions, we see time- and dose- dependent changes in TE transcript expression. Each quantified region has unique TE expression profiles. We identify predominantly downregulated TEs in NAc, whereas DS TEs are upregulated, and PFC displays TE profiles sensitive to the route of cocaine administration (self- vs investigator- administered). We also investigated cell type differences in the PFC and NAc. In the PFC, we found that neurons experience more dynamic regulation at all time points compared to glia. In the NAc, we observe opposing regulation of many of the same TE transcripts at the acute timepoint in D1 and D2 MSNs, with D1 MSNs experiencing up-regulation of TEs and D2 MSNs experiencing down-regulation of these same TE transcripts.
Conclusion: Following cocaine exposure in mice, TEs experience dynamic and distinct brain-region and cell type-specific expression. These insights may add an additional dimension of the brain molecular mechanisms involved in cocaine use disorder. Future studies include characterization of TE transcript competency followed by preliminary analysis of cocaine-induced transposition events.

Disclosures: S.R. Strandberg: None. **P.J. Hamilton:** None.

Poster

PSTR149: Mechanisms of Cocaine Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR149.18/GG24

Topic: H.08. Drugs of Abuse and Addiction

Title: Exendin-4-Phe1 reduces cocaine-mediated behaviors and suppresses locomotor activity in rats

Authors: *M. C. DALALO[1], X. ZHANG[2], A. CAFFREY[1], R. PETRILLI FORTUNA[3], H. D. SCHMIDT[2];
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Abstract: Emerging studies show that glucagon-like peptide-1 receptor (GLP-1R) agonists are promising candidates for reducing cocaine-mediated behaviors. However, the gastrointestinal effects they produce, including nausea and emesis, often limit their clinical use. This study investigates the effects of Exendin-4-Phe1 (Ex-Phe1), a biased GLP-1R agonist, on voluntary cocaine taking and seeking in male (n=8) and female (n=10) Sprague-Dawley rats. Rats were surgically implanted with indwelling jugular catheters and trained to self-administer cocaine (0.25 mg cocaine/59 µl saline/infusion) on a fixed-ratio schedule of reinforcement for 21 days. Rats were then pre-treated with vehicle or Ex-Phe1 (3.0 or 10.0 µg/kg, i.p.) 30-min prior to test sessions. Cocaine self-administration dose-response curves were generated using different unit doses of cocaine (0.25, 0.625, and 1.0 mg cocaine). Motivation to self-administer cocaine was assessed using a progressive ratio schedule of reinforcement. Ex-Phe1 dose-dependently attenuated cocaine self-administration in rats responding on fixed-ratio and progressive ratio schedules of reinforcement. Cocaine-taking behavior was subsequently extinguished, and the effects of Ex-Phe1 on cue- and cocaine-primed (10 mg/kg, i.p.) reinstatement were assessed as an animal model of relapse. Ex-Phe1 dose-dependently attenuated cocaine reinstatement in both male and female rats. Malaise-like effects were evaluated by measuring body weight and food, water, and kaolin intake in rats 24-h after systemic Ex-Phe1 administration during both the self-administration and reinstatement testing phases. Ex-Phe1 doses that reduced cocaine taking and seeking did not induce malaise-like effects in cocaine-experienced rats, but these doses were found to suppress locomotor activity and produce anxiety-like behaviors in the open field test. Together, our findings indicate that Ex-Phe1 dose-dependently reduces cocaine-mediated behaviors. However, the locomotor suppression and anxiety-like effects produced at these doses may limit the clinical potential of Ex-Phe1.

Disclosures: M.C. Dalalo: None. **X. Zhang:** None. **A. Caffrey:** None. **R. Petrilli Fortuna:** None. **H.D. Schmidt:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.01/HH1

Topic: H.08. Drugs of Abuse and Addiction

Title: Dissecting Cell-Type-Specific Mu Opioid Receptor Mechanisms Underlying Ketamine Reward Using Conditional Gene Knockout Mice

Authors: *G. ADAMSON[1], Z. XI[2];
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Abstract: Ketamine [(R,S)-ketamine] is a dissociative anesthetic used clinically since the 1970s and, more recently, used as an off-label treatment for treatment-resistant depression and other psychiatric disorders. Despite its therapeutic and abuse-related properties, the neural mechanisms underlying its antidepressant and rewarding effects remain unclear. Emerging evidence implicates μ-opioid receptor (MOR) signaling in ketamine reinforcement, but the relevant MOR-expressing neuronal populations are unknown. To address this, we used Cre-LoxP strategies to selectively delete MORs from GABAergic neurons in Vgat-Cre mice (Vgat-MOR-KO) or from subcortical glutamatergic neurons in VgluT2-Cre mice (VgluT2-MOR-KO). Naloxone pretreatment significantly reduced intravenous ketamine self-administration in wild-type mice, supporting MOR involvement in ketamine reward. MOR deletion from VgluT2-positive glutamatergic neurons, but not GABAergic neurons, markedly reduced ketamine self-administration and shifted the dose-response curve downward, indicating a critical role for glutamatergic MOR signaling in ketamine reward. To further define relevant circuitry, we ablated VgluT2-positive neurons in the paraventricular nucleus of the thalamus (PVT), which reduced ketamine self-administration under a progressive-ratio schedule but not a fixed-ratio 1 schedule, suggesting this region plays a role in ketamine motivation. GRAB-DA fiber photometry showed that ketamine increased dopamine release in the nucleus accumbens in wild-type mice, an effect absent in both Vgat-MOR-KO and VgluT2-MOR-KO mice. Unexpectedly, ketamine did not produce conditioned place preference and dose-dependently reduced optical intracranial self-stimulation in DAT-Cre mice. These results provide more support for a glutamatergic MOR mechanism underlying ketamine reward and provide new insight into the circuitry that may contribute to ketamine's antidepressant effects. Future studies will further delineate the specific neural circuits underlying the rewarding and antidepressant effects of ketamine.

Disclosures: G. Adamson: None. **Z. Xi:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.02/HH2

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA053743
NIH Grant R01DA054714
T32 MH129274

Title: A spatially and transcriptionally defined mu-opioid receptor-enriched MSN subtype mediates opioid reward learning

Authors: *O. R. DRAKE, E. JORGENSEN, C. E. NEWMAN, L. IANOV, J. PETERS, J. HEINSBROEK, J. J. DAY;
Univ. of Alabama at Birmingham, Birmingham, AL

Abstract: Opioid use disorder (OUD) remains a public health challenge, with limited treatments that directly target the neural substrates of opioid reward. Opioids exert their reinforcing effects through mu opioid receptors (MORs), encoded by *Oprm1*, within mesolimbic reward circuits, including in the nucleus accumbens (NAc). However, *Oprm1* expression is unevenly distributed across NAc medium spiny neurons (MSNs), and the specific neuronal populations through which MOR signaling promotes opioid reward remain poorly defined. Here, we combine single-nucleus RNA sequencing (snRNA-seq), spatial transcriptomics, electrophysiology, and cell type-specific genetic manipulations to identify and functionally characterize a MOR-enriched MSN population. We identified a transcriptionally distinct MSN subtype marked by *Chst9* (Chst9-MSNs) that exhibits exceptionally high *Oprm1* expression and is spatially clustered along the medial and ventral borders of the NAc shell. Although Chst9-MSNs comprise only ~7% of NAc cells, they contain more than one-third of all *Oprm1* transcripts detected in the region. Comparative analyses across mouse, rat, nonhuman primate, and human datasets revealed that this population is conserved across species. To enable selective access to Chst9-MSNs, we generated a Chst9-Cre-tdTomato rat line. Anatomical tracing revealed that Chst9-MSNs preferentially project to the ventral pallidum, suggesting a specialized circuit through which MOR signaling may influence opioid reward. Whole-cell recordings showed that Chst9-MSNs are robustly inhibited by the MOR agonist DAMGO, an effect reversed by naloxone. Finally, Cre-dependent deletion of *Oprm1* in Chst9-MSNs abolished fentanyl conditioned place preference in female rats, suggesting that MOR signaling in this sparse MSN population is necessary for opioid reward learning. Together, these findings identify Chst9-MSNs as a conserved, spatially and transcriptionally defined MOR-enriched MSN subtype that is both directly responsive to opioids and necessary for opioid reward learning. This work demonstrates how transcriptionally defined neuronal populations can serve as critical cellular substrates for reward-related behaviors and highlights a potential cell type-specific target for OUD therapeutics.

Disclosures: O.R. Drake: None. **E. Jorgensen:** None. **C.E. Newman:** None. **L. Ianov:** None. **J. Peters:** None. **J. Heinsbroek:** None. **J.J. Day:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.03/HH3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA035943

Title: Fentanyl enhances perseveration through altered outcome encoding in striatal D2 neurons without disrupting model-based learning

Authors: *E. GARR[1], Z. ZHANG[2], J. GU[3], P. H. JANAK[3];
[1]Natl. Inst. of Mental Hlth., Bethesda, MD; [2]UCLA, Los Angeles, CA; [3]Johns Hopkins Univ., Baltimore, MD

Abstract: Drug addiction is commonly thought to involve a transition to habitual control of behavior, where the choice to consume drugs becomes automatic and reflects a failure to consider negative outcomes. However, the term "habit" encompasses multiple definitions, each suggesting a different underlying cognitive mechanism. Building on previous work where we isolated the effects of oral fentanyl reinforcement on independent components of habitual decision-making, we sought to uncover a neurobiological correlate of fentanyl-induced habits. Using a two-step decision-making task, we trained wildtype Long-Evans rats (8 males, 10 females) to earn sucrose rewards for many sessions followed by a brief set of sessions that alternated between sucrose and oral fentanyl rewards. We replicated the finding that a brief history of fentanyl leads to heightened perseveration during fentanyl versus sucrose sessions, independent of any effect on model-free bias. Fiber photometry recordings from neurons expressing the D2 dopamine receptor in the posterior dorsomedial striatum showed similarly negative responses to sucrose and fentanyl rewards, but a stronger positive response to sucrose versus fentanyl omission (upper bound of bootstrapped confidence intervals for outcome and outcome x reward type LASSO coefficients < 0). The neuronal responses to rewards and omissions predicted perseveration in opposite directions for sucrose and fentanyl (outcome x reward type assessed with linear mixed effects model, $p < .01$), suggesting that the neural mechanism underlying drug-induced choice repetition is fundamentally different from that of food rewards. Neuronal activity was also modulated by state transition probability in a manner that predicted model-free bias (upper bound of bootstrapped confidence interval for transition LASSO coefficient < 0), and transition encoding was temporally close but non-overlapping with outcome encoding. Finally, using a reinforcement learning model, we found that D2 type neurons show activity aligned with temporally distinct action value updates that match the times of transition and outcome encoding and belong to model-based and perseverative learning rules, respectively. Together, these results show how a potent opioid boosts perseveration independent of goal-directed decision-making by altering how outcomes are encoded separately from the state transition encoding that is required for model-based behavior.

Disclosures: E. Garr: None. **Z. Zhang:** None. **J. Gu:** None. **P.H. Janak:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.04/Web Only

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant GR040337
NIDA Grant P30 DA048736

Title: Functional subpopulations within the medial prefrontal cortex during rat model of opiate withdrawal and subsequent psilocybin treatment

Authors: *V. HONES[1], S. J. MIZUMORI[2];
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Abstract: The medial prefrontal cortex (mPFC) plays a central role in reward processing and goal-directed behavior, and is known to undergo long-lasting structural and functional changes following repeated opiate exposure (Zhao, Zhang, & Bai, 2025). Opioid addiction remains a major driver of mortality and morbidity in the U.S., and current medication-assisted treatments are hampered by their own addictive properties (Kolodny et al., 2015; Volkow et al., 2018). Psilocybin, a serotonergic psychedelic with a non-addictive profile, has emerged as a promising therapeutic treatment across several psychiatric conditions, including depression, alcohol use disorder, and nicotine dependence (Bogenschultz et al., 2015; Johnson et al., 2014; Carhart-Harris et al., 2017). Notably, psilocybin has strong functional and plasticity effects in the mPFC to support flexible behavior (Shao et al., 2021; Morgan et al., 2023). To investigate whether psilocybin is an effective treatment at counteracting the prefrontal dysregulation driven by opioid exposure, we modeled opiate withdrawal in rats. Our paradigm involved twice-daily injections of morphine, followed by abrupt cessation, as rats were performing on the novel object recognition task (NORT). We evaluated their behavior, as well as the activity in the mPFC using one-photon calcium imaging in the mPFC (Inscopix). We show that withdrawal produced hypofunction in the mPFC, which mirrored the impairments in novel object discrimination. A single dose of psilocybin was sufficient to restore mPFC calcium dynamics and rescue recognition memory. Furthermore, by using an unsupervised clustering algorithm, we show that there are three distinct clusters within the mPFC that support responses to novel and familiar objects. Importantly, these clusters are differentially affected by our drug (morphine) and treatment (psilocybin). These results support the claim that distinct subpopulations within the mPFC support novelty-driven memory processes, which become impaired during opiate withdrawal but may be reversed with psilocybin.

Disclosures: V. Hones: None. **S.J. Mizumori:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.05/HH4

Topic: H.08. Drugs of Abuse and Addiction

Title: Systemic GLP-1R activation suppresses fentanyl-related behaviors and remodels mesolimbic neural and transcriptional signaling

Authors: *S. LIU[1], S. GANAPATHY-KANNIAPPAN[2], M. LOBO[3];
[1]Neurobio., [3]Anat. and Neurobio., [2]Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: Systemic GLP-1R activation suppresses fentanyl-related behaviors and remodels mesolimbic neural and transcriptional signaling Shuai Liu, Shanmugasundaram Ganapathy-Kanniappan, Mary Kay Lobo Department of Neurobiology, University of Maryland School of Medicine. Baltimore, MD USA. The opioid crisis continues to be a major cause of death, with fentanyl posing a particularly severe threat due to its high potency and widespread availability. There is an urgent need for non-opioid pharmacotherapies that target the neural mechanisms underlying opioid use disorder (OUD). Glucagon-like peptide-1 receptor agonists (GLP-1RAs), approved for type 2 diabetes and obesity, have emerged as promising therapeutics for substance use disorder. Preclinical studies show that GLP-1RAs reduce alcohol and cocaine self-administration (SA) and relapse-like behaviors. However, their effects on fentanyl-related behaviors and underlying neural and molecular mechanisms remain poorly understood. Using a mouse fentanyl SA model, we investigated the effects of systemic GLP-1RAs administration on multiple fentanyl-related behaviors in both male and female mice, including fentanyl taking, cue-induced fentanyl seeking following different withdrawal periods, and drug- and cue-primed reinstatement. GLP-1RAs significantly reduced all of these behaviors, indicating a broad suppression of fentanyl-motivated behaviors. We then identified brain regions engaged by GLP-1R activation. c-*fos* expression was quantified across different brain regions following acute GLP-1RA administration. GLP-1RA induced robust c-*fos* activation in multiple reward- and motivation-associated regions, indicating widespread recruitment of networks involved in behavioral regulation. In addition, we evaluated molecular adaptations associated with these behavioral effects, qPCR analyses were performed in the nucleus accumbens, ventral tegmental area, and several other mesolimbic regions following fentanyl or saline seeking tests in GLP-1RA and saline-treated mice. GLP-1RA altered the expression of genes associated with dopaminergic signaling, opioid receptor signaling, and activity-dependent plasticity. Furthermore, GLP-1RA regulated mitochondrial gene expression across reward-related regions, suggesting a metabolic adaptation may contribute to reduced fentanyl seeking. These findings demonstrate that systemic GLP-1R activation suppresses fentanyl-related behaviors while producing widespread neural and transcriptional adaptations within multiple brain regions. These results support GLP-1RAs as promising therapeutic candidates for OUD.

Disclosures: S. Liu: None. **S. Ganapathy-Kanniappan:** None. **M. Lobo:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.06/HH5

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant 5R33DA052101-04

Title: CRISPR epigenome editing of Hdac1 in D1-MSNs during fentanyl abstinence

Authors: *M. GREEN[1,2], M. ROWELL[2], S. PATEL[2], S. GANAPATHY-KANNIAPPAN[2], R. CHANDRA[2,3], M. LOBO[2];
[1]Neurobio., Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [2]Neurobio., [3]Virus Vector Core, Univ. of Maryland Sch. of Med., Baltimore, MD

Abstract: CRISPR epigenome editing, using CRISPR-activation or CRISPR-interference (CRISPRa/i) allows for more physiologically relevant manipulation of gene expression. Due to size constraints of adeno-associated virus (AAV) packaging, we are using a CRISPRi mouse line that contains a Cre-dependent SpdCas9-KRAB. The advantage of these mice is only needing viral delivery of the small gRNA plasmid, a one vector system for cell type specific regulation of gene expression. Hdac1 is one of the genes that we targeted using this CRISPRi mouse line. Using cell type specific RNA sequencing, Hdac1 was found to be significantly upregulated in nucleus accumbens (NAc) D1-MSNs during abstinence from fentanyl. As a master regulator of chromatin accessibility and transcription, Hdac1 is an ideal candidate for targeting large gene expression signatures. Our lab previously showed that prolonged abstinence from fentanyl increases anxiety-like and negative affective behaviors in rodents. Hdac1 inhibition in the NAc has been shown to have anti-depressive-like effects after chronic stress. Based on these findings, we hypothesize that by inhibiting Hdac1 in D1-MSNs during fentanyl exposure and abstinence, we will prevent dysregulated behaviors that occur in prolonged fentanyl abstinence. Baseline behavioral testing consisting of open field test (OFT) elevated zero maze (EZM), and sucrose self-administration testing was conducted using CRISPRi x D1-Cre mice which confirmed the viability of this mouse line for future studies, as well as western blotting which confirmed expression of SpCas9 in the NAc of these mice. SpCas9 compatible gRNAs targeting Hdac1 were designed and tested in-vitro in N2a cells to verify inhibition efficacy before packaging in AAVs. gRNAs were then validated in-vivo by intracranial stereotaxic infusions into the NAc of CRISPRi x D1-Cre followed by RNAscope, where we also saw significant decreases in Hdac1 expression. To investigate the impact of CRISPRi inhibition of Hdac1 in fentanyl abstinence, CRISPRi x D1-Cre mice received gRNA viruses targeting either Hdac1 or a LacZ control. After recovery from surgery, the mice underwent 5 days of fentanyl in the drinking water followed by 10 days of forced abstinence. Following abstinence, mice went through social preference test, OFT, spinning disc test, sucrose splash test, and EZM. Mice that received the Hdac1 gRNA and are fentanyl abstinent show reductions in anxiety like and negative affective behaviors across multiple tests compared to mice that receive the control LacZ gRNA, which points to Hdac1 as a viable therapeutic target in the context of fentanyl abstinence and relapse prevention.

Disclosures: M. Green: None. **M. Rowell:** None. **S. Patel:** None. **S. Ganapathy-Kanniappan:** None. **R. Chandra:** None. **M. Lobo:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.07/HH6

Topic: H.08. Drugs of Abuse and Addiction

Title: Predicting latent opioid withdrawal states using genotype specific, high-dimensional, behavior signatures.

Authors: *J. A. BEIERLE[1], G. SABNIS[2], V. KUMAR[3];
[1]The Jackson Lab., Bar Harbor, ME; [2]The Jackson Lab., Bar Harbor, ME, ; [3]Neurosci., Jackson Lab., Bar Harbor, ME

Abstract: Opioid withdrawal, the negative physical and affective consequences of abstinence after prolonged opioid use, is a key driver of continued drug use, and blunting withdrawal enables patients to better recover from Opioid Use Disorder (OUD). OUD has a known genetic component in humans and mice, and leveraging genetic diversity can reveal novel biology and punitive druggable targets. Historically, the complex latent state of withdrawal has been inferred using jumping behavior or strain-specific indexes of behavior. These measures are inherently limited, as jumping represents only one facet of the withdrawal syndrome and does not correlate genetically with other withdrawal outcomes, and it is unclear if indexes of behaviors identified in C57BL/6J mice generalize across genetic diversity. Here, we extend withdrawal phenotyping to high-dimensional behavior datasets using the JAX Animal Behavior System (JABS), an integrated, high-throughput computer vision platform that provides access to high-dimensional behavioral features for withdrawal assessment. Across 9 genetically diverse inbred strains, we observed profoundly strain-dependent withdrawal behaviors encompassing traditional measures such as jumping and freezing, as well as novel measures including stretch attend posture and wall facing. Sparse PCA and sparse PLS-DA revealed that within-strain behavioral variation was sufficient to detect withdrawal in all 9 strains and 3 aggregated models (high activity mice, low activity mice, and all mice). Cross model performance indicated that aggregate models robustly identify withdrawal across strains where strain-specific struggle to perform. Finally, when assessing withdrawal severity in 3 levels of opioid exposure in 4 genetically distinct strains we successfully discriminate withdrawal intensity across strain and opioid dose across strains. Together these findings support the power of high-dimensional behavior, accessed through computer vision, to confidently and sensitively resolve opioid withdrawal severity across and within genetic diversity. They also support strain specific indexes as powerful high-throughput tools that provide platforms for genetic and pharmacological screening. Future work should tie neuronal anatomical markers to behavioral indices to refine the behavioral representation of the latent state of opioid withdrawal.

Disclosures: J.A. Beierle: None. **G. Sabnis:** None. **V. Kumar:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.08/HH7

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Award 1R44DA059302-01

Title: Morphine-Pramipexole Treatment has Sex-Specific effects on Withdrawal Behaviors in Opioid-Tolerant Rats

Authors: A. BEAMAN[1], O. MARTINEZ[1], A. BENTON[2], S. AZAM[2], S. CLEMENS[3], *K. L. BREWER[1];
[1]Brody Sch. of Med. @ East Carolina Univ., Greenville, NC; [3]Physiol., [2]East Carolina Univ., Greenville, NC

Abstract: Opioids remain a mainstay for moderate to severe pain analgesia. Chronic use of opioids, however, can lead to tolerance and dependence, and create withdrawal when treatment must be stopped. When used as an adjuvant, Pramipexole (PPX), a dopamine D3 agonist, enhances analgesia while reducing the opioid dose needed to achieve the desired analgesic effects. Our study explored whether PPX as an adjuvant to morphine (MOR) reduces withdrawal (WD) symptoms in opioid-tolerant rats. Over a period of 12 days, male and female Long-Evans rats received continuous MOR infusions (64 mg/mL; 0.5 μL/hr) via subcutaneous osmotic pumps in order to promote opioid tolerance. Following removal of the pumps, one group of rats, considered the treatment group, received twice daily injections of MOR (2mg/kg)+PPX (0.1mg/kg) for 7 days. A second group, considered the control group, received twice daily saline injections during the same 7 day period. WD behaviors were observed, quantified, and weighted using a behavioral scoring system and compared between the two groups during days 1-3 of the treatment period. Following the 7 day treatment period, all injections were stopped and both groups were observed for 3 days in a post-treatment period. The same behavioral scoring system was used to observe WD behaviors during the 3 day post-treatment period. Female rats treated with MOR+PPX showed WD scores similar to control rats both during the treatment and post-treatment assessment periods. In contrast, male rats treated with MOR+PPX had significantly lower WD scores vs. control at day 1 of treatment ($p=0.008$) and days 1-2 of the post-treatment period ($p<0.001$ and $p<0.03$, respectively). These findings support the potential of PPX as an adjunctive therapy to reduce opioid withdrawal and improve the tolerability of long-term opioid treatment. Based on the sex-dependent response to this treatment, further investigation into the mechanisms underlying dopaminergic regulation of opioid dependence is necessary to inform more personalized approaches to opioid use management.

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Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.09/HH8

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA052618

Title: Cycles of tolerance and withdrawal with oral fentanyl gel self-administration in a mouse model

Authors: *M. T. RICE[1,3], A. COYNE[1,3], L. E. HONAN[3], J. F. NEUMAIER[2,3];
[2]Psychiatry, [1]Univ. of Washington, Seattle, WA; [3]VA Puget Sound Hlth. Care Syst., Seattle, WA

Abstract: We have developed a novel mouse model for chronic, episodic opioid use disorder that emulates the escalating dosage of fentanyl that is common in humans who rapidly develop tolerance to opioids and leads to severe opioid withdrawal syndromes. An advantage of noncontingent drug administration in mice is that the exact dose and timing of fentanyl administration can be consistently controlled, however, a pitfall of this model is that twice daily noncontingent fentanyl injections are quite stressful for both the control (saline-treated) and experimental (fentanyl-treated) mice. For this reason, we are testing a new method involving voluntary oral fentanyl gel self-administration, using the same dosage schedule as our previous approach, to allow comparisons of this novel route of fentanyl administration. To begin, the mice habituate to the palatable chocolate Ensure gel in their home cage for 4-consecuative days prior to the beginning of the cycles. The cycles consist of mice given either a water control or fentanyl-containing gel while being singly housed for an hour, twice a day, for five days, with the dose of fentanyl doubling each day (0.5 to 8 mg/kg). This schedule of escalating fentanyl produces tolerance and is then followed by a four-day period of forced abstinence, and the cycle is repeated five times. We find that most mice readily consume the fentanyl or control gel quickly, allowing individual mice to consume much higher doses of fentanyl than is the case with liquid self-administration such as in the two-bottle choice model. At the beginning of this testing, we chose 1-1.5 mL amounts for the mice to consume. During the end of the first cycle, the mice were unable to finish their fentanyl gel due to the strong effects of the drug. For this reason, we decided to increase concentration to reduce gel volume during the following week. This resulted in 57-71% completion during day 5 of cycle 2 compared to 14-43% during day 5 of cycle 1 (N=13, n=6-7). We tested for the presence and severity of withdrawal signs following completion of the fifth administration cycle using the presence of hyperalgesia and behavioral testing (locomotion, body posture, spontaneous behavior, anxiety-like behavior). Some of the mice consistently did not consume all the gel, regardless of concentration, so this procedure may also be used to evaluate fentanyl preferring vs. fentanyl non-preferring phenotypes. Our main aim is to lower the stress the mice are experiencing while yielding similar tolerance and withdrawal results, so we can use it in the future to further understand fentanyl in the brain and introduce novel therapies to help alleviate severe opioid withdrawal syndrome.

Disclosures: M.T. Rice: None. **A. Coyne:** None. **L.E. Honan:** None. **J.F. Neumaier:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR150.10/HH9

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH intramural program

Title: Altered dopamine D1R/ D2R receptor expression in the striatum enhances vulnerability towards opioid abuse in mouse and human

Authors: *D. DIAZ-URBINA[1], R. BOCK[3], F. N. VEENKER[4], A. E. TISCHER[5], P. MANZA[6], M. MICHAELIDES[7], N. D. VOLKOW[8], V. A. ALVAREZ[2];
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Abstract: Synthetic opioids (e.g fentanyl) are strong analgesics used for the control of severe pain. However, opioids use increased risk of addiction, which can lead to opioid-use disorder (OUD). Recent evidence showed that not all opioid users develop OUD, raising the possibility that some biological factors confer vulnerability towards OUD. Evidence indicates that opioids alter dopaminergic neurotransmission in the striatum and Nucleus accumbens (NAcc), brain regions involved in rewarding processing and drug-seeking. Recently, we found that mice with high striatal dopamine D1R/ D2R ratios (product of low expression of D2R) promote alcohol abuse, indicating that altered D1/ D2 ratios might also increase vulnerability towards fentanyl. Here, we tested whether mice with enhanced striatal D1R/ D2R ratios (MSN-KD mice) exhibit vulnerability towards fentanyl and whether restoring normal striatal D1R/ D2R expression (Auto-KD mice) prevents this propensity. Male and female mice were trained to intravenous self-administered fentanyl (3 μg/kg). We assessed five key addictive-like behaviors: fentanyl intake, compulsive seeking, motivation, naloxone-punished intake, and opioid-related mortality. We combined these observations to create a multidimensional OUD-like index. We found that MSN-KD mice exhibited higher scores across addiction-like measures, whereas Auto-KD and control mice expressed similar addition-like behavior scores. Furthermore, using radioligand binding, we assessed dopamine D2-like and D1-like expression striatum and NAcc of fentanyl-self-administered mice. Binding for the D1-like did not show differences, but binding for D2-like increased the NAcc of control and MSN-KD mice ($p < 0.05$). These changes promoted that both control and MSN-KD displayed a reduced D1R/ D2R ratio, without changes in auto-KD mice ($p < 0.01$). Our data suggests that the pre-existing imbalance in the D1R/ D2R ratios enhances susceptibility towards OUD. We corroborated the findings from our mouse model by conducting brain imaging in people recovering from prolonged OUD. Brains scans showed that OUD patients displayed an imbalance D1R/D2R ratios in caudate/putamen (human homolog of mouse striatum). However, the imbalance of D1R/D2R ratios were not associated with some key clinical characteristics of OUD patients, e.g. lifetime duration of opioid use, indicating that D1R/ D2R imbalance might reflect a persistent/ predisposing risk factor rather than a consequence of OUD.

Disclosures: D. Diaz-Urbina: None. **R. Bock:** None. **F.N. Veenker:** None. **A.E. Tischer:** None. **P. Manza:** None. **M. Michaelides:** None. **N.D. Volkow:** None. **V.A. Alvarez:** None.

Poster

PSTR150: Mechanisms of Opioid Use and Addiction

Location: WCC Halls A-C

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Program #/Poster #: PSTR150.11/HH10

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Title: Endocannabinoid modulation of morphine preference and NAc dopamine dynamics via CB1 in RMTg to VTA projecting neurons

Authors: *C. MADDOX, A. MARTINEZ-RIVERA, L. PASSARELLI-ROBERTS, A. BAROT, K. MADHAV, A. M. RAJADHYAKSHA;
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Abstract: The rewarding properties of opioid drugs continues to drive one of the most devastating public health crises in United States history, despite the ongoing clinical need for opioid analgesics for effective treatment of acute, intense pain. Current pharmacotherapies to treat opioid use disorder (OUD) can mitigate craving in opioid-dependent individuals, but no prophylactic treatments to prevent OUD development in patients prescribed opioid analgesics exist presently. Prior work in our lab demonstrated that targeting the endocannabinoid (eCB) system reduces opioid-associated reward, finding that systemic elevation of levels of the major eCB 2-arachidonoylglycerol (2-AG) through selective inhibition of its catabolic enzyme monoacylglycerol lipase (MAGL) with JZL184 reduced morphine and oxycodone conditioned place preference (CPP) and associated nucleus accumbens (NAc) dopamine dynamics. Given that JZL184's reduction of opioid reward depended on expression of CB1 receptors in the ventral tegmental area (VTA), we next sought to identify VTA circuit-specific mechanisms underlying JZL184's impact on opioid reward and associated mesolimbic dopamine. One major site of regulatory control over the VTA is the rostromedial tegmental nucleus (RMTg), which sends substantial GABAergic projections to VTA dopaminergic cells that are robustly inhibited by opioids to disinhibit mesolimbic dopamine activity. Given our RNAscope finding that most GABAergic cells in the RMTg co-express both μ-opioid and CB1 receptors, we hypothesized that JZL184's impact on opioid reward may occur through endocannabinoid-opioid receptor crosstalk in RMTg neurons projecting to the VTA. Through conditional knockout of *Cnr1* in VTA-projecting RMTg neurons in conjunction with fiber photometry of a genetically encoded dopamine biosensor (*GRAB-DA*) in the NAc, we sought to determine the relevance of the RMTg-VTA circuit to JZL184's behavioral and neurophysiological effects in our morphine CPP paradigm. Preliminary findings suggest that CB1 expression in this pathway is necessary for morphine-associated NAc dopamine dynamics, but not morphine CPP.

Disclosures: C. Maddox: None. **A. Martinez-Rivera:** None. **L. Passarelli-Roberts:** None. **A. Barot:** None. **K. Madhav:** None. **A.M. Rajadhyaksha:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01DA054368-02

Title: MAG Lipase inhibition Attenuates Morphine Preference via CB1 Receptors in the RMTg→VTA Pathway

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Abstract: As opioid use disorder remains a major public health concern in the United States, efforts are focused on developing approaches to curb its impact. Endocannabinoids (eCBs) have emerged as promising modulators of opioid reward. Previous studies from our lab have demonstrated that JZL184, a monoacylglycerol lipase (MAGL) inhibitor that elevates levels of the eCB 2-arachidonoylglycerol (2-AG), blunts opioid conditioned place preference (CPP) and reduces oxycodone self-administration. However, the neural circuits mediating this effect remains unknown. Classically, mu opioid receptors (MORs) on GABAergic interneurons in the ventral tegmental area (VTA) were thought to disinhibit these nucleus accumbens (NAc)-projecting dopaminergic neurons, driving opioid reward. More recent evidence implicates MORs on GABAergic projection neurons in the rostromedial tegmental area (RMTg) projecting to the VTA as the primary site of opioid-mediated disinhibition of the NAc. Here, we tested whether MORs and cannabinoid 1 receptors (CB1s) in VTA-projecting RMTg neurons are required for JZL184's attenuation of morphine reward. Using a conditional viral knockout (cKO) strategy in *Oprm1* and *Cnr1* floxed mice respectively, we selectively deleted these receptors in RMTg→VTA projections. Mice then underwent morphine CPP, receiving either JZL184 (10 mg/kg, i.p.) or vehicle two hours before morphine (10 mg/kg, i.p.). As predicted by prior studies, *Oprm1*$^{RMTg→VTA}$ cKO mice failed to acquire morphine CPP, confirming MOR dependence in this projection, with JZL184 having no effect. In contrast, *Cnr1*$^{RMTg→VTA}$ cKO mice acquired morphine CPP, but JZL184 no longer attenuated CPP, indicating that MAGL inhibition requires CB1s within this projection to blunt morphine reward. To determine if this was a reward specific phenotype, pain assays (hot plate and tail flick tests) were conducted to assess whether morphine's analgesic properties were altered. Both assays showed no change in morphine's analgesic properties when either *Oprm1* or *Cnr1* were deleted in this projection. These findings identify RMTg→VTA CB1s as a critical locus through which pharmacological MAGL

inhibition selectively suppresses opioid reward. Ongoing work will determine whether this reflects direct MOR-CB1 crosstalk or indirect modulation via enhanced 2-AG signaling.

Disclosures: L. Passarelli-Roberts: None. **A. Barot:** None. **K. Madhav:** None. **A.M. Rajadhyaksha:** None. **A. Martinez-Rivera:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA054368-02

Title: GPCR crosstalk underlying endocannabinoid blunting of opioid reward

Authors: *A. GHOSH, L. PASSARELLI-ROBERTS, P. ZHAO, C. CHEN, A. MARTINEZ-RIVERA, L.-Y. LIU-CHEN, A. M. RAJADHYAKSHA;
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Abstract: Despite their utility as frontline analgesics, opioids display high abuse liability, and there is a critical need to develop therapeutic strategies that can attenuate the addictive, but not the analgesic, properties of opioids. We have shown that enhancing levels of the endocannabinoid 2-arachidonoglycerol (2-AG) through pharmacological inhibition of its catabolic enzyme monoacylglycerol lipase (MAGL) blunts opioid-reward learning processes, decreasing acquisition of opioid conditioned place preference (CPP) and intravenous self-administration, without affecting opioid analgesia (Martinez-Rivera et al., 2024). While the endocannabinoid (eCB) and opioid systems have been shown to interact to influence neurobiological functions, this finding challenges the prevailing assumption that these systems interact synergistically, i.e., eCB agonism potentiates opioid reward-learning processes. Ongoing work in our lab has shown this behavioral phenotype is driven through cannabinoid receptor 1 (CB1) and mu opioid receptor (MOR) within neural reward circuitry, specifically within GABAergic projections from the rostromedial tegmental nucleus (RMTg) to ventral tegmental area (VTA). Furthermore, preliminary *in vitro* studies have shown that 2-AG induces MOR internalization in a CB1-dependent manner. Thus, identifying signaling mechanisms behind this "crosstalk" might elucidate a novel modality of GPCR signaling and/or regulation, and could inform future therapeutic targets for GPCR modulation. We are utilizing *in vitro* and *in vivo* models to assess phosphorylation dynamics of both CB1 and MOR in response to 2-AG application (*in vitro*) or MAGL inhibition (*in vivo*) to elucidate molecular mechanisms behind receptor crosstalk, as receptor phosphorylation has been well established to modulate receptor trafficking and internalization. Additionally, we are utilizing immunohistochemical staining methods to assess changes in MOR trafficking within $RMTg_{GABA}\rightarrow VTA$ projections upon opioid exposure with or without MAGL inhibition. Our central hypothesis is that

pharmacological elevation of 2-AG levels through MAGL inhibition alters MOR phosphorylation and trafficking dynamics through CB1 activation to alter MOR function within $RMTg_{GABA}$→VTA reward circuitry, subsequently decreasing opioid reward-learning processes. These findings will progress our understanding of mechanisms behind GPCR-GPCR interactions and will inform therapeutic strategies to modulate opioid abuse liability without altering opioid analgesic properties.

Disclosures: A. Ghosh: None. **L. Passarelli-Roberts:** None. **P. Zhao:** None. **C. Chen:** None. **A. Martinez-Rivera:** None. **L. Liu-Chen:** None. **A.M. Rajadhyaksha:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA IRP 1ZIADA000434-25
NIDA IRP ZIADA000069
NIDA IRP ZIADA000642

Title: Neurometabolic and synaptic correlates of heroin addiction vulnerability: a PET study in rats

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Abstract: Background: Only a subset of heroin users develop addiction, yet determinants of addiction vulnerability remain unclear. We developed a rat model featuring choice between heroin and social interaction that produces substantial individual variability in heroin intake, binge-like taking, and preference. We combined this model with PET imaging to assess relationship between addiction vulnerability and brain metabolism (using FDG), and structural changes in synaptic density (using SynVesT-1).
Methods: In Exp. 1, we trained rats to self-administer heroin (or saline) and social interaction, then tested heroin- and social-seeking and heroin-vs.-social choice. During 3-5 abstinence weeks, we used FDG and scanned awake rats at rest and during social- and heroin-seeking tests. In Exp. 2, using the same model, we scanned rats before heroin self-administration (SA), after choice, and after 3 abstinence weeks using FDG and SynVesT-1.
Results: In Exp. 1, addiction severity was primarily associated with metabolic alterations at rest, rather than during reward-seeking. At rest, severity was associated with lower uptake in piriform

cortex and higher uptake in ventral hippocampus. During heroin seeking, severity was associated with lower uptake in postsubiculum and cerebellum. Severity was not associated with social SA and social seeking at early and late abstinence, or FDG uptake during social seeking. In a pilot study, we scanned high- and low-severity rats from Exp. 1 with SynVesT-1 and found reduced whole-brain uptake in high-severity rats. Data from Exp. 2 will be presented at the meeting. **Conclusions:** Addiction severity is primarily associated with resting metabolic and synaptic alterations, rather than reward-seeking brain activity.

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Poster

PSTR150: Mechanisms of Opioid Use and Addiction

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Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000467
ZIA-DA000434

Title: Persistent vulnerability to heroin relapse after more than one year of abstinence in rats

Authors: *A. SOBUKUNOLA[1], J. LEE[1], O. R. DRAKE[2], D. PHAM[3], V. A. LENNON[4], S. J. WEBER[5], A. R. HOLMES[6], O. NURUDEEN[1], Y. SHAHAM[7], B. T. HOPE[8], R. MADANGOPAL[9];
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Abstract: Background: Relapse to opioid use during abstinence is often triggered by drug-associated cues, but the persistence of this vulnerability across prolonged abstinence is unknown. We previously reported that rats' response to cocaine-associated discriminative stimuli (DSs) progressively increases (*or incubates*), during the first 60 abstinence days and persists to 300 days. Here, we used the same trial-based discrimination procedure to assess relapse vulnerability following exposure to heroin-availability DSs over more than one year of abstinence.
Methods: We trained rats to self-administer heroin during DS+ trials (heroin available upon lever press; 0.025 mg/kg/infusion; no drug-paired CSs), but not DS− trials (heroin unavailable) in the same session. In Experiment 1, we repeatedly tested rats for DS-controlled heroin seeking under extinction conditions after 1, 21, 60, 120, 200, 300 and 385 abstinence days. In Experiment 2, we tested the independent contributions of the DS+ and DS− after 21 abstinence days using no-DS,

DS+, DS−, and both-DS trials.
Results: DS-controlled heroin relapse was higher after 21 and 60 days than after 1 abstinence day and persisted to 385 days. Responding on abstinence day 21 was low during DS− trials, intermediate during *no-DSs*, and *both-DSs* trials, and maximal during *DS+* trials.
Conclusions: Incubation of DS-controlled drug seeking generalizes to heroin and relapse vulnerability persists across more than half the adult rat lifespan with DS+ and DS- independently controlling expression and suppression of heroin seeking. Treatments that reduce the motivational impact of drug-availability cues or strengthen behavioral control using non-drug-availability stimuli, may help reduce relapse vulnerability.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA-IRP 1ZIADA000434-25

Title: Claustrum circuits associated with incubation of oxycodone seeking after voluntary abstinence

Authors: *K. NEGISHI[1], M. PISHGAR[4], F. RICCIARDI[2], K. BANKSTON[5], H.-L. WANG[2], J. M. BOSSERT[6], Y. SHAHAM[3];
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Abstract: Background: We recently identified a role of claustrum in incubation of opioid seeking after electric barrier-induced voluntary abstinence (Negishi et al. *J Neurosci* 2025). The claustrum sends projections to multiple cortical areas, including anterior cingulate cortex (ACA) and retrosplenial cortex (RSP). We study the role of these projections in incubation.
Methods: We trained rats (n=38; 18 females) to self-administer oxycodone (6-h/day) for 14 days. We then induced abstinence by introducing an electric barrier of increasing intensity near the drug-paired lever. On abstinence days 1 and 20, we tested the rats for oxycodone seeking under extinction conditions (no shock, no drug). We injected cholera toxin B subunit (CTb) into ACA or RSP for dual retrograde tracing and used the activity marker Fos to examine whether claustrum-to-ACA and claustrum-to-RSP projections is associated with incubation. In ongoing work, we injected retrograde AAV into RSP and AAVs encoding Cre-dependent hM4Di in claustrum and will test the effect of projection-specific chemogenetic inhibition of these

projections on oxycodone seeking on days 1 and 20, and on drug reinstatement.
Results: The rats showed reliable incubation of oxycodone seeking (higher lever presses on abstinence day 20 than on day 1). This incubation was associated with increased Fos expression RSP (but not ACC), and claustrum-to-RSP (but not claustrum-to-ACC projections), measured by percentage of Fos/CTb double-labeled cells in claustrum.
Conclusions: Incubation of opioid seeking after voluntary abstinence is associated with selective activation of claustro-RSP but not claustro-ACC projections, suggesting a role of this projection in incubation of heroin seeking.

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Poster

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Title: Intermittent access to oxycodone self-administration and alcohol alters oxycodone intake and the reinforcing efficacy of oxycodone in a sex-specific manner

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Abstract: Opioid use continues to be a public health emergency in the United States, and co-use of alcohol with opioids worsens treatment outcomes and increases overdose risk. Prior work in rats shows that oral alcohol intake immediately following 3 hr/day oxycodone intravenous self-administration (IVSA) alters the motivation to seek oxycodone. In an effort to back-translate accurate patterns of opioid-alcohol co-use, we first characterized daily and hourly patterns of opioid (± alcohol) intake in individuals with past-30 day opioid use, finding that the most common pattern of opioid intake was repeated administrations throughout the day interspersed with periods of no intake lasting for several hours. Individuals who consumed alcohol typically did so at the end of the day, after the last opioid administration. Here, we backtranslated these patterns into a rodent model to investigate the impact on opioid taking and seeking. Male and female Sprague-Dawley rats were trained on oxycodone IVSA in a 2-lever operant chamber for 3 hr/day for 3 days (0.1 mg/kg/infusion). Rats then underwent either Continuous (3 hr/day) or Intermittent (three 1 hr sessions separated by 2 hrs with no access) IVSA for 21 consecutive days. A subset of rats that were in the intermittent IVSA condition received 2-bottle choice water/alcohol (20%) in the home cage for 5 hours after IVSA every other day. A dose-response curve for IV oxycodone was then assessed in each condition, followed by progressive ratio

testing, 14 days of abstinence, and a cue-primed relapse test. Oxycodone intake differed by access condition in a sex-specific manner, with increased intake in the female intermittent access + water condition relative to continuous male and female conditions. There was no effect of access condition on the breakpoint for oxycodone or cue-primed relapse, suggesting that motivation to seek oxycodone is not affected by the pattern of intake. Intermittent self-administration shifted the dose-response curve for IV oxycodone upwards, an effect that was enhanced by alcohol and driven by males. Female rats consumed more alcohol than male rats. These results indicate that the pattern of oxycodone self-administration and alcohol co-use influences the reinforcing effects of oxycodone in a sex-specific manner, without affecting motivation to seek oxycodone under high effort and relapse-like conditions.

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Poster

PSTR150: Mechanisms of Opioid Use and Addiction

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Program #/Poster #: PSTR150.18/HH17

Topic: H.08. Drugs of Abuse and Addiction

Support: Trone Family Eminent Scholar Chair in Neuroscience and Behavior, American University
College of Arts and Sciences Graduate Student Research Award, American University

Title: Morphine Stimulus Control in F344 and LEW Rats: Implications for Regulated and Dysregulated Drug Intake

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American Univ., Washington, DC

Abstract: Lewis (LEW) and Fischer 344 (F344) rats are inbred strains that differ in their responsivity to various drugs of abuse, with LEW rats acquiring drug-induced conditioned place preferences and intravenous self-administration more rapidly than F344 rats. Although these behavioral differences are generally attributed to differential sensitivity to drug reward, variations in interoceptive stimulus processing may also contribute. Previous work has shown that interoceptive drug states may regulate intake by signaling the aversive consequences of continued drug use, thereby terminating a drug-taking bout. Accordingly, the present study investigated whether strain differences in addiction vulnerability are associated with differences in the interoceptive control of drug-taking behavior. Adult male LEW, F344, and outbred Sprague-Dawley (SD) rats (n = 16 per strain) were trained over seven cycles in which morphine (3 mg/kg; IP) preceded the pairing of saccharin and the emetic LiCl (1.2 mEq; IP) or saline (equivolume; IP). On intervening “safe” days, all animals were injected with saline before access

to saccharin alone. Conditioned F344 and SD rats acquired the conditional discrimination by the fourth conditioning cycle, reducing saccharin intake during morphine sessions relative to their baseline, unconditioned controls, and vehicle sessions. In contrast, conditioned LEW rats did not differ from baseline saccharin consumption during morphine sessions, although intake was reduced relative to controls and vehicle sessions by the fifth conditioning cycle. Subsequent dose-response assessments showed that morphine administration (1-7.5 mg/kg) produced a dose-dependent decrease in saccharin intake across strains in both conditioned and unconditioned animals, with conditioned animals consuming less saccharin overall. Finally, morphine impacted locomotor activity comparably in the three strains, indicating that impaired acquisition of the discrimination did not reflect reduced sensitivity to the training drug in the LEW rats. These results suggest that disruptions in interoceptive control in LEW rats may mediate the dysregulated drug intake reported in this strain and provide insight into a genetic component underlying abuse vulnerability.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: Cure Addiction Now 30047721
Braind and Behavior Foundation 30057821

Title: Molecular Characterization of the Parabrachial Nucleus after Opioid Exposure and Withdrawal

Authors: *I. WILLIAMSON[1], B. ASARE-OWUSU[2], K. J. FLORES-FELIX[4], B. JUAREZ[3]; [1]Univ. of Maryland Sch. of Med. Program In Neurosci., Baltimore, MD; [3]Neurobio., [2]Univ. of Maryland, Baltimore, Baltimore, MD; [4]Neurobio., Univ. of Maryland Baltimore, Baltimore, MD

Abstract: Cycles of opioid exposure and withdrawal leads to distinct recruitment and long-lasting alterations in neural circuits that have been implicated in reward and aversive information processing. This contributes to the progression of opioid use disorders (OUDs) and the cycle of intake, withdrawal and relapse. By improving our understanding of the molecular adaptations of distinct circuits implicated in specific phases of OUD, we may discover better treatments. The extended amygdala has been canonically studied to investigate the aversive symptoms and negative affective states involving opioid withdrawal. A region upstream of the extended amygdala, the parabrachial nucleus (PBN) has been implicated in relaying aversive sensory and visceral information and regulating associative learning. We found that opioid withdrawal increased cFos mRNA levels within the PBN when compared to non-dependent mice. We also detected alterations in the mu opioid receptor expression. These data led us to hypothesize that

opioid withdrawal induces cellular and molecular alterations in the PBN that increase excitability and synaptic function and alter the translatome of genes associated with ion channel expression and synaptic receptors. To induce opioid dependence (Dep), male and female mice received twice daily injections for five days of escalating doses (20-100 mg/kg) of morphine. Non-dependent (ND) mice received saline injections. Mice then either had their tissue collected with morphine still on board (Dep:Mor), underwent either naloxone injection to precipitate withdrawal (ND:Nal or Dep:Nal) or saline injection as a control (ND:Sal), or underwent spontaneous withdrawal (Dep:Spont). PBN tissue for each group was also collected. Bulk RNA was then isolated and RNAseq was performed. Differential expression analysis (DEG) , gene ontology (GO) analysis, and rank-rank hypergeometric overlap analysis (RRHO) were performed. Overall, analysis showed 357 DEGs across males and females when compared to ND:Sal. When observing different withdrawal types, we discovered naloxone precipitated withdrawal induced 296 DEGs and spontaneous withdrawal induced 632 DEGs in males and females when compared to the dependent group that did not undergo any withdrawal (Dep:Mor). GO analysis revealed changes in specific ion channels and cellular activity. RRHO analysis revealed concordant and discordant gene expression between males and females in the Dep:Nal vs Dep:Spont comparison, whereas the Dep:Spont vs Dep:Mor showed discordant gene expression. These findings contribute to a better understanding of how opioid exposure and withdrawal affect the PBN.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: BBRF NARSAD Young Investigator Award (EL)
University of Minnesota Undergraduate Research Opportunity Program (AS)

Title: Heat shock protein gene expression is dysregulated in the nucleus accumbens and cerebellum following fentanyl self-administration in mice.

Authors: *A. SCHAFFER[1], K. JOHNSON[2], E. LEFEVRE[2];
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Abstract: Opioid addiction remains a major health crisis in the United States, with millions of people misusing opioids every year. More than 70 thousand people die annually from opioid-related overdoses, and synthetic opioids, predominantly fentanyl, are responsible for roughly 80% of these deaths. Examining the drug-induced gene expression changes can help identify biological mechanisms that underlie addiction. Although transcriptional changes have been

investigated in opioid addiction, current research is often limited to select brain regions and relatively little is known about how fentanyl self-administration alters gene expression across distinct brain regions. Prior research in the Lefevre Lab has shown that heat shock protein gene expression was induced following repeated, interrupted non-contingent morphine administration, specifically in the nucleus accumbens and the dorsal striatum. Here, I tested the hypothesis that contingent self-administration of fentanyl would evoke similar transcriptional changes in the nucleus accumbens and cerebellum. The mice received a jugular catheter implant, then mice were subject to ten days of fentanyl self-administration. Brain samples were collected 24 hours after the final self-administration session, and RT-qPCR was used to measure expression of Hspa5 and Hspb1. Mice that underwent fentanyl self-administration successfully distinguished between active and inactive levers across the 10 day paradigm ($p<0.05$), whereas mice in the saline group did not. Compared with the saline controls, Hspa5 expression was significantly downregulated in both the nucleus accumbens and cerebellum ($p<0.05$), while Hspb1 was significantly downregulated in the nucleus accumbens but not in the cerebellum. These preliminary results suggest that heat shock protein gene expression following fentanyl self-administration shows opposite regulatory patterns compared to prior findings after interrupted, non-contingent morphine administration.

Disclosures: A. Schaffer: None. **K. Johnson:** None. **E. Lefevre:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.01/HH20

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R00DA048974

Title: Rodent behavioral allocation between social and heroin reinforcement is sensitive to changing effort costs

Authors: *C. A. LIS, E. LACEY, G. GIANNOTTI;
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Abstract: Opioid Use Disorder (OUD) can be conceptualized as a disorder of maladaptive behavioral allocation, in which effort is directed toward opioids despite the availability of nondrug alternatives. Rodent choice models identify social interaction as a translationally relevant nondrug alternative capable of attenuating drug-seeking. However, existing choice models rarely quantify the economic thresholds at which active competition between opioid and nondrug rewards shifts behavioral allocation between reinforcers, because social reward often immediately outcompetes opioids during choice. To address this gap and investigate how effort costs regulate allocation between social and heroin rewards, we developed a within-session

social and heroin self-administration training procedures, in which both reinforcements were acquired in parallel. Male and female Wistar rats were trained for 12 daily sessions to self-administer social interaction for 30 min, followed by 2.5 hours of heroin self-administration under FR1 schedule of reinforcement. Following acquisition, rats underwent daily discrete-choice trials. During choice rats exhibited a robust preference for heroin when both reinforcers were available at FR1. To quantify the economic threshold at which social reinforcement overcomes established opioid demand, heroin response cost was escalated across FR1, FR3, FR8, and FR20, while social cost remained fixed at FR1. Under these conditions, rats progressively reallocated their behavior toward social reward. To determine whether social reinforcement altered heroin demand relative to each animal's maximal heroin seeking effort, we compared choice demand indices with single-commodity progressive-ratio breakpoints obtained when heroin was the only available outcome. First, we derived an equal-allocation threshold or FR_{50}, defined as the heroin response cost at which predicted rodent choice is equally allocated between heroin and social reward. We next fit heroin intake under concurrent social access using the Hursh-Silberberg exponential demand function to estimate P_{max}, the price at which heroin responding peaked before demand became elastic. We found that both FR_{50} and P_{max} were significantly lower than each rat's heroin-only breakpoint. These results demonstrate that the rodent's behavioral allocation between reinforcers is an active dynamic process driven by access costs. Importantly, this model successfully preserves a measurable state of motivational conflict, providing a highly translational behavioral-economic platform for identifying the specific neural circuits underlying this process.

Disclosures: C.A. Lis: None. **E. Lacey:** None. **G. Giannotti:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.02/HH21

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA Grant R15DA055201

Title: Investigating the Role of Estradiol in Morphine Withdrawal-Induced Anxiety

Authors: *D. VAN DYK, L. I. PERROTTI;
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Abstract: Opioid withdrawal triggers negative affect, including anxiety, that drives relapse in opioid use disorder (OUD). Women report more severe affective states during withdrawal than men, yet how ovarian hormones influence these sex differences remains unclear. NMDA receptors mediate the synaptic adaptations underlying opioid withdrawal and are regulated by both morphine and estradiol. Adult female Long-Evans rats, intact or ovariectomized (OVX),

received escalating subcutaneous (s.c.) morphine (2.5 to 40 mg/kg, twice daily for 10 days) or saline (0.1 ml/kg); a subset of OVX morphine-withdrawn females received 17β-estradiol (E2; 2 µg in 0.1 mL peanut oil, s.c.) every 4 days during morphine treatment with the final dose administered 30 minutes before morphine withdrawal-induced anxiety testing. Three hormone conditions were compared with saline treated animals: intact morphine-withdrawn females (int), OVX morphine-withdrawn females (OVX), and OVX morphine-withdrawn females given E2 (OVX + E2). Morphine groups lost weight at 24 hours of morphine withdrawal, confirming it was successfully induced. On 5-minute percent open-arm time, OVX morphine plus E2 females did not differ from OVX morphine alone; however, 1-minute binning revealed a significant Time by Hormone Treatment interaction, with saline-treated animals exploring the open arms more than the intact morphine and OVX morphine plus E2 groups at minute 5 ($p < .05$). This work builds on our prior finding that high-estradiol cycling females showed the strongest morphine-versus-saline anxiety difference ($p = .037$). Estradiol replacement alone did not reproduce that behavioral phenotype, indicating that estradiol on its own is not necessary for producing morphine withdrawal-induced anxiety. Total GluN1 expression was quantified using Western blot in pooled tissue from the basolateral amygdala (BLA), central amygdala (CeA), and ventral hippocampus (vHipp), limbic regions engaged during opioid withdrawal. Compared to saline females, int showed decreased GluN1 expression during morphine withdrawal-induced anxiety. OVX + E2 animals also showed decreased GluN1 expression compared to OVX during morphine withdrawal-induced anxiety. This suggests that morphine withdrawal-induced anxiety decreases NMDA receptor expression in BLA, CeA, and Vhipp and that this effect is dependent on E2. Because NMDA receptor function is a pharmacological target, this hormone-state-dependent regulation supports sex-specific, hormone-state-aware approaches to opioid use disorder.

Disclosures: D. Van Dyk: None. **L.I. Perrotti:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.03/HH22

Topic: H.08. Drugs of Abuse and Addiction

Support: Binghamton University Subvention Award

Title: Adolescent social isolation produces female-specific increases in oxycodone reinforcement and ventral pallidal MOR function

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Abstract: Adverse experiences during adolescence increase vulnerability to opioid use disorders in adulthood, but the mechanisms underlying this risk are not yet fully understood. We examined the impact of adolescent social isolation (aSI) on reinforcing efficacy and consumption of oxycodone. We further probed mu-opioid receptor (MOR) mediated inhibition of dopamine (DA) release in the ventral pallidum (VP), a region implicated in reward valuation and social stress. Male and female rats were exposed to aSI (1 rat/cage) or group housing during adolescence (aGH; 3-4 rats/cage) for at least six weeks beginning on postnatal day (PD) 28 and underwent experimental assessments in adulthood. We measured oxycodone (0.06 mg/mL; 3 hrs/day) consumption using a forced consumption model and conditioned place preference (CPP) oxycodone (1 mg/mL) using a 10-day biased-conditioning protocol. In addition, we measured the impact of aSI on oxycodone and MOR activation mediated changes in pallidal DA transmission using ex vivo fast-scan cyclic voltammetry (FSCV). Finally, using a competitive ELISA, we measured pallidal concentrations of enkephalin, an endogenous ligand of the MOR. aSI increased oxycodone intake, with females consuming significantly more oxycodone than males. aSI females also demonstrated increased preference for oxycodone compared to aGH females, an effect that was not observed in males. aSI did not alter baseline pallidal DA release, but MOR activation with DAMGO or oxycodone produced greater inhibition of DA release in aSI females, but not males, compared to their respective aGH counterparts, indicating a sex-specific enhancement of MOR functional responsivity following aSI. Pallidal enkephalin concentrations were not affected by aSI, suggesting that aSI likely induces receptor-level regulation rather than changes in the endogenous ligand. Our findings indicate that aSI produces enduring, sex-specific alterations in MOR modulation of DA in the VP, potentially promoting the female-specific effects of reinforcing efficacy of oxycodone and the greater consumption. This study identifies pallidal DA as a crucial neural substrate driving adolescent stress associated risk of developing opioid use disorder.

Disclosures: G. Vaughan: None. **A. Karkhanis:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.04/HH23

Topic: I.03. Decision Making

Support: NIMH 129320
NIDA 051977
NIDA 051598

Title: Feedback-guided decision-making reveals sex-dependent predictors of oxycodone addiction vulnerability

Authors: *A. G. SHIN[1], I. D. DALY[1], C. PARKER[2], A. SERRATOS[2], S. KIM[2], A. ZHANG[2], H. LOVE[2], S. MAGNUS[2], S. M. GROMAN[3];
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Abstract: Introduction: Decision-making deficits driven by disruptions in feedback sensitivity have been observed in individuals with opioid use disorders, but it is not known whether these cognitive impairments contribute to the emergence and/or persistence of opioid taking and relapse behaviors. This study examined whether individual differences in decision-making functions predicted oxycodone taking, seeking, and relapse-like behaviors in adult male and female rats.
Methods: Decision-making was assessed in male and female Long Evans rats in adulthood using a three-choice probabilistic reversal learning (PRL) task. Rats were subsequently implanted with intra-jugular catheters and trained to self-administer intravenous oxycodone (0.15 mg/kg/infusion) in 5-hour long access sessions for 20 days. We also assessed drug sensitivity using a five-point dose response curve and economic value for drug using an economic demand task. Motivation, extinction, and cue-induced reinstatement were measured to assess addiction-relevant behaviors. Decision-making was reassessed on the PRL task after 10 days of abstinence to investigate post-oxycodone-induced changes in decision-making.
Results: Sensitivity to positive feedback, as measured by win-stay behavior, correlated with subsequent oxycodone self-administration in males but not in females. Greater win-stay behavior was predictive of fewer oxycodone infusions and reduced drug-seeking in extinction. In contrast, sensitivity to negative feedback, measured by lose-shift behavior, correlated with subsequent oxycodone self-administration in both sexes. Lose-shift behavior was associated with addiction-related measures only in females: greater lose-shift behavior was associated with increased drug seeking during progressive ratio testing and greater active lever responding during reinstatement. These data suggest that sensitivity to positive outcomes may modulate oxycodone-related behaviors in males, whereas sensitivity to negative outcomes may play a larger role in predicting these behaviors in females.
Conclusion: Our findings suggest that pre-existing individual differences in feedback-guided decision-making are associated with later vulnerability to oxycodone-related behaviors. These results support the existence of sex-dependent decision-making phenotypes that differentially contribute to oxycodone addiction-related outcomes. Identifying these phenotypes may help inform the development of sex-specific therapeutic strategies for opioid use disorders. Ongoing studies are investigating biological and circuit-level mechanisms underlying these sex differences.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.05/HH24

Topic: H.08. Drugs of Abuse and Addiction

Title: Light at night exposure influences fentanyl seeking behavior and impairs extinction in female mice

Authors: *P. SHARMA[1,2], T. J. POLING[2], J. C. WALTON[2], V. SETOLA[5], R. FAMA[3], G. THARP[3], N. ZHANG[2], B. D. ELLIOTT[4], A. C. DEVRIES[2], R. J. NELSON[6];
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Abstract: Light at Night Exposure Influences Fentanyl Seeking Behavior and Impairs Extinction in Female Mice Pallavi Sharma, Terri J. Poling, James C. Walton, Vincent Setola, Ning Zhang, Brittany Elliott, Rachel Fama, Grace Tharp, A. Courtney DeVries, Randy J. NelsonDepartment of NeuroscienceRockefeller Neuroscience InstituteWest Virginia UniversityMorgantown, WV 26506 USA**Abstract:** Fentanyl is a major contributor to opioid-related overdose deaths, and the contribution of environmental factors to opioid use disorder vulnerability is becoming increasingly recognized. Circadian rhythm disruption (CRD) alters neural circuits involved in reward and motivation and may influence opioid-seeking behavior. This study examined whether chronic exposure to dim light at night (dLAN) alters fentanyl reward and drug-seeking behavior in adult female CFW (Swiss Webster) mice. Animals were housed under either a 14:10-h light-dark cycle (LD; 150:0 lux) or dLAN (150:5 lux) conditions for four weeks prior to behavioral testing. Fentanyl increased locomotor activity in a dose-dependent manner during conditioned place preference (CPP) testing; however, dLAN exposure did not significantly alter fentanyl-CPP. In contrast, dLAN produced marked effects on operant fentanyl self-administration. A separate cohort underwent jugular catheterization and training in fentanyl intravenous self-administration (IVSA). Acquisition and stabilization of responding was assessed under fixed-ratio schedules (FR1, FR2, FR4). Acquisition of fentanyl IVSA was similar between LD and dLAN mice during FR1 and FR2 training sessions, with no differences in active lever responding or reinforcements earned. However, during the final days of FR4 training, dLAN mice earned more fentanyl reinforcements than LD controls. Mice then underwent daily extinction sessions in which lever presses no longer produced fentanyl infusions. Most notably, LD mice exhibited the expected progressive extinction of fentanyl-seeking behavior and reached extinction criteria within approximately 9 sessions. In contrast, dLAN mice continued responding throughout the extinction phase and failed to extinguish drug-seeking behavior after 21 extinction sessions. These results indicate that disrupted circadian rhythms induced by dim light at night may hinder recovery from opioid-seeking behavior and increase the vulnerability to relapse. **Key words:** Circadian rhythm disruption, conditioned place preference (CPP), dim light at night, extinction, fentanyl, intravenous self-administration (IVSA)

Disclosures: P. Sharma: None. **T.J. Poling:** None. **J.C. Walton:** None. **V. Setola:** None. **R. Fama:** None. **G. Tharp:** None. **N. Zhang:** None. **B.D. Elliott:** None. **A.C. DeVries:** None. **R.J. Nelson:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.06/HH25

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH K99/R00 DA-058049
NIH U54 DA-016511 pilot

Title: Relapse is orchestrated by sex-specific prefrontal cortex ensemble dynamics and tuned by ovarian hormones

Authors: *B. REED[1], L. GREEN[3], R. I. GRANT[3], J. M. OTIS[3], E. M. DONCHECK[2];
[1]Psychology, [2]Neurobio., Univ. of Alabama at Birmingham, Birmingham, AL; [3]Neurosci., Med. Univ. of South Carolina, Charleston, SC

Abstract: Dysregulated prefrontal cortex (PFC) activity is a hallmark of addiction, with baseline hypoactivity co-emerging alongside relapse-predictive hyperactivity. We previously used a head-fixed murine heroin self-administration assay paired with two-photon calcium imaging to resolve these emergent PFC computations, and found heroin exposure reduced baseline excitatory activity in most, but not all, prelimbic cortex (PrL) neurons. Spared neurons sorted into distinct ensembles differentiated by unique, phasic excitatory activity predictive of drug seeking, and seeking could be driven by holographic optogenetic stimulation of one specific ensemble in all animals. A marked sex difference emerged as, in contrast to males, seeking could be driven by stimulation of a second distinct ensemble in females. Stimulation of either ensemble triggered feedforward recruitment of the 'universal' ensemble, and the number of neurons recruited in that ensemble was positively correlated with seeking. This indicates females possess convergent paths to recruit relapse-driving excitatory PFC activity, aligning with how females exhibit greater PFC excitatory activity than males during seeking and craving. Excitatory PFC activity and relapse vulnerability in females vary, however, with cyclical ovarian hormone levels. We previously found that estradiol acts in PrL to disinhibit excitatory activity and promote drug seeking, suggesting it facilitates activation of relapse-driving PFC computations. In contrast, progesterone (PROG) is relapse-protective, but its effects on PFC activity are unclear. To resolve this, we first tested whether PROG can suppress reinstatement in our head-fixed model. We found systemic PROG pretreatment blocks cue-induced heroin seeking in females, but not in males, consistent with freely moving studies. As PROG effects may be mediated by its metabolite allopregnanolone (ALLO), we next tested and found systemic ALLO pretreatment does block reinstatement, in both sexes. This suggests ALLO may have sex-agnostic therapeutic potential, highlighting the importance of consideration of 'female-specific' mechanisms in scientific research. To localize ALLO's effects, intra-PrL ALLO was next administered and again found to block reinstatement in both sexes, suggesting it modulates PrL neuronal activity. Given that ALLO is a positive allosteric modulator of GABA-A receptors, its protective effects may arise from constraining activity within relapse-driving ensembles. Ongoing two-photon calcium

imaging studies are examining how PROG and ALLO shape PrL computations during reinstatement and whether these mechanisms differ by sex.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.07/HH26

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant U01DA045300
NIDA Grant K99/R00DA057390

Title: Distinct region-specific neuroplastic adaptions underlying heroin vulnerability and resilience

Authors: *A. M. BERCKMUELLER[1], C. WERNETTE[1], S. J. WALTERHOUSE[2], B. N. KUHN[1,2];
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Abstract: The global rise in opioid use disorder (OUD) highlights the need to elucidate the neurobiological circuitry underlying the propensity for drug use and relapse. Using a validated preclinical rat model of OUD that phenotypes animals based on unique behavioral signatures, structural plasticity patterns in the prelimbic (PrL), infralimbic (IL), nucleus accumbens core (NAcc), and ventral pallidum (VP) were assessed in OUD vulnerable and resilient rats following extinction (Ext) training and a cued reinstatement (CR) test. These regions converge in a series of circuits necessary to initiate cued drug-seeking behavior, thus warranting further investigation into their associated neuroadaptations. Male and female heterogeneous stock rats underwent heroin self-administration and were sacrificed following either Ext training or a 15-minute CR test. Phenotypic differences in two non-neuronal markers of synaptic plasticity were analyzed: perineuronal nets (PNNs), a component of the extracellular matrix that restricts synaptic plasticity, and microglia, resident immune cells of the brain that promote neuroplasticity when reactive. PNN density increased in the PrL and VP following Ext and CR in resilient rats, suggesting PNN preservation may promote refraining behavior in these regions. In contrast, PNN degradation was observed in the VP of vulnerable rats, demonstrating the VP's bidirectional influence on heroin-seeking behavior. Furthermore, PrL microglia trended toward a neuroplastic state in vulnerable rats following CR, whereas microglia in resilient animals became more homeostatic. Conversely, VP microglia in vulnerable rats undergoing cued reinstatement shifted toward a more surveillant phenotype, whereas resilient rats developed a more reactive,

amoeboid-like microglial morphology. NAcc microglia morphological analysis is currently underway. Lastly, dendritic spine head diameter and spine density were measured to evaluate alterations in synaptic connectivity within the NAcc following Ext and CR testing. Unexpectedly, dendritic spine morphology exhibited no measurable differences between resilient or vulnerable rats after the CR test. However, protracted abstinence and Ext training resulted in decreased spine density in vulnerable rats compared to saline controls. Current analyses are dissecting NAcc cell-specific alterations in dendritic spine morphology. Taken together, these findings reveal that distinct plasticity-related changes across brain regions could underlie individual differences in OUD vulnerability and may be particularly important in supporting resilience to opioid-related behaviors.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

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Program #/Poster #: PSTR151.08/HH27

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH/NIDA R00DA048974

Title: Chemogenetic Inhibition of Withdrawal-Encoding PVT Ensembles Reduces Cued Heroin Seeking in Rats

Authors: *M. NASH, A. L. JENSEN, C. LIS, G. GIANNOTTI;
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Abstract: Opioid use disorder (OUD) is a major global health crisis characterized by high relapse rates and limited long-term treatment success. When opioid use is discontinued, severe emotional and physical symptoms emerge, creating an aversive state that persists beyond the acute withdrawal phase. As a result, relapse to opioid use can become a means of alleviating withdrawal-related distress. Although the negative affective state associated with withdrawal is a critical component of this cycle, the neurobiological mechanisms through which withdrawal states drive relapse remain poorly understood. The paraventricular thalamus (PVT) has emerged as a key node in the neural circuits underlying OUD. Previous work shows that the PVT is engaged during both spontaneous and naloxone-precipitated opioid withdrawal. However, whether discrete PVT neurons that encode the aversive withdrawal state are re-engaged to drive heroin seeking remains unknown. To investigate this possibility, we implemented viral Targeted Recombination in Active Populations (TRAP) technology together with intra-PVT injection of a Cre-dependent inhibitory hM4Di-DREADD, enabling activity-dependent genetic access to, and chemogenetic inhibition of, PVT ensembles activated during spontaneous or naloxone-

precipitated heroin withdrawal. Male and female Wistar rats underwent 12 days of heroin self-administration in daily 3-h sessions. Rats were then assigned to naloxone-precipitated or spontaneous withdrawal conditions. In the precipitated withdrawal group, rats received naloxone 2 hours after the final heroin self-administration session, followed 20 minutes later by 4-hydroxytamoxifen (4-OHT; 10 mg/kg, IP) to enable recombination in withdrawal-activated PVT neurons. In the spontaneous withdrawal group, rats were returned to the home cage after the final heroin session and received 4-OHT 24 hours later to capture PVT ensembles activated during early spontaneous withdrawal. Following 21 days of home-cage abstinence, rats received the DREADD ligand J60 15 minutes before a cue-induced heroin seeking test, during which active lever presses resulted in presentation of the heroin-associated cues without heroin delivery. We found that chemogenetic inhibition of PVT ensembles activated during either spontaneous or naloxone-precipitated heroin withdrawal suppressed cue-induced heroin seeking. Together, these findings suggest that opioid withdrawal and heroin seeking converge within the PVT, identifying withdrawal-activated neuronal ensembles as potential targets for disrupting the withdrawal-relapse cycle and improving long-term outcomes in OUD.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.09/HH28

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH R01 DA057790
NIH R01 DA059978

Title: Characterization of MRS7414, a mixed action kappa-opioid receptor partial agonist, for treatment against cocaine-seeking behavior

Authors: *J. P. MCLAUGHLIN[1], S. O. EANS[2], R. SHINOUCHI[3], A. K. WILLIAMS[2], B. A. TSAI[2], A. M. PATEL[2], C. Y. KIM[2], D. K. TOSH[4], M. PAVAN[4], Q. JIANG[6], T. CHE[7], K. A. JACOBSON[5];
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Abstract: Nucleoside analogues containing a bicyclo[3.1.0]hexane ring system (termed “methanocarba”) in place of ribose show promise as a privileged but not promiscuous structural

class for interaction with diverse protein targets (Jacobson et al., 2017). Recently, certain (N)-methanocarba nucleosides were shown to also antagonize opioid receptors (ORs): δ- (DOR), κ- (KOR), and μ- (MOR), with moderate preference for KOR (Tosh et al., 2018). Expanding on this earlier report, and given the therapeutic value of KOR ligands in the treatment of pain and psychostimulant abuse, we employed a structure-guided design strategy informed by cryo-EM structural insights, coupled with semi-synthetic modification of a nucleoside compound to generate 10 novel methaocarba nucleosides for potential activity at the KOR. Pharmacological characterization began in vitro with functional cell-based assays (BRET imaging of Gi and beta-arrestins) for agonist or antagonist activity at all three OR. Analog MRS7299 displayed KOR antagonism, whereas MRS7414 displayed KOR-selective partial agonism. MD simulations and biophysical examination suggested the orientation and engagement with the KOR dictated the activity of the analogs. Behavioral studies in mice were conducted to evaluate antinociception (55ºC warm-water tail-withdrawal model), confirming MRS7299 is a potent KOR antagonist with poor BBB-penetration. Testing also confirmed MRS7414 was a KOR-selective partial agonist, reaching only a ~50% antinociceptive response after administration of a 30 mg/kg s.c. dose. Tested at the estimated ED_{50} value of 41 mg/kg, s.c., MRS7414 increased respiration without sedative effects or conditioned place-aversion characteristic of KOR full agonists. However, pretreatment with MRS7414 prevented cocaine-conditioned place preference, consistent with the activity of KOR agonism. These data highlight the potential of structure-guided design to intentionally tune receptor agonist efficacy, identifying a promising potent KOR antagonist (MRS7299) and partial agonist (MRS7414) as potentially promising strategy to separate analgesia from opioid liabilities as well as new potential treatments for cocaine abuse.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

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Program #/Poster #: PSTR151.10/HH29

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant NS121780

Title: KCC2-Dependent Inhibitory Signaling in the Substantia Nigra Pars Reticulata Regulates Behavioral State Transitions Following Morphine Exposure

Authors: *A. C. PEARSON[1], A. OSTROUMOV[2];
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Abstract: Opioid use disorder (OUD) is associated with persistent alterations in behavior, including disruptions in how organisms select and regulate actions in response to environmental stimuli. These maladaptive behaviors often persist even when environmental conditions change (for instance: when alternative rewards are available, when drugs are unavailable, or when punishments are introduced). The substantia nigra pars reticulata (SNr), a major basal ganglia output nucleus, is well positioned to regulate these behaviors through its inhibitory control over downstream motor and thalamocortical circuits. Understanding how SNr dysfunction contributes to these behavioral alterations may reveal novel mechanisms underlying the persistent behavioral changes observed in OUD. The neuron-specific potassium-chloride cotransporter KCC2 is a critical regulator of inhibitory signaling through its control of intracellular chloride in GABAergic neurons. Disruption of KCC2 function can shift GABAergic transmission from hyperpolarizing to depolarizing, with significant consequences for circuit function. Previous work has shown that exposure to addictive drugs reduces KCC2 expression in midbrain GABAergic neurons, contributing to maladaptive behavioral outcomes. However, whether KCC2 dysfunction in the SNr contributes to maladaptive behavioral persistence and deficits in the regulation of ongoing actions is unknown. Here, we test whether restoring KCC2 function in the SNr can reduce the persistence of maladaptive behaviors following opioid exposure. Our preliminary data demonstrate that KCC2 downregulation in the SNr is sufficient to disrupt adaptive transitions between behavioral states; virally-mediated upregulation of KCC2 in the SNr following morphine self-administration improves social interaction and normalizes threat perception. In parallel, KCC2 downregulation in opioid-naïve animals is sufficient to recapitulate multiple behavioral alterations observed following morphine exposure, including reduced social interaction and heightened threat perception, while also increasing approach behavior during a virtual prey capture task. These findings suggest that disrupted SNr inhibitory signaling alters the ability to appropriately enter, maintain, and exit behavioral states. Together, these findings identify KCC2-dependent inhibitory signaling in the SNr as a novel mechanism regulating behavioral state transitions and the control of ongoing actions, highlighting this circuit as a potential target for correcting maladaptive behavioral states associated with chronic opioid exposure.

Disclosures: A.C. Pearson: None. **A. Ostroumov:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.11/HH30

Topic: H.08. Drugs of Abuse and Addiction

Support: R01 DA049257

Title: Effects of Intranasal Galanin on Morphine-Induced Conditioned Place Preference

Authors: *E. GUO, B. S. PATE, J. C. WONG, D. WEINSHENKER;
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Abstract: Opioid use disorder (OUD) is driven in part by the rewarding and reinforcing effects of opioids on mesolimbic dopamine circuitry. Galanin, an endogenous neuropeptide, has been shown to attenuate opioid reward when administered intracerebroventricularly, but its therapeutic application is limited by poor blood-brain barrier permeability. This study evaluated whether intranasal (IN) delivery of galanin-loaded nanoparticles could provide a noninvasive strategy for central nervous system (CNS) galanin delivery and modulate opioid reward-related behavior. To assess CNS delivery, mice received IN galanin nanoparticles and were tested in a flurothyl-induced seizure susceptibility assay. IN galanin nanoparticles (1.4 mg total nanoparticles; 140 μg galanin, 10% loading) produced a borderline significant decrease in generalized tonic-clonic seizure onset latency, suggesting CNS penetration. To assess opioid reward, mice underwent a morphine conditioned place preference (CPP) paradigm. Morphine (1 mg/kg) induced significant place preference. While IN galanin nanoparticles (0.5 mg total nanoparticles; 50 μg galanin, 10% loading) did not significantly attenuate morphine-induced CPP compared with IN vehicle, the galanin-treated group showed a non-significant trend toward lower preference. Analysis of locomotor activity during conditioning indicated that IN galanin did not alter morphine-induced changes in activity, suggesting that group differences in CPP cannot be attributed to gross locomotor effects. Together, these findings suggest that IN galanin-loaded nanoparticles may provide a promising approach for CNS galanin delivery. Future studies optimizing dose, delivery efficiency, assay reliability, and sample size are needed to better evaluate the therapeutic potential of IN galanin for OUD.

Disclosures: E. Guo: None. **B.S. Pate:** None. **J.C. Wong:** None. **D. Weinshenker:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.12/HH31

Topic: H.08. Drugs of Abuse and Addiction

Support: , New Jersey Commission on Brain Injury Research Grant CBIR25IRG022

Title: Effects of Repetitive Mild Traumatic Brain Injury on Oxycodone Taking, Seeking, and Accumbal AMPAR Subunit Expression

Authors: *T. M. BRISCOE[1], C. BEAULIEU[1], E. PAPADOPOULOS[2], R. L. NAVARRA[2], J. A. LOWETH[2];
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Abstract: Experiencing repeated mild head injuries such as concussions can alter reward processing and increase addiction liability. Consequently, individuals suffering from traumatic

brain injuries (TBIs) are at heightened risk for misusing prescription opioids such as oxycodone used to treat injury-induced pain. This risk may be particularly high following repetitive mild TBIs (rmTBIs), as these individuals often experience persistent pain symptoms that may increase exposure to prescription opioids. However, the neuronal mechanisms through which rmTBI increases prescription opioid addiction and relapse vulnerability remain poorly understood. Drug-associated cues are among the most common relapse triggers. In preclinical rodent models, cue-induced oxycodone seeking progressively increases during abstinence and is widely used as a measure of relapse vulnerability. These time-dependent increases in oxycodone seeking are mediated by enhanced excitatory transmission within the nucleus accumbens (NAc) driven by the accumulation of higher-conductance, calcium-permeable AMPA receptors (CP-AMPARs). CP-AMPARs also accumulate following TBI in brain regions proximal to the injury. However, how rmTBI impacts CP-AMPAR accumulation within the mesolimbic reward circuitry remains unknown. We assessed this using a closed head controlled cortical impact model to induce 3 head injuries to mimic rmTBI. Male and female Sprague-Dawley rats underwent rmTBI or sham procedures beginning at 8–10 weeks of age and tissue was collected 48 hrs following the third and final injury (n=7) or sham surgery (n=9). Interestingly, rmTBI increased NAc GluA1 expression without altering GluA2 expression, consistent with CP-AMPAR accumulation. When a separate group of animals self-administered oxycodone (0.1 mg/kg/infusion; 6 hrs/day for 10 d) 3 days following the final injury, injured animals (n=9) exhibited greater oxycodone intake over the last five days of self-administration compared to sham controls (n=9). These same injured animals showed enhanced cue-induced oxycodone seeking during early abstinence (day 1), a time point at which seeking behavior is low in non-injured animals. Ongoing studies are determining the time course of NAc AMPAR subunit expression to better understand whether these neuroadaptations contribute to the initiation and/or maintenance of injury-induced increases in oxycodone taking and seeking. Together, these findings suggest a potential neurobiological mechanism through which rmTBI alters reward circuitry to increase oxycodone addiction vulnerability.

Disclosures: T.M. Briscoe: None. **C. Beaulieu:** None. **E. Papadopoulos:** None. **R.L. Navarra:** None. **J.A. Loweth:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.13/HH32

Topic: H.08. Drugs of Abuse and Addiction

Support: DA25267
DA048353

Title: Differential Reinforcing and Respiratory Profiles of Natural and Semi-Synthetic Kratom Alkaloids in Rats

Authors: *J. D. ZUARTH GONZALEZ[1], C. R. MCCURDY[2], J. WILKERSON[3], L. R. MCMAHON[1], S. OBENG[1];
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Abstract: Kratom (Mitragyna speciosa) is widely used to self-treat a plethora of ailments, including pain and opioid use disorder, but the abuse potential and respiratory safety of its individual alkaloids and of emerging semi-synthetic analogs remain poorly described. We characterized the reinforcing and respiratory effects of mitragynine (MG), its metabolite 7-hydroxymitragynine (7-HMG), three minor alkaloids (speciociliatine, speciogynine, paynantheine), and three semi-synthetic analogs (analogs 1, 2, and 3) in male and female Sprague-Dawley rats. Reinforcing effects were assessed by intravenous self-administration using a within-session, multi-component procedure (FR5) in rats trained on remifentanil. Each compound was substituted across a range of doses, and reinforcing efficacy was quantified as area under the dose-response curve and compared to vehicle by one-way repeated-measures ANOVA. Respiratory effects were measured separately by whole-body plethysmography after intravenous bolus infusion, with respiratory frequency, tidal volume, and minute ventilation expressed as percent of pre-drug baseline. In self-administration, remifentanil and 7-HMG were reliably self-administered above vehicle, whereas MG and the three minor alkaloids were not. All three analogs maintained responding above vehicle, with analog 3 producing a remifentanil-like profile. In plethysmography assay, morphine produced dose-dependent decreases in frequency, tidal volume, and minute ventilation, and 7-HMG produced comparable dose-dependent respiratory depression, whereas intravenous MG did not significantly affect any parameter. The analogs produced milder and more variable effects, none reaching the sustained respiratory depression of 7-HMG: analog 1 produced brief decreases in frequency and minute ventilation at 15 min followed by increased frequency at 60 min, analog 2 increased frequency with no respiratory depression, and analog 3 decreased frequency and minute ventilation only at 15 min. These results show that reinforcing effects and respiratory depression dissociate across this compound set. 7-HMG carries both reinforcing and respiratory liability, MG carries little of either by the intravenous route, and the semi-synthetic analogs retain abuse-related effects while producing only transient or stimulatory respiratory effects. Notably, analog 3 has recently appeared in consumer products and forensic casework as MGM-15, making its strong reinforcing profile a pressing concern alongside concentrated 7-HMG products.

Disclosures: J.D. Zuarth Gonzalez: None. **C.R. McCurdy:** None. **J. Wilkerson:** None. **L.R. McMahon:** None. **S. Obeng:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.14/II1

Topic: H.08. Drugs of Abuse and Addiction

Support: NIMH Grant R01MH137057

Title: A comparison of oxycodone and fentanyl consumption in an oral self-administration model

Authors: *Z. A. HUSAINI[1,2], M. R. MASI[1,2], K. N. HOFFMANN[2], G. V. CARR[1,2]; [1]Physiology, Pharmacol. & Therapeut., Johns Hopkins Sch. of Med., Baltimore, MD; [2]Drug Discovery, Lieber Inst. for Brain Develop., Baltimore, MD

Abstract: In the face of the opioid epidemic, which has been persisting as a critical global public health issue for approximately 30 years, modeling addiction and measuring the subjective effects of opioids are crucial to understanding opioid use disorder (OUD). In this study, we established a stable consumption model of oral self-administration (SA) for oxycodone and fentanyl and conducted a direct comparison of the two with respect to SA behavior. Male and female C57BL/6J mice were 9 weeks old at the start of experiments. One cohort completed oxycodone SA and another completed fentanyl SA, with each cohort consisting of 16 males and 8 females. Mice underwent the SA training postprandially, beginning with fixed-ratio (FR) 1 water SA, then progressing to an FR2 schedule of increasing oxycodone or fentanyl concentrations, self-administering each dose for 3 days. After completing this training, mice then underwent non-postprandial testing. Mice self-administered oxycodone or fentanyl at 1 mg/mL or 0.04 mg/mL, respectively, on an FR2 schedule for 12 days. Rewards earned and drug consumed (mg/kg) were analyzed during the postprandial (PP) and non-postprandial (NPP) phases, with sex as an independent variable. During the PP phase, females consumed significantly more oxycodone than males (2-way ANOVA, $p=0.0097$). During the NPP phase, males and females demonstrated stable responding across 12 days for both oxycodone and fentanyl. The number of rewards earned was not significantly different between oxycodone and fentanyl for males and females. Females consumed significantly more oxycodone (2-way ANOVA, $p<0.0001$) and fentanyl (2-way ANOVA, $p<0.0001$) than males during the NPP phase. Our findings establish this SA method as a reliable way to measure the subjective effects of opioids. We successfully modeled stable consumption of oxycodone and fentanyl, demonstrating the reinforcing nature of these substances and showing that mice titrate consumption based on the subjective effects. Additionally, we observed notable sex differences, with females consuming significantly more oxycodone and fentanyl than males during stable consumption, which is consistent with pre-clinical and clinical literature. Overall, this study provides a key comparison between the reinforcing effects of oxycodone and fentanyl and establishes a useful model to study stable consumption of drugs of abuse. Modeling these steps in addiction - establishment and maintenance - furthers our understanding of the beginning phases of opioid addiction and the role positive reinforcement plays in developing OUD.

Disclosures: Z.A. Husaini: None. **M.R. Masi:** None. **K.N. Hoffmann:** None. **G.V. Carr:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Own stock options in LongTermGevity, Inc. F. Consulting Fees (e.g., advisory boards); Scientific advisor to LongTermGevity, Inc.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.15/II2

Topic: H.08. Drugs of Abuse and Addiction

Support: R00DA054265
30044641S2

Title: Profiling Fentanyl Opioid-associative Learning Phenotypes in Male and Female Mice

Authors: *K. J. FLORES-FELIX[1,3], B. ASARE-OWUSU[1,3], N. SHARMA[4], C. NELSON[2,3], B. JUAREZ[1,3];
[1]Neurobio., [2]Psychiatry, Univ. of Maryland Baltimore, Baltimore, MD; [3]Kahlert Inst. for Addiction Med., Baltimore, MD; [4]Univ. of Maryland, Col. Park, College Park, MD

Abstract: Opioid use disorder is considered a global public health crisis, with fentanyl driving the latest opioid overdose wave. Fentanyl is described as a potent opioid with high mortality. Due to this, it is essential that we understand the effects of fentanyl on the reward circuit and its relationship with the progression from binge opioid use to opioid use disorder. Recent findings have identified recruitment of functionally diverse dopamine subpopulations of the ventral tegmental area (VTA) to opioids such as morphine and heroin. However, fentanyl's effect on these populations remains understudied. In our lab, we use genetically identified dopamine neurons that have been shown to be anatomically and functionally diverse and drive distinct aspects of food reward. We use cholecystokinin (Cck) neurons to identify VTA dopamine neurons projecting to the nucleus accumbens (NAc) medial shell and corticotropin-releasing hormone type 1 high-affinity (Crhr1) neurons to identify VTA dopamine neurons projecting to the NAc core. Here, we seek to elucidate how fentanyl impacts opioid reward learning and the recruitment of subpopulations of VTA dopamine neurons. We used a conditioned place preference (CPP) behavioral paradigm to study the opioid-associative learning behavior of male and female C57BL/6J mice using different fentanyl concentrations (0.2 and 0.05 mg/kg). We found that male mice develop CPP with both fentanyl doses when compared to their saline counterparts, whereas female mice developed a fentanyl CPP only with 0.2 mg/kg fentanyl dose, but not with 0.05 mg/kg dose. In order to determine if this is due to differential fentanyl-mediated activation of VTA dopamine subpopulations, we performed immunohistochemistry for cFos, an immediate early gene and indicator of increased neuronal activity, after a single exposure to fentanyl at those two doses. Our cFos quantification results showed that VTA^{Cck} dopamine subpopulations are preferentially activated in males after a single injection of 0.05 mg/kg and 0.2 mg/kg of fentanyl. Female cFos data shows increase in expression only with the highest fentanyl dose (0.2 mg/kg). These data suggest that fentanyl produces opioid associative learning, but males and females might have different sensitivities to fentanyl concentrations, while the cFos data suggest that VTA^{Cck} dopamine neurons might be preferentially activated during initial exposure to opioids.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.16/II3

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA Grant 5R01DA056658
NRF Grant RS-2023-00245060

Title: Opposing opioid actions in the brainstem dissociate analgesia and seeking

Authors: *H. KIM[1], G. PYEON[1], S. J. KANG[1], M. YE[2,1], R. POLT[3], J. M. STREICHER[4], S. HAN[1];
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Abstract: Opioid drugs remain the most effective treatments for severe pain, yet their clinical use is limited by the risk of addiction. Both analgesia and reinforcement are widely attributed to activation of the same opioid receptor, creating a longstanding paradox in which a single receptor produces opposing behavioral outcomes through unknown circuit mechanisms. Resolving how opioids produce these opposing behavioral effects remains a central challenge in addiction biology. Here we show that distinct neuronal circuits in the lateral parabrachial nucleus dissociate opioid reinforcement from analgesia. Projection-specific manipulations reveal that neurons in the external lateral parabrachial nucleus projecting to the central amygdala are required for opioid analgesia, whereas neurons in the dorsolateral parabrachial nucleus projecting to the ventral tegmental area drive opioid reinforcement. Opioids inhibit the analgesia-mediating pathway but activate the reinforcement-mediating pathway, which in turn promotes dopamine release in the nucleus accumbens. This excitation requires signaling through heterodimers of μ- and δ-opioid receptors expressed in reinforcement-driving parabrachial neurons. Selective disruption of this heterodimer signaling suppresses opioid reinforcement without impairing analgesia. These findings identify the parabrachial nucleus as a central hub that separates the beneficial and addictive actions of opioids and suggest a strategy for reducing opioid addiction liability while preserving pain relief.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.17/II4

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH K99DA056691

Title: Central amygdala neurons activated during opioid withdrawal drive aversion in mice

Authors: *R. SLIVICKI[1], R. W. GEREAU, IV[2];
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Abstract: Opioid use disorder remains a major driver of morbidity and mortality, with withdrawal-associated aversive states contributing to relapse. The central amygdala (CeA) has been implicated in opioid withdrawal, but the specific subpopulations driving the somatic versus affective components remain poorly defined.
To map CeA activation during withdrawal, we precipitated withdrawal with naloxone in mice rendered opioid-dependent through repeated oxycodone administration. Whole-CeA cFos quantification showed broad activation across CeA subregions in withdrawn animals relative to naive and saline controls.
To gain genetic access to the withdrawal-activated population, we used Fos2A-iCreER (FosTRAP2) mice in combination with AAV-DIO-hM3D(Gq)-mCherry, capturing CeA neurons active during oxycodone withdrawal. Reactivation of these tagged neurons with clozapine N-oxide (CNO) in drug-naive animals produced a robust conditioned place aversion, indicating that this ensemble is sufficient to drive negative valence in the absence of the withdrawal state.
These data identify a withdrawal-activated CeA ensemble that is sufficient to encode the aversive component of opioid withdrawal, corroborating and extending recent work implicating the CeA in opioid withdrawal-induced negative affect.

Disclosures: R. Slivicki: None. **R.W. Gereau:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.18/II5

Topic: H.08. Drugs of Abuse and Addiction

Support: VA Merit Review BX006167

Title: Novel cyclic glycopeptide endomorphin-1 analog A2 provides potent and prolonged inhibition of pain signaling (antinociception) without reward-related behaviors of conditioned place preference and self-administration, or locomotor effects in male and female rodents.

Authors: *A. T. AMGOTT-KWAN[1,3], L. FERREIRA NAKATANI[1,2,3], U. KUMAR-MONTEI[3], R. POLT[4], J. E. ZADINA[1,3];
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Abstract: Opioids acting at the mu opioid receptor remain the gold standard for moderate to severe pain relief; however serious side effects, particularly abuse liability, limit their use and development. We previously showed that ZH853, a cyclized analog of endomorphin-1, provided inhibition of pain-like behaviors comparable to that of morphine in rodents. These analgesic-like effects were coupled with reduced or absent side effects, including abuse liability. More recently, we demonstrated that A2, a new glycosylated cyclic analog of endomorphin-1, further improved pain-inhibiting effects in mice by providing 2- to 8-fold (mg/kg and μmol/kg respectively) more potent than morphine with longer duration reflected by 5-to 20-fold greater area under the curve. Here we examine the effects of glycosylated analog A2 in rodent models of drug reward and locomotor behavior. Morphine produced conditioned place preference (CPP), locomotor activation, and locomotor sensitization in male mice while equi-antinociceptive doses of A2 did not. Furthermore, oxycodone, but not equi-antinociceptive A2, induced self-administration (SA) and locomotor activation in male and female rats. Lastly, we found that fully antinociceptive A2 did not induce motor impairment as indicated by a lack of suppression of operant responding for sucrose and no effect on performance in the rotarod test of motor coordination in male rats. The results support the development of the novel analog A2 as a highly effective pain medication with low or absent abuse liability.

Disclosures: A.T. Amgott-Kwan: None. **L. Ferreira Nakatani:** None. **U. Kumar-Montei:** None. **R. Polt:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on patents covering compounds characterized here. These are assigned to Tulane University under joint agreement with The Department of Veterans Affairs and University of Arizona. **J.E. Zadina:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); inventor on patents covering compounds characterized here. These are assigned to Tulane University under joint agreement with The Department of Veterans Affairs and University of Arizona..

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.19/II6

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA R01DA014133
NIMH R01MH129306

Title: Divergent transcriptional states distinguish high- and low-escalating oral oxycodone self-administration and persist into protracted abstinence

Authors: *B. T. KIPP[1], T. M. GYLES[3], C. A. MCLAIN[2], N. NAKATSUKA[5], V. KONDEV[1], L. HOLT[6], E. J. NESTLER[4];
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Abstract: Why only some individuals exposed to opioids develop persistent, compulsive use remains a central unanswered question in opioid use disorder (OUD). Most work on opioid-induced molecular adaptation reflects the acute or actively-using state, leaving unclear whether the neurobiological differences accompanying divergent drug-taking trajectories are transient features of exposure or stable states that emerge during abstinence. Using a homecage oral oxycodone self-administration paradigm, singly housed adult male and female C57BL/6 mice received increasing oxycodone concentrations in drinking water before 14 days of 1 mg/mL two-bottle choice, or water (CON). A clustering-based approach separated consumers into High Escalators (HE), which escalate to high oxycodone intake, and Low Escalators (LE), which consume far less while still developing dependence. Thirty days into abstinence, HE and LE mice remained behaviorally divergent, with HE animals showing greater oxycodone seeking and negative affective behavior consistent with the clinical course of OUD. RNA sequencing of the prefrontal cortex (PFC) and nucleus accumbens (NAc) followed by Multiscale Embedded Gene Co-expression Network Analysis (MEGENA) revealed that LE mice mount a robust, coordinated transcriptional reorganization during abstinence that is markedly attenuated in HE mice. Despite their lower intake, LE animals show more active molecular response to abstinence, suggesting that recovery from opioid dependence is an active transcriptional process, a form of adaptive resilience, that is blunted in animals that escalate their use.Supported by NIDA

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.20/II7

Topic: H.08. Drugs of Abuse and Addiction

Support: Brain and Behavior Research Foundation Young Investigator Grant 33167
Research Corporation for Science Advancement Scialog Grant SA-MBC-2024-067a

Title: Investigating the properties of fentanyl-paired cues using Pavlovian-to-Instrumental Transfer

Authors: *S. MILLER[1], K. M. FRASER[2];
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Abstract: We know much about the properties of cues paired with natural rewards but have considerably less understanding of drug-paired cues, owing to difficulty in Pavlovian conditioning with intravenous drugs as the reward. This leaves the field with a dearth of understanding of whether these cues are imbued with general reward motivation or drug-specific motivation. Our first aim was to develop a model for homecage oral fentanyl intake and assess the ability of oral fentanyl to serve as a reward in Pavlovian conditioning. For our second aim, we utilized a Pavlovian-to-Instrumental Transfer task to investigate how Pavlovian cues paired with an opioid contribute to complex motivational processes to sustain drug-seeking. First, we allowed 36 Long-Evans rats (18 males, 18 females) the opportunity to consume 20 µg/mL fentanyl citrate in water for 24 hours, 3 days a week for 1 month on an intermittent access schedule. A subset of these rats (6 males, 6 females) were then given varying concentrations of fentanyl (10, 20, 40 and 80 µg/mL). We found reliable homecage consumption of fentanyl (on average 1.79 mg/kg for males; 2.097 mg/kg for females) and that rats exhibited increases in consumption at increasing doses up to 80 µg/mL fentanyl. When we attempted Pavlovian conditioning where an auditory cue predicted fentanyl delivery (CS+) we found that, despite reliable homecage consumption, rats would not consume fentanyl during training. When water-restricted (1 hour water/day), rats reliably consumed fentanyl during conditioning - a valuable result for the field. Next, we conducted 3 experiments with different variations of the Pavlovian-to-Instrumental Transfer (PIT) task. General PIT examines the general increase in instrumental responding that a stimulus elicits through its association with reinforcement generally, whereas Specific PIT investigates a potentially outcome-specific enhancement of an instrumental action based on the distinct properties of a unique outcome. Each cohort of rats contained 6 males and 6 females, and were water restricted (1 hour water/day). One group of rats underwent a General PIT test with only a fentanyl (40 ug/mL) reward, one group underwent a Specific PIT test with both a fentanyl (40 ug/mL) and a 5% sucrose reward and one group underwent a Specific PIT test with 5% sucrose and 5% maltodextrin rewards. Across these 3 experiments, we assessed how cues paired with fentanyl enhance fentanyl-seeking actions, whether fentanyl-cues specifically enhance fentanyl-seeking actions or generalize to sucrose-seeking actions, and if homecage fentanyl consumption alters the ability to express reward-specific motivation more broadly.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

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Program #/Poster #: PSTR151.21/II8

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000644
ZIA-AA000218

Title: Combined mineralocorticoid and glucocorticoid receptor antagonism suppresses fentanyl vapor self-administration in mice

Authors: *Z. GACSO[1], C. S. WILKINSON[2], F. BURTON[3], G. F. KOOB[4], L. LEGGIO[5], L. F. VENDRUSCOLO[6];
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Abstract: Opioid use disorder remains a significant public health burden, with high rates of overdose-related mortality and limited treatment efficacy. Chronic opioid exposure and repeated cycles of withdrawal dysregulate stress signaling within the hypothalamic-pituitary-adrenal axis and extrahypothalamic brain regions, contributing to opioid dependence and compulsive drug intake. Restoration of stress-related circuitry may therefore represent a potential therapeutic target for addiction. Sixteen male mice underwent either short-access (ShA; 1 h) or long-access (LgA; 6 h) fentanyl vapor self-administration sessions to model nondependent and dependent opioid intake, respectively. The effects of the mineralocorticoid receptor (MR) antagonist finerenone and the glucocorticoid receptor (GR) antagonist miricorilant were evaluated on fentanyl self-administration under a fixed-ratio 1 schedule of reinforcement and during progressive ratio 6 testing. Both antagonists reduced fentanyl vapor self-administration and motivation to obtain fentanyl in ShA and LgA male mice. Next, combined treatment with low, individually ineffective doses of finerenone and miricorilant was evaluated. We found that this combination produced greater reductions in fentanyl self-administration in dependent mice. These findings support a mechanistic link between stress signaling and the neurobiological processes underlying opioid dependence and suggest that combined GR+MR antagonism may represent a potential strategy for the treatment of opioid use disorder. This strategy has translational relevance because both compounds have been evaluated in humans: finerenone is FDA-approved, whereas miricorilant is an investigational compound with a favorable safety profile.

Disclosures: Z. Gacso: None. **C.S. Wilkinson:** None. **F. Burton:** None. **G.F. Koob:** None. **L. Leggio:** None. **L.F. Vendruscolo:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.22/II9

Topic: H.08. Drugs of Abuse and Addiction

Support: DA059601

Title: Roles of nucleus accumbens D1 and A2a medium spiny neurons and the prefrontal cortex-nucleus accumbens pathway in incubated oxycodone craving

Authors: *L. L. HUERTA SANCHEZ[1], H. M. KUHN[2], G. S. DRISCOLL[2], L. R. TEPE[1], J. G. WESTLAKE[2], T. YIU[2], M. E. WOLF[2];
[2]Behavioral Neurosci., [1]Oregon Hlth. & Sci. Univ., Portland, OR

Abstract: The incubation of craving is a behavioral phenomenon in which cue-elicited craving increases during a period of drug abstinence. Previous work from our laboratory demonstrated that Ca^{2+}-permeable AMPA receptors (CP-AMPARs) upregulate in the nucleus accumbens (NAc) after oxycodone (Oxy) self-administration, and that this adaptation is required for the expression of incubated Oxy craving. Although enduring neuroadaptations occur throughout the NAc and prelimbic cortex (PL) of the medial prefrontal cortex, their specific contributions to Oxy seeking remain unclear. We used both chemogenetic strategies to elucidate the role of D1 and A2a MSN in incubated Oxy seeking (Study 1) and fiber photometry to record Ca^{2+} activity within NAc nerve terminals of the PL-NAc core (NAcC) pathway on abstinence day (AD) 1 or 21 (Study 2). In Study 1, adult male and female D1-Cre and A2a-Cre transgenic rats received a bilateral injection of AAV-hM4Di (inhibitory DREADD) into the NAcC and then underwent IV self-administration training (IV-SA) (6 h/day x 10 days) for Oxy reinforcement paired with a light cue. On AD21, when incubation has occurred, rats were injected systemically with the DREADD ligand J60 or vehicle and then underwent a test for cue-elicited Oxy seeking. In Study 2, wildtype male and female rats received bilateral injection of the Ca^{2+} indicator jGCaMP8s into the PL and an optic fiber was implanted into the NAcC to record nerve terminal Ca^{2+} activity during AD1 and AD21 seeking tests. Preliminary data from Study 1 show that chemogenetic inhibition of A2a MSN within the NAcC reduced cue-elicited Oxy seeking, while chemogenetic inhibition of D1 MSN did not produce a significant effect. In Study 2, preliminary fiber photometry recordings have not shown significant alterations in PL-NAcC Ca^{2+} activity during expression of Oxy incubation. Other rats received retrograde Cre in the NAcC and Cre-dependent jGCaMP8s in the PL, and recordings from PL are underway. For both Study 1 and 2 additional animals are needed to confirm these effects. Altogether, these data show that D1 and A2a MSN in the NAcC may have distinct roles in the expression of incubated Oxy craving, while the role of the PL-NAcC pathway remains to be determined.

Disclosures: L.L. Huerta Sanchez: None. **H.M. Kuhn:** None. **G.S. Driscoll:** None. **L.R. Tepe:** None. **J.G. Westlake:** None. **T. Yiu:** None. **M.E. Wolf:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.23/II10

Topic: H.08. Drugs of Abuse and Addiction

Support: DA059601
DA064365

Title: The role of glutamatergic inputs and the μ-opioidreceptor expressing medium spiny neurons of the rat nucleus accumbens in mediating oxycodone incubation

Authors: *H. M. KUHN, E.-K. HWANG, L. L. HUERTA SANCHEZ, L. R. TEPE, J. G. WESTLAKE, M. E. WOLF;
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Abstract: One diagnostic criterion for opioid use disorder is craving, which can persist even after long periods of abstinence. To investigate the neural basis of this phenomenon, we study the incubation of oxycodone (Oxy) craving in adult male and female rats. Rats self-administer Oxy (6 h/d x 10 d, 0.1 mg/kg/infusion) followed by forced abstinence. During abstinence, cue-induced Oxy seeking progressively increases (incubates) and remains elevated for 40+ days following the last self-administration session. Using whole cell patch clamp recordings, we have shown that Ca^{2+}-permeable AMPARs (CP-AMPARs) upregulate in nucleus accumbens (NAc) synapses during Oxy incubation and are required for its expression. CP-AMPAR upregulation after Oxy incubation occurs in both major NAc medium spiny neuron (MSN) subtypes: D1+ MSNs and D2/A2a+ MSNs (A2a colocalizes with D2). This differs from psychostimulant incubation, where CP-AMPAR upregulation is restricted to D1+ MSNs, suggesting distinct forms of plasticity during Oxy incubation. The first goal of this project was to investigate the role of specific glutamate inputs to the NAc in mediating Oxy incubation. The paraventricular nucleus of the thalamus (PVT)-NAc pathway (implicated in both rewarding and aversive behaviors) and the basolateral amygdala (BLA)-NAc pathway (which encodes cue-driven behaviors) are two strong candidates. Whole cell patch clamp recordings combined with optogenetics found synaptic adaptations following Oxy incubation in both PVT-NAc core and PVT-NAc shell pathways although CP-AMPAR upregulation is confined to the latter. Cell type-specific recordings are underway. CP-AMPAR upregulation also occurs in the BLA-NAc core pathway on both D1+ and A2a+ MSN; recordings in BLA-NAc shell are underway. The second goal was to investigate the role of MSNs that express the μ-opioid receptor (MOR+ MSN). RNAscope was used to confirm that MOR is expressed in a subset of D1 and A2a MSN. We then performed chemogenetic studies in which a Cre-dependent inhibitory DREADD was expressed in the NAc core of MOR-Cre rats. Inhibition of MOR+ MSNs by administering the DREADD ligand J60 (0.3 mg/kg, i.p.) prior to a late-abstinence seeking test reduced incubated

Oxy seeking. Together, these results suggest input-specific and MSN subtype-specific roles in Oxy incubation.

Disclosures: H.M. Kuhn: None. **E. Hwang:** None. **L.L. Huerta Sanchez:** None. **L.R. Tepe:** None. **J.G. Westlake:** None. **M.E. Wolf:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.24/II11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA R15 DA058910

Title: Opioid Reward in the CMOR Mouse Line - Mu-opioid receptor Deletion on the Cholinergic Interneurons

Authors: *M. JACOBSON[1], S. MONROE[2], C. BEANE[4], A. SHAHANE[3], M. WITTLICH[3], A. K. RADKE[1];
[1]Psychology, Miami Univ., Oxford, OH; [2]Miami Univ., Cincinnati, OH; [3]Miami Univ., Oxford, OH; [4]Auburn Univ., Opelika, AL

Abstract: Opioid Reward in the CMOR MouseLine- Mu-opioid receptor Deletionon the Cholinergic InterneuronsAuthors: Molly C. Jacobson, Sean C. Monroe, Cambria Beane, Anushri Shahane, Matthew J. Wittlich, & Anna K. RadkeKeywords: Opioids, addiction, mu-opioid receptors, reward, motivation
Striatal cholinergic interneurons (CINs) have been implicated in reward and addictive behavior through their ability to regulate dopamine release. These neurons express the mu-opioid receptor (MOR), suggesting they may play a role in opioid reward. Using a line of mice with genetic deletion of MOR on cholinergic neurons (ChAT-Cre/Oprm1fl/fl), we have previously found that manipulation of cholinergic MOR alters locomotor behavior, sucrose intake, and nicotine preference, with some behavioral changes dependent on sex. Here, we examined the effect of cholinergic MOR deletion on opioid-related behaviors, including morphine-induced conditioned place preference (CPP), oral fentanyl intake in the home cage and in an operant task, and locomotor sensitization to morphine. Conditioned place preference (two sessions of 30mg/kg morphine vs. two sessions of saline) did not differ between Cre- controls and Cre+ mice with the deletion. Oral fentanyl intake was unaffected by genotype in the home cage (10ug/mL for two hours during the dark cycle), but was transiently higher in Cre+ mice using an operant task (10ug/mL for two hours, FR1). Most strikingly, locomotor sensitization (20mg/kg morphine for 8 sessions) was absent in male mice with ChAT-MOR deletion. These results demonstrate a sex-dependent role for cholinergic MOR in locomotor sensitization to opioids, suggesting they may play an important role in addiction.

Disclosures: M. Jacobson: None. **S. Monroe:** None. **C. Beane:** None. **A. Shahane:** None. **M. Wittlich:** None. **A.K. Radke:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.25/II12

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA R15 DA058910

Title: A supporting role for nucleus accumbens shell cholinergic mu opioid receptors in opioid withdrawal

Authors: *E. A. CITOLER[1], S. MONROE[2], A. K. RADKE[1];
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Abstract: The opioid epidemic is one of the most concerning public health crises to arise in the last 30 years. Opioid Use Disorder (OUD) is a chronic brain disease characterized by cravings, repeated usage of the drug despite aversive consequences, and the experience of withdrawal. Withdrawal is a particularly debilitating symptom of OUD, and a major driver of relapse. Mu opioid receptors (MORs) have been established as a primary mediator of opioid related behaviors, but their specific role in cholinergic interneurons (CINs) in the striatum has yet to be fully investigated. To address this gap, a study was conducted utilizing a line of ChAT-Cre/Oprm1$^{fl/fl}$ mice, which have a genetic deletion of MOR in cholinergic cells. Conditioned Place Aversion (CPA) was used to examine how the genetic manipulation of MORs impacts withdrawal. Each mouse received a total of 6 sessions: a baseline session, 4 alternating sessions of morphine + naloxone and saline, and a test session. CPA was assessed via the amount of time spent on the morphine/naloxone-paired side of the chamber. With 4 conditioning sessions, CPA was observed and there was a trend for reduced time spent in Cre+ male mice with MOR deletion. An ongoing follow-up study is examining whether larger differences between Cre- and Cre+ mice are observed with additional conditioning sessions. A second set of experiments examined the influence of CINs in the nucleus accumbens shell (NAcs) using a chemogenetic approach.A viral vector containing hSyn-hM3Dq-mCherry was infused in the NAcs of ChAT-Cre mice. Preliminary results suggest stronger withdrawal when NAcs CINs are stimulated ($p = 0.055$). Together, these results suggest that striatal CINs may participate in the aversive signs of opioid withdrawal.

Disclosures: E.A. Citoler: None. **S. Monroe:** None. **A.K. Radke:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.26/II13

Topic: I.03. Decision Making

Support: Mellon Application

Title: Chronic Oxycodone Exposure Disrupts Interoceptive Regulation of Intake in a Conditional Drug Discrimination Procedure

Authors: *N. GHASEM ARDABILI[1], A. L. RILEY[2], K. JIMENEZ[3];
[1]American Univ. DC, Washington DC, MD; [2]Neurosci., American Univ., Washington, DC;
[3]American Univ., Montgomery Village, MD

Abstract: Interoceptive drug-induced state cues present during a drug-taking bout predict that continued use leads to aversive effects and, thus, terminating a drug-taking behavior (Huang et al., 2023; Huang and Riley, 2024). Such findings implicate within-session regulation of drug intake. In this context, factors that impair the ability of interoceptive state cues to signal these aversive outcomes might be expected to contribute to continued/escalated consumption, i.e., substance use disorder (Clasen et al., 2020). One such factor is chronic opioid exposure that has been reported to produce neuroadaptations in systems supporting learning, memory, and behavioral regulation. Less is known about whether such exposure disrupts the use of interoceptive drug cues to control intake. In this context, the present study examined whether chronic oxycodone pre-exposure alters morphine-based conditional stimulus control in a conditioned taste avoidance/drug discrimination (CTA/DDL) procedure in which interoceptive drugs states predict aversive effects. Specifically, male Sprague-Dawley rats were exposed to oxycodone (3 mg/kg, IP) or vehicle once daily for 18 days, followed by an 8-day drug-free termination period. Animals were then trained in a conditional discrimination procedure in which morphine (5 mg/kg, IP) preceded access to saccharin followed by lithium chloride-induced illness, whereas saline preceded saccharin access without illness. Vehicle-pre-exposed animals acquired the discrimination, suppressing saccharin intake on morphine sessions while maintaining intake on saline sessions. In contrast, oxycodone-pre-exposed animals failed to show this conditional pattern and continued to consume saccharin across morphine and saline conditions. Subsequent morphine and oxycodone dose-response assessments, along with locomotor testing following morphine, indicated that oxycodone-pre-exposed animals remained sensitive to the general behavioral effects of opioids. Thus, the deficit did not appear to reflect a loss of morphine's pharmacological effectiveness or a generalized inability to respond to opioid effects. Rather, chronic oxycodone history impaired the ability to use morphine's interoceptive state as a regulatory cue signaling when intake predicts adverse effects. These findings suggest that prior opioid exposure may weaken interoceptive inhibitory control, providing a potential behavioral mechanism through which opioid history contributes to dysregulated drug intake.

Disclosures: N. Ghasem Ardabili: None. **A.L. Riley:** None. **K. Jimenez:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.27/II14

Topic: H.08. Drugs of Abuse and Addiction

Support: The Foundry Ministries, Bessemer, Alabama

Title: Microcurrent Neurofeedback and Attentional Processing of Drug-Related Cues During Substance Use Rehabilitation

Authors: *G. KRISTIANSON[1], S. D. NEWMAN[2];
[1]Alabama Life Res. Institute, Univ. of Alabama, Tuscaloosa, AL; [2]Alabama Life Res. Inst., Univ. of Alabama, Tuscaloosa, AL

Abstract: Substance use disorders are associated with attentional biases toward drug-related cues that may reinforce drug-seeking behavior and contribute to relapse. Few studies have examined whether microcurrent neurofeedback (MCN) influences behavioral and neural responses to drug-related cues during substance use treatment. Drug-cue oddball tasks can assess attentional processing of these cues, while simultaneous EEG recordings provide information about the neural activity associated with cue detection. This study examined whether MCN treatment produced greater improvements in responses to drug-related cues than standard substance use rehabilitation treatment. Sixty individuals undergoing rehabilitation for substance use disorders, approximately half of whom were opioid users, completed a drug-cue oddball task while EEG activity was recorded. Participants were assigned to either standard treatment or MCN treatment. Outcome measures included target detection performance, reaction time, and EEG measures of cue processing. Baseline analyses indicated a stronger P3 event-related potential (ERP) response to opioid-related cues among opioid users compared to non-users, consistent with enhanced attentional allocation to substance-specific stimuli. Post-treatment comparisons showed that the MCN group demonstrated greater improvements in target detection performance, including increased true-positive responses and decreased false-negative responses, with small-to-moderate effect sizes ($d \approx 0.44$). Reaction time and EEG indices were also examined as additional measures of cue processing. These preliminary findings suggest that MCN may be associated with improved behavioral efficiency during drug-cue detection, with ongoing analyses evaluating potential effects on cue-related neural processing. Further work is needed to clarify the robustness and clinical relevance of these effects.

Disclosures: G. Kristianson: None. **S.D. Newman:** None.

Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.28/II15

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA040644

Title: Human Laboratory Analysis of Ovarian Hormone Influence on Opioid Drug Effects in Healthy Participants

Authors: *M. KLAUSNER[1], K. DUNN[1], C. BERGERIA[1], M. SMITH[2], J. STRICKLAND[1]; [1]Univ. of Maryland, Baltimore, Baltimore, MD; [2]Davidson Col., Davidson, NC

Abstract: Opioid use disorder (OUD) is a persistent public health crisis that uniquely impacts women. Biological factors, such as the influence of ovarian hormones, may underlie sex differences in the expression and impact of OUD. Despite this potential influence of ovarian hormones, there are limited clinical data evaluating the association between opioid response and ovarian hormones in humans. This secondary analysis of two completed within-subject human laboratory studies examines how natural variations in baseline ovarian hormone levels were associated with response to acute opioid administration. Healthy women (N = 29) provided blood samples and then received double-blind oral opioid agonist hydromorphone (4mg) or placebo across two experimental sessions. Primary outcomes included subjective effects indicative of abuse liability (e.g., drug effect), analgesic effects using quantitative sensory testing (e.g., cold pressor testing), and physiological effects (e.g., heart rate). There was a significant relationship between estradiol levels and hydromorphone-induced drug effect, such that higher levels of circulating estradiol were associated with higher peak drug effect ($p = .001$). A higher ratio between progesterone and estradiol levels was associated with a lower peak drug effect ($p = .015$). Hormone levels were not associated with physiological effects. There was an association between lower progesterone levels and higher thermal tolerance ($p = .022$) and a lower progesterone to estradiol ratio was related to higher thermal tolerance ($p = .009$) prior to hydromorphone administration. There were no associations of hormone levels with hydromorphone-induced analgesic effects. These data provide an initial evaluation of the relationship between ovarian hormones and hydromorphone-induced effects in humans. Future studies should evaluate similar responses in clinical populations and under greater dose-effect conditions towards the goal of informing treatment approaches for OUD and the use of opioids in co-morbid conditions, like chronic pain.

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Poster

PSTR151: Neural and Behavioral Mechanisms of Opioid Seeking, Withdrawal, and Relapse

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR151.29/II16

Topic: H.08. Drugs of Abuse and Addiction

Title: A Decade of Pediatric Surgical Care at Stanford: Building an Electronic Health Record Dataset for Studying Pediatric Postoperative Pain and Opioid Use

Authors: *B. MINHAS[1], M. ABATE[1], R. MATHER[2], N. YERRAGUNTLA[1], M. ZHANG[1], S. KUNTIPURAM[1], A. SUJAN[1], J. BHAMIDIPATI[1], H. SINGH[1], P. L. PURDON[1], C. GROENEWALD[1], J. RABBITTS[1];
[1]Dept. of Anesthesiology, Perioperative and Pain Med., Stanford Univ. Sch. of Med., Palo Alto, CA; [2]Harvard/MIT MD-PhD Program, Boston, MA

Abstract: Pediatric postoperative pain is frequently undertreated. Opioids, central to its management, carry risks of acute complications, persistent use, misuse and addiction. Identifying interventions that improve pain trajectories without increasing opioid exposure requires longitudinal data at scale. Therefore, we developed and characterized a pediatric surgical cohort derived from the Stanford electronic health record (EHR) to support such investigations. We extracted all surgical encounters from the EHR in patients <18 years at Stanford Children's Health from 2014-2024. Demographics, past medical history (ICD/CPT codes), anesthetic and regional techniques, characteristics of surgery, intraoperative variables, and postoperative outcomes were extracted. Opioid doses were extracted from medication records, weight-normalized, and converted to IV morphine milligram equivalents (MME). 66,513 pediatric patients across 140,312 surgical encounters were included, with annual volume more than doubling from 6,868 (2014) to 15,044 (2024). Patients spanned the pediatric age range; 57% were male and 35% Hispanic/Latino. Race distribution was predominantly Other (36%), White (35%), and Asian (16%). Top services were Otolaryngology (16.9%), General (11.2%), and Orthopedics (9.7%). 128,208,782 pain flowsheet assessments were recorded up to 30 days postoperatively with six developmentally-appropriate instruments (FLACC [81.6M]; NRS 0-10 [34.0M]; N-PASS [7.1M]; Wong-Baker FACES [5.5M]; NVPS [55K]; FPS-R [10K]). 76.0% of encounters received day-of-surgery opioids, with median IV MME of 0.18 mg/kg (IQR 0.09-0.38). Broad trends in pain scores and opioid usage are shown in Figure 1. Our institutional EHR integrates preoperative, intraoperative, and postoperative data across the full pediatric surgical population, enabling causal inference and comparative-effectiveness analyses of intraoperative interventions on postoperative pain and opioid outcomes.

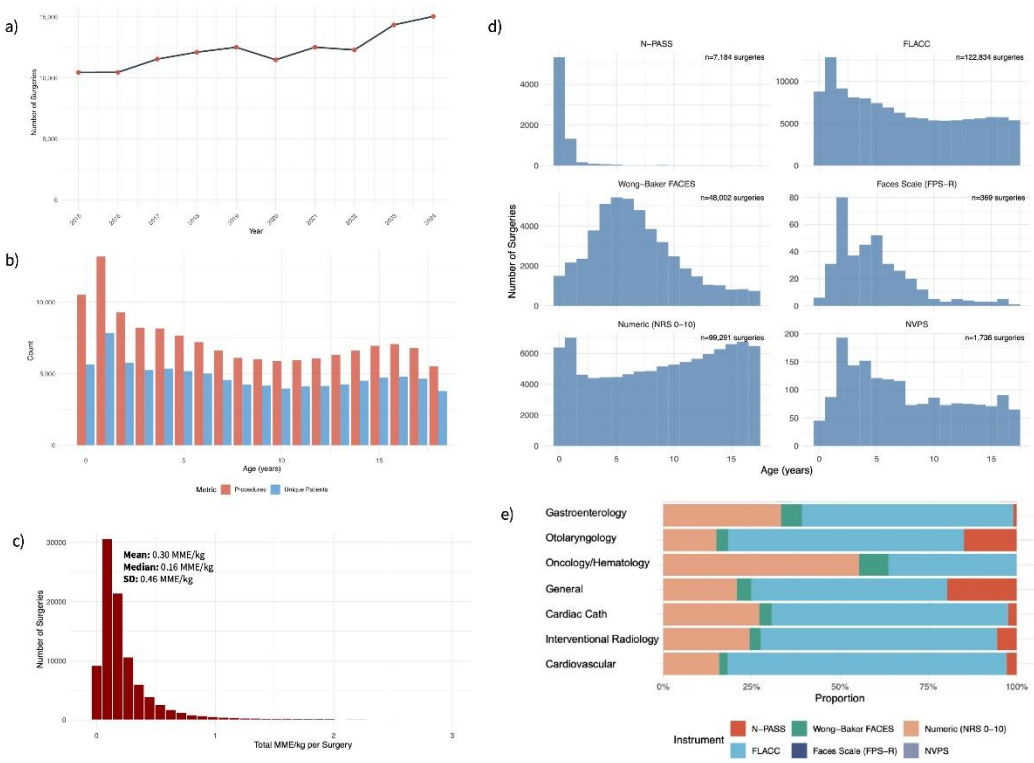


Figure 1. Pain Scores and Opioid Usage Trends
a) Number of Pediatric Surgeries Per Year; b) Distribution at Age of Surgery; c) Total MME/kg Administered Day of Surgery (Intraop and PACU); d) Age Distribution By Pain Score Instrument; e) Pain Score Instrument Proportion by Specialty (Top 7)

Disclosures: B. Minhas: None. **M. Abate:** None. **R. Mather:** None. **N. Yerraguntla:** None. **M. Zhang:** None. **S. Kuntipuram:** None. **A. Sujan:** None. **J. Bhamidipati:** None. **H. Singh:** None. **P.L. Purdon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cofounder, PASCALL Systems (developer of closed-loop physiological control systems for anesthesiology). **C. Groenewald:** None. **J. Rabbitts:** None.

Poster

PSTR152: Neural Substrates of Opioid Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.01/II17

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH NIDA IRP ZIADA000595

Title: Morphine-induced modulation of lateral hypothalamic GABAergic neurons disrupts feeding

Authors: *A. GARCIA[1], H. KIM[1], A. KIM[1], A. F. HOFFMAN[1], D. GUTEMA[1], A. KOTIYAL[2], S. SARSFIELD[1], A. A. PRADHAN[2], C. R. LUPICA[1], Y. APONTE[1]; [1]NIH/NIDA IRP, Baltimore, MD; [2]Ctr. for Clin. Pharmacol., Washington Univ. in St. Louis, St. Louis, MO

Abstract: Opioid use disorder has been associated with maladaptive feeding. In mice, both acute and chronic morphine administration have been shown to reduce food intake and body weight. The GABAergic neurons of the lateral hypothalamus (LH^{VGAT}) regulate feeding and appetitive behaviors and their activation is rewarding and triggers voracious intake of both palatable and non-palatable foods. However, it remains unclear how LH^{VGAT} neurons modulate food intake and body weight during opioid dependence. Here, we used chemogenetics to test whether activation of LH^{VGAT} neurons could overcome the anorexigenic effects of acute morphine administration. Concurrent activation of LH^{VGAT} neurons with morphine administration significantly attenuated morphine-induced hypophagia, increased exploration of the food zone, and blunted morphine-induced hyperlocomotion. We next asked whether LH^{VGAT} activation during morphine dependence could influence feeding behavior and body weight. Although activation increased food intake during dependence, it did not restore body weight, suggesting that LH^{VGAT}-induced feeding does not mitigate morphine-associated weight loss. To determine whether altered thermogenesis contributed to this effect, we recorded core body temperature (CBT) using an intraperitoneal telemetry device before and after chemogenetic activation. Activation of LH^{VGAT} neurons triggered a sustained increase in CBT, consistent with enhanced thermogenesis. We then assessed LH^{VGAT} neuronal activity during acute morphine administration, chronic dependence, and naloxone-precipitated withdrawal using single-photon calcium imaging in awake mice. Acute morphine evoked dynamic changes in LH^{VGAT} responses, including a subpopulation responsive to both saline and morphine. Across dependence and withdrawal, we recorded activity from 157 LH^{VGAT} neurons and identified distinct subpopulations: 6% responded selectively to morphine, 17% responded selectively to naloxone, 10% exhibited opposing responses to morphine and naloxone, and 35% were co-modulated by both drugs. Finally, *in situ* hybridization revealed that approximately 40% of LH^{VGAT} neurons express μ-opioid receptors (MORs). Together, our findings identify LH^{VGAT} neurons as positive modulators of energy balance during morphine exposure and dependence and suggest that increased thermogenesis may limit their ability to restore body weight. Future studies will directly dissect the functional role of MOR-expressing LH^{VGAT} neurons in modulating feeding.

Disclosures: A. Garcia: None. **H. Kim:** None. **A. Kim:** None. **A.F. Hoffman:** None. **D. Gutema:** None. **A. Kotiyal:** None. **S. Sarsfield:** None. **A.A. Pradhan:** None. **C.R. Lupica:** None. **Y. Aponte:** None.

Poster

PSTR152: Neural Substrates of Opioid Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.02/II18

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Intramural Research Program

Title: Control of synaptic GABA release in the lateral hypothalamus by μ-opioid receptors.

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Abstract: Opioid use disorder disrupts feeding by reducing food seeking. Lateral hypothalamic GABAergic neurons (LH^{VGAT+}) regulate feeding, and their activation attenuates anorexigenic effects of morphine. *In situ* hybridization shows that ~40% of LH^{VGAT+} neurons express μ-opioid receptor (MOR) mRNA, though effects of MOR activation on LH^{VGAT+} neurons are unknown. Here, we investigated MOR effects in these neurons using intracellular recordings in fluorescently labeled LH^{VGAT+} cells in transgenic mice. While the MOR agonist DAMGO did not hyperpolarize randomly selected LH^{VGAT+} neurons, the agonist reliably generated hyperpolarizing outward currents in every (6/6) LH neuron co-expressing VGAT and MOR ($LH^{VGAT+/OPRM1+}$). Moreover, this was reversed by the MOR antagonist, CTAP in 1 cell in which recording was maintained long enough for antagonist application. These findings confirm somatodendritic MOR expression in a subset of LH^{VGAT+} neurons. Next, to determine whether MORs also regulate synaptic input to LH cells, we measured spontaneous synaptic currents in LH^{VGAT+} neurons. Whereas DAMGO did not alter glutamatergic sEPSCs, it reduced sIPSC and mIPSC frequency, and this was reversed by CTAP. This shows that GABAergic axon terminals targeting LH^{VGAT+} neurons express MORs. We next evaluated MOR control of GABA release from LH^{VGAT+} inputs targeting LH^{VGAT-} cells. Cre-dependent channelrhodopsin-2 (ChR2) was expressed in LH^{VGAT+} neurons and photoactivated GABAergic oIPSCs were recorded in nearby non-fluorescent, LH^{VGAT-} cells. DAMGO significantly reduced ChR2-evoked oIPSCs in LH^{VGAT-} cells, and this was partially reversed by CTAP. These results show that LH^{VGAT+} neurons provide local circuit inhibition of LH^{VGAT-} neurons and demonstrate MOR control of GABA release at these synapses. Together, our findings indicate that MORs directly inhibit $LH^{VGAT+/OPRM1+}$ neurons, and control GABA release from unknown inputs to LH^{VGAT+} neurons, and at LH^{VGAT+} to LH^{VGAT-} synapses.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.03/II19

Topic: H.08. Drugs of Abuse and Addiction

Title: Anterior insula to anterior cingulate projections regulate cue-induced morphine seeking in rats

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Abstract: Background

Opioid Use Disorder (OUD) is a chronic condition in which exposure to drug-associated cues triggers craving-like states and precipitates relapse. While the anterior insular cortex (AIC) and anterior cingulate cortex (ACC) are important regions related to addiction, the specific contribution of their connectivity to craving-related behavior remains unclear. This study aimed to determine the role of this circuit in morphine-seeking behavior.

Methods

Male and female Wistar rats were trained under operant conditioning schedules (FR1, FR3, and PR; 40 days) to self-administer morphine (0.1 mg/kg/infusion) or saline by lever pressing. After a 10-day extinction period, craving-like behavior was evaluated in a final cue-exposure test under FR1 conditions, in which the light and tone cues previously associated with morphine delivery were presented in the absence of drug availability. Cue-evoked responding was quantified as active lever presses during this test. Circuit organization was evaluated using: 1) retrograde tracing with Fluoro-Gold to determine AIC-ACC projections; and 2) neuronal depletion through viral induction of caspases within this circuit. 3. ResultsThe morphine self-administration model was successfully established, followed by extinction of lever pressing. During the cue-exposure test, rats previously exposed to morphine showed a significant increase in active lever pressing in response to the morphine-associated light and tone cues ($p < 0.05$), indicating cue-induced craving-like behavior. Retrograde tracing confirmed projections from the AIC to the ACC, including bilateral connectivity, with additional labeling observed in the claustrum. Caspase-induced neuronal depletion reduced cue-evoked active lever pressing, suggesting that the AIC-ACC pathway contributes functionally to morphine seeking triggered by conditioned drug cues.

Conclusion

These findings provide anatomical and functional evidence supporting the involvement of the AIC-ACC pathway in cue-driven morphine seeking. The results suggest that this circuit participates in the processing of conditioned drug cues and their ability to elicit craving-like

behavioral responses, highlighting the AIC-ACC pathway as a potential target for modulating opioid-seeking behavior.

Disclosures: B. Martínez Arteaga: None. **S. Maya:** None. **S. Aguilar:** None. **J. García Ochoa:** None. **M.S. Mendoza Trejo:** None. **M. Carbajo Mata:** None. **A. González-Hernández:** None. **G. Martinez-Lorenzana:** None. **L.A. Tellez:** None. **E.A. Garza-Villarreal:** None. **C.J. Carranza-Aguilar:** None.

Poster

PSTR152: Neural Substrates of Opioid Seeking

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Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA061766
R01DA045836

Title: Heroin-cue encoding in prefrontal cortex neurons reveals distinct functional ensembles controlling heroin seeking

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Abstract: Opioid use remains a major health challenge in the United States, accounting for nearly 70% of drug-associated deaths in 2021. Addiction to opioids is characterized by pervasive opioid seeking that results from dysfunction in brain circuits after chronic opioid use. The prefrontal cortex is central to these dysfunctional circuits, but little is known about the microcircuitry and cell types within the prefrontal cortex that regulate opioid addiction and relapse. Using a preclinical model of opioid addiction, we trained adult female and male rats to self-administer intravenous heroin over a period of weeks. We implemented in vivo fiber photometry and optogenetics, combined with a circuit-specific viral approach, to examine the neuronal activity and function of two anatomically distinct prefrontal cortex ensembles. Within the ventromedial prefrontal cortex, one ensemble projects to the nucleus accumbens shell, while the other projects to the lateral hypothalamus. Only a small percentage of collateralization between these targets was observed (~5%). These anatomically distinct neuronal ensembles were found to be activated during heroin-associated cues (tone+light paired with heroin infusions), but not during noncontingent heroin infusions or unrewarded lever presses, measured by calcium transients recorded at the cell bodies (n = 4 rats per ensemble). However, distinct functions for each ensemble were revealed by optogenetic manipulation during the cue-reactivity window (nucleus accumbens shell ensemble: n = 10-11 rats; lateral hypothalamus ensemble: n = 6-7 rats),

with the ensemble projecting to the nucleus accumbens shell functioning as a limiter of heroin seeking, and the lateral hypothalamus-projecting ensemble functioning as a driver of heroin seeking. Importantly, targeting both cue-reactive ensembles simultaneously, using optogenetic activation of the limiter ensemble and inhibition of the driver ensemble (n = 9 rats), was necessary to reduce heroin relapse. This work underscores the importance of cell-type and circuit-specific intervention strategies to more effectively target persistent opioid seeking and relapse in individuals with opioid use disorder.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

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Title: Transcriptional changes in the ventromedial prefrontal cortex following tabernanthalog treatment to reduce heroin seeking

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Abstract: Opioid use disorder (OUD) is a significant global health challenge, and FDA-approved treatments fall short in reducing relapse rates long-term. Psychedelics and psychedelic-like compounds such as ibogaine show promise for treating OUD but are limited by side-effects such as hallucinations and cardiotoxicity. Tabernanthalog (TBG) is a synthetic ibogaine analog capable of inducing structural plasticity in cortical neurons that lacks these side-effects, and a single treatment of TBG reduces long-term heroin relapse in rats. The prefrontal cortex is crucial in regulating drug seeking, with the ventromedial portion (vmPFC) acting to suppress drug seeking via its projections to the nucleus accumbens shell (NASh). The molecular mechanisms by which TBG elicits its therapeutic effects on heroin seeking are unknown.To address this question, we performed single nucleus RNA sequencing (snRNAseq) in the vmPFC following TBG treatment in rats with a history of intravenous self-administration (IVSA) of heroin. Rats received intravenous catheter surgery, and after recovery underwent IVSA of either saline or

heroin in operant boxes for 15 days. On the last day of IVSA rats underwent a progressive ratio test and received either TBG (30mg/kg; i.p.) or vehicle (saline) 30 min prior to the start of the session. TBG treatment reduced heroin break points compared to vehicle controls but had no effect on saline break points. Immediately following the session brains were flash frozen and vmPFC punches were collected for snRNAseq, and we used the 10x genomics chromium platform to prepare cDNA libraries for sequencing. Our 2x2 study design with saline vs. heroin IVSA and vehicle vs. TBG treatment used n=6 rats/group comprised of n=3/sex/group.After raw files were processed in CellRanger and quality control steps taken, the final data set included ~210k cells, and principal component analysis revealed 22 unique clusters of cellular populations. Examining differentially expressed genes (DEGs) revealed that heroin had the greatest impact on excitatory neurons with layer 6 corticothalamic neurons having the most DEGs. Looking at the interaction of heroin and TBG we found the most DEGs in layer 5 extratelecephalic (L5 ET) neurons and layer 2/3 intratelecephalic neurons. A separate snRNAseq study using retrograde AAV tracing revealed that vmPFC neurons projecting to the NASh arise from the L5 ET cluster. Thus, TBG induces transcriptional changes in a population of neurons that includes the vmPFC-NASh projection, a circuit well characterized for its role in the suppression of drug seeking. These transcriptional changes may underlie TBG's therapeutic mechanism of action in OUD treatment.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

Location: WCC Halls A-C

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Program #/Poster #: PSTR152.06/II22

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH NIDA R00DA030002

Title: Sex-dependent remodeling of nucleus accumbens parvalbumin microcircuits in opioid signaling and fentanyl self-administration

Authors: *G. PAN, K. JOHNSON, E. LEFEVRE;
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Abstract: Opioid use disorder involving fentanyl is marked by persistent drug seeking and high relapse vulnerability. The nucleus accumbens (NAc) is a well-characterized substrate of opioid addiction, but the roles of inhibitory interneuron circuits that regulate medium spiny neuron (MSN) output remain less defined. NAc parvalbumin (PV) interneurons provide fast inhibition to

D1- and D2-expressing MSNs, positioning them to strongly regulate accumbal output and drug-seeking behavior. Because ovarian hormones and estrous-cycle state can modulate fast-spiking/PV interneuron physiology and opioid receptor availability in cortical and hippocampal circuits, we tested whether opioid signaling and fentanyl self-administration remodel PV-dependent NAc microcircuits in a sex-dependent manner. In PV-Cre mice expressing Cre-dependent ChR2 in NAc PV interneurons, optically evoked PV-mediated IPSCs were recorded from identified D1- or D2-MSNs before, during, and after DAMGO application. Brief application of DAMGO (1 μM), a μ-opioid receptor agonist, produced long-lasting depression of PV→MSN inhibition, with greater depression of PV→D1 transmission in males than females. To determine whether PV output regulates fentanyl motivation, PV axonal signaling was suppressed using inhibitory DREADDs during progressive-ratio testing after fentanyl intravenous self-administration (IVSA). PV suppression increased motivation for fentanyl only in males and not females, suggesting that loss of PV-mediated inhibition may preferentially disinhibit D1-MSN-associated motivational circuitry in males. In addition, fentanyl IVSA altered PV intrinsic firing in a sex-dependent manner. Together, these data support a model in which opioids remodel NAc PV microcircuits at multiple levels—PV intrinsic excitability and PV→D1/D2 synaptic output—in a sex-dependent manner, revealing potential circuit mechanisms for opioid seeking.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

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Topic: H.08. Drugs of Abuse and Addiction

Support: Burroughs Wellcome Fund
HHMI Freeman Hrabowski

Title: The role of vlPAG disinhibitory circuits in the context of opioid exposure

Authors: *K. ADAMS, M. ANGUIANO, K. GIRI, H. MALI, S. BENNETT, C. K. KIM; Princeton Univ., Princeton, NJ

Abstract: A pressing issue for opioid use in the clinic is the development of tolerance in patients. The changes in neural circuitry that occur due to opioid tolerance in vivo are still being uncovered; research in this field could provide important insights regarding the use of opioids in patients and potential candidates for targeted therapies for pain management. In the present study, we use in vivo fiber photometry and optogenetics in mice to investigate the changes occurring in neural activity after morphine exposure in midbrain circuits relevant to the modulation of pain and how perturbing these circuits affects behavioral responses to pain. To record activity using fiber photometry in GABAergic neurons in the ventrolateral periaqueductal

gray area (vlPAG), we injected AAV5-Syn.Flex.GCaMP6f.WPRE.SV40 in VGAT-IRES-Cre mice, and implanted an optical fiber above. We delivered a s.c. injection of morphine (10 mg/kg) to mice, and observed a morphine-induced decrease in basal peak activity in vlPAG^{vGAT+} neurons (n=4 male, n=2 female mice; p=0.0027; paired t-test); this confirms that morphine canonically works to disinhibit glutamatergic output neurons via inhibition of tonically active GABAergic interneurons. To determine whether this morphine-induced decrease in vlPAG^{vGAT+} activity is affected by morphine tolerance, we administered daily 10 mg/kg morphine for 7 more days and then recorded activity after the last morphine dose. While we did observe thermal nociceptive tolerance occur, we did not observe any significant differences in vlPAG^{vGAT+} activity when compared to the activity after the first morphine dose; this implies that tolerance could be occurring more downstream of this population. We then injected VGAT-IRES-Cre mice with AAV5-Ef1a-DIO eNpHR 3.0-EYFP and implanted an optical fiber to allow optogenetic inhibition of vlPAG GABAergic neurons during a thermal nociception assay. Control animals were injected with AAV5-Syn.Flex.GCaMP6f.WPRE.SV40. We found that optogenetic inhibition of vlPAG^{vGAT+} neurons was sufficient to significantly decrease thermal nociception at baseline as well as rescue the diminished antinociceptive effect of morphine due to tolerance to repeated morphine doses (n=3-4 male and female mice/group). To complement these results, future directions include using membrane-targeted protein labeling and isolation in a cell-type specific manner to investigate the molecular changes occurring at the membrane due to opioid exposure. In addition to this, we plan to use activity-dependent labeling strategies to explore how morphine-activated ensembles in the vlPAG are involved in different aspects of opioid exposure.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

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Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000644

Title: Distinct amygdala neuronal population control opioid use and withdrawal in mice

Authors: *L. SILVA TORTORELLI[1], H. OO[1], S. HAHN[1], Y. ALVAREZ[1], Y. CARRASQUILLO[2], L. F. VENDRUSCOLO[1];
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Abstract: Opioid use disorder (OUD) is a chronic and recurring psychiatric disorder that is associated with high morbidity and mortality. The central nucleus of the amygdala (CeA)

undergoes neuroadaptations in both humans with OUD and opioid-dependent rodents. As part of a heterogeneous microcircuit, the CeA integrates internal and external sensory inputs that drive innate and adaptive behaviors. Key CeA neuronal populations, including protein kinase C-δ (PKC-δ), corticotropin-releasing factor (CRF), and somatostatin (SST) neurons, regulate behaviors that are disrupted in addiction, such as pain, stress, reward function, and anxiety/arousal. We hypothesized that these CeA neuronal populations differentially regulate opioid-related behaviors. We used in situ hybridization to characterize the expression of μ opioid receptor (MOR) (*Oprm1*), and we used behavioral and molecular approaches to assess the functional role of these CeA neuronal populations in opioid-dependent mice. We identified a decrease in *Oprm1* messenger RNA (mRNA) expression in the CeA in opioid-dependent mice that were undergoing withdrawal compared with nondependent mice. In contrast, the expression of PKC-δ (*Prkcd*), CRF (*Crh*), and SST (*Sst*) mRNA levels remained unchanged. The chemogenetic inhibition of $CeA^{PKC\text{-}\delta}$ neurons decreased fentanyl vapor self-administration and alleviated fentanyl withdrawal-induced hyperalgesia. The inhibition of CeA^{CRF} neurons reduced irritability and somatic withdrawal signs. The activation of CeA^{SST} neurons reduced somatic withdrawal signs. These findings suggest that distinct CeA neuronal populations uniquely regulate different aspects of opioid use and withdrawal, highlighting cell type-specific targets for potential therapeutic interventions.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

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Stanford University School of Medicine Department of Psychiatry & Behavioral Sciences 2024 Innovator Grants Program

Title: De Novo Generation of a Habenula-Raphe Social Avoidance Circuit During Fentanyl Abstinence

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Abstract: Social withdrawal is a debilitating and persistent feature of opioid abstinence, yet the circuit adaptations that drive it remain poorly defined. The habenula (Hb), a hub for aversive

processing, is heavily enriched in mu-opioid receptors (Oprm1), positioning it to translate opioid neuroadaptations into negative affect. Using escalating fentanyl dosing followed by naloxone-precipitated withdrawal in mice, we found that protracted abstinence produces robust, progressively worsening social deficits that peak three weeks after the last exposure. Activity-dependent genetic tagging (TRAP2) revealed that acute withdrawal recruits a discrete, spatially restricted ensemble in the medial lateral habenula (LHbM). This same ensemble was selectively reactivated by social stimuli during protracted abstinence, and optogenetic inhibition of these neurons rescued social deficits without altering despair-like behavior, mechanical sensitivity, or producing intrinsic reinforcement. We identified the withdrawal ensemble as Calb1-expressing, Oprm1-enriched neurons concentrated at the MHb–LHb border; fiber photometry showed that both Calb1 and Oprm1 Hb populations are acutely silenced by fentanyl and rebound upon naloxone, and that Calb1 neurons acquire a social-evoked response that emerges only during protracted withdrawal. Anterograde and retrograde tracing established the LHbM–dorsal raphe (DR) projection as the dominant Calb1 output to monoaminergic targets. Inhibition of Calb1/withdrawal-ensemble terminals in the DR was sufficient to restore sociability. Together, these findings define a Calb1/Oprm1 habenula→raphe circuit whose sensitization during opioid abstinence generates a de novo social avoidance state. We are currently evaluating whether this circuit leads to dysregulated habenular 5-HT signaling. These circuit components have future potential as a therapeutic target for the social morbidity of opioid use disorder.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

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Topic: H.08. Drugs of Abuse and Addiction

Support: T32DA007278
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R00DA052571

Title: Astronomy of the Brain: Neural Reorganization Across Persistent Fentanyl Use

Authors: *A. PEDEN ASARCH[1], J. SANDERS[1], J. BAI[2], S. SIEVERTSEN[4], C.-Y. LIN[1], K. COFFEY[5], J. F. NEUMAIER[3];
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Abstract: Tracking neural ensemble dynamics across days requires both scalable single-session processing and reliable cross-session neuron registration - capabilities existing pipelines struggle to deliver for the multi-hour recordings typical of addiction paradigms. We developed two complementary tools to address this gap: the Miniscope Processing Suite (MPS), a no-code GUI pipeline that processes long-duration one-photon calcium imaging via NNDSVD-initialized CNMF with parallel out-of-core execution, and Stars2Cells (S2C), an astrometry-inspired neuron tracking algorithm that matches neurons across sessions using geometric quad descriptors invariant to rotation, translation, and scaling. Together these tools enabled us to process ~77 hours of miniscope data (7.26 TB) and track lateral habenula (LHb) neurons across four sessions in rats (n=8) performing oral fentanyl self-administration under escalating footshocks; S2C achieved ~75% cross-session matching across the four recording days. Under escalating shock, rats did not completely cease taking, but reorganized their taking at a within-session strategy-shift point. Locking LHb activity to this reorganization revealed that the trial-onset cue became an LHb-driving event: cue activity was elevated specifically on takes that resumed after an active-withhold bout, across all shocked sessions (0.2, 0.8 mA, and relapse) but not in the no-shock control, consistent with the cue acquiring aversive value as the animal takes despite it. Classifying tracked neurons by responsive epoch further revealed a striking cross-session asymmetry: pre-shock decision-responsive neurons dropped from 20% overlap (0.2→0.8 mA) to just 4% (0.8 mA→relapse), while post-shock outcome-responsive neurons maintained ~21-23% overlap across both transitions. Together these results indicate that the LHb rapidly reorganizes its decision-related ensembles while partially preserving outcome-encoding populations, and that the predictive cue is recruited into LHb conflict encoding precisely when taking becomes aversion-resistant - dynamic coalition formation with differentially stable functional streams rather than fixed cell-type assignments.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

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Program #/Poster #: PSTR152.11/II27

Topic: H.08. Drugs of Abuse and Addiction

Title: Role of Fkbp5 in Astrocyte Reactivity and Involvement in Opioid-Related Behavior

Authors: *A. CLEERE[1], R. A. PHILLIPS, III[2], G. TWA[3], N. ROBINSON[4], L. IANOV[5], R. E. SORGE[6], J. J. DAY[4], J. J. TUSCHER[1];
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Abstract: Acute morphine and pain have been shown to induce transcriptional changes in the ventral tegmental area (VTA), a brain structure important for reward processing and motivated behavior. We recently used single-nucleus RNA sequencing (snRNA-seq) in the VTA of adult rats to identify cell-type-specific changes in gene expression after acute morphine experience in a chronic pain model. Surprisingly, glia had more changes in gene expression than neuronal cell populations. Astrocytes were particularly transcriptionally responsive to acute morphine and showed strong induction of Fkbp5, a marker of reactive astrocytes, regardless of pain state. Here, we used human and rodent glial culture models to investigate the mechanisms driving opioid-induced expression changes observed in vivo. We found treatment of human astrocytes and rodent glial cells with DAMGO, a μ opioid receptor agonist, did not alter FKBP5 expression. In contrast, treatment with either the endogenous glucocorticoid cortisol (or corticosterone in rat), and the GR agonist dexamethasone, increased FKBP5 expression. Pretreatment with the GR antagonist mifepristone blocked cort and GR agonist-induced transcriptional changes. To improve both cell-type and receptor specificity, we used an astrocyte-selective CRISPR interference tool for targeted silencing of NR3C1, the glucocorticoid receptor. Selective repression of NR3C1 in astrocytes blocked induction of FKBP5 following cortisol treatment, suggesting some opioid-induced gene expression changes observed in astrocytes in vivo are mediated via GR vs. μ opioid receptor activation. Given that opioid-induced glial reactivity has been implicated in opioid misuse, and FKBP5 is a marker of astrocyte reactivity, ongoing studies are investigating morphological changes in astrocytes after prolonged opioid exposure. Toward this goal, IMARIS 3D reconstruction combined with immunofluorescence targeting of GFAP, GLT-1, and FKBP5 are being leveraged to map opioid-induced morphological changes in astrocytes across reward-relevant brain regions. Collectively these studies will advance our understanding of the molecular, cellular, and structural mechanisms through which astrocytes contribute to opioid misuse.

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Poster

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Title: Role of submedius thalamus and its interaction with orbitofrontal cortex in incubation of oxycodone craving

Authors: *X. LUO[1], H. LIN[1], S. HUSSAIN[2], X. LI[1,3,4];
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Abstract: A major obstacle in oxycodone addiction treatment is relapse during abstinence. In rats, oxycodone seeking intensifies during abstinence, and orbitofrontal cortex (OFC) is critical for this incubation. Here we studied the role of submedius thalamus (Sub) and its reciprocal connections with OFC in this incubation. First, using the pharmacological inactivation approach, we examined the causal role of Sub in incubation of oxycodone craving. Next, combining fluorescence-conjugated cholera toxin subunit B (a retrograde tracer) with Fos (a neuronal activity marker), we assessed whether the activation of OFC and Sub connections was associated with incubated oxycodone seeking on abstinence day 15. Using a pharmacological asymmetrical disconnection procedure, we then examined the causal role of interactions between OFC and Sub in incubated oxycodone seeking. We also tested the effect of unilateral Sub inactivation on incubated oxycodone seeking, and contralateral disconnection of OFC and Sub on non-incubated oxycodone seeking on abstinence day 1. We found that bilateral Sub inactivation decreased oxycodone seeking on abstinence day 15 but not on day 1, and incubated oxycodone seeking was associated with activation of both OFC->Sub and Sub->OFC projections. Further, both contralateral and ipsilateral disconnection of OFC and Sub decreased incubated oxycodone seeking. Unilateral Sub inactivation had no effect on the total responding during oxycodone seeking but impacted within-session extinction responses. Lastly, contralateral disconnection of OFC and Sub had no effect on non-incubated oxycodone seeking. Together, these results demonstrated a novel role of Sub and its interactions with OFC in incubation of oxycodone craving.

Disclosures: X. Luo: None. **H. Lin:** None. **S. Hussain:** None. **X. Li:** None.

Poster

PSTR152: Neural Substrates of Opioid Seeking

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R21DA058805

Title: Overexpression of the mitochondrial ubiquitin ligase in the orbitofrontal cortex potentiates incubation of oxycodone craving

Authors: *C. MATHESON[1,2], P. COUSENS[1,2], X. LUO[1], M. BURKE[1], E. MEADOWS[1], R. CHANDRA[4], X. LI[1,2,3];
[2]Neurosci. and Cognitive Sci. Program, [3]Brain and Behavioral Inst., [1]Univ. of Maryland, College Park, MD; [4]Viral vector core, Univ. of Maryland, Baltimore, Baltimore, MD

Abstract: High relapse rates are a major challenge in treating chronic opioid use, including oxycodone, a commonly abused prescription opioid. In rats, oxycodone seeking progressively increases during abstinence, a phenomenon known as incubation of oxycodone craving. We previously demonstrated a critical role of orbitofrontal cortex (OFC) in this incubation and have been investigating the underlying molecular mechanisms, with a focus on mitochondrial dynamics. Recently, we found that incubation of oxycodone craving was associated with a time-dependent increase in mitochondrial fission in OFC neurons, but the specific mitochondrial dynamics regulator(s) mediating this enhanced mitochondrial fission are unknown. Here, we examined the role of the mitochondrial ubiquitin ligase (MITOL, also known as March5), an E3 ubiquitin ligase that indirectly regulates mitochondrial dynamics by ubiquitinating mitochondrial fission and fusion proteins to target them for degradation. In Experiment 1, we overexpressed MITOL in OFC by injecting an adeno-associated virus (AAV) expressing MITOL (AAV2-CMV-MITOL-GFP) or AAV2-CMV-GFP (control) bilaterally into the OFC. Next, we trained rats to self-administer oxycodone (0.1 mg/kg, 6 h/d) for 10 days and then tested rats for oxycodone seeking on abstinence days 1 and 15. In Experiment 2, we trained rats to self-administer either oxycodone or saline for 10 days, and collected OFC on abstinence day 15. Next, we performed Western blotting and measured MITOL protein levels in OFC. In Experiment 3, we performed co-immunoprecipitation (IP) in the frontal cortex of naïve rats to pull down endogenous MITOL and probed for its interaction with previously identified mitochondrial fission and fusion protein substrates. We found that overexpressing MITOL in the OFC significantly increased both oxycodone intake during self-administration and oxycodone seeking on abstinence day 15, but not on abstinence day 1. Moreover, although there were no changes in MITOL protein levels in OFC on AD15, MITOL coprecipitated with mitochondrial fusion proteins. These results suggest that MITOL positively regulates incubation of oxycodone craving not through changes in protein abundance, but rather by promoting ubiquitination and degradation of mitochondrial fusion protein and shifting mitochondrial dynamics toward fission. Ongoing work is examining the effects of MITOL overexpression in OFC on mitochondrial morphology and ubiquitination of mitochondrial dynamics-associated proteins.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R21DA060380

Title: Proteomic profiling of projection-specific orbitostriatal synaptoneurosomes during incubation of oxycodone craving in male and female rats.

Authors: *P. M. COUSENS[1], L. G. RODRIGUEZ[1], E. UKPONG[2], E. R. MEADOWS[1], S. HUSSAIN[1], C. MATHESON[1], X. LUO[1], C. DUNN[3], F. RUBIO[2], B. T. HOPE[2], P. NEMES[1], X. LI[1];
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Abstract: A major obstacle in treating and managing addiction is the propensity for individuals to relapse during abstinence, often triggered by exposure to drug-associated cues. In rodents, cue-induced oxycodone craving progressively increases during abstinence, a phenomenon known as incubation of oxycodone craving. We previously demonstrated a critical role of orbitofrontal cortex (OFC) to dorsal striatum (DS) projections in this incubation. However, the distinct cellular and molecular adaptations in this circuit underlying oxycodone relapse are unknown. Given that many synaptic proteins are involved in drug-induced plasticity, and some are critical for incubation of craving, here we focused on synaptoneurosomes (SNs), a subcellular fraction containing both pre- and post-synaptic material. We aimed to combine viral-mediated anterograde tracing and fluorescence-activated SN sorting (FASS) with ultra-sensitive high-resolution mass spectrometry (HRMS) to profile the proteome in OFC-to-DS projection-specific SNs associated with oxycodone craving after prolonged abstinence. We first characterized the proteome of OFC-to-DS projection-specific SNs in naïve male rats. We injected adeno-associated virus (AAV) expressing yellow fluorescent protein (YFP) bilaterally into OFC to label terminals in DS. Two months later, we processed the DS for FASS, followed by a liquid chromatography high-resolution mass spectrometry analysis. We pooled tissue from two rats per sample and identified an average of 2,869 proteins from sorted SNs. Pathway analysis revealed statistically significant enrichment of canonical components of corticostriatal SNs, including presynaptic, postsynaptic membranes, and glutamatergic synapses. Ongoing work is applying this established workflow to profile the proteome of OFC-to-DS projection-specific SNs associated with incubation of oxycodone craving in male and female rats.

Disclosures: P.M. Cousens: None. **L.G. Rodriguez:** None. **E. Ukpong:** None. **E.R. Meadows:** None. **S. Hussain:** None. **C. matheson:** None. **X. Luo:** None. **C. Dunn:** None. **F. Rubio:** None. **B.T. Hope:** None. **P. Nemes:** None. **X. Li:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Title: Circuit-level directed connectivity and dynamic brain-state alterations during incubation of oxycodone craving after forced abstinence in male rats

Authors: *E. R. MEADOWS[1], L. HOHEISEL[2], N. SANTIAGO[1], X. LUO[1], C. MATHESON[1,3], P. COUSENS[1,3], K. CHERKAS[4], X. LI[1,3,4], N. XU[2,3,4,5];
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Abstract: A major challenge in the treatment of opioid addiction is relapse, often triggered by exposure to drug-associated cues. In rats, cue-induced oxycodone seeking progressively increases during abstinence, a phenomenon termed incubation of drug craving. This incubation occurs either after forced abstinence, which mimics relapse after hospitalization or incarceration, or after voluntary abstinence, which mimics relapse after removal of negative consequences or alternative rewards. Recent work demonstrated alterations of static whole-brain functional connectivity (FC) during incubation of oxycodone craving following electric-barrier-induced voluntary abstinence in male rats. However, whether incubation of oxycodone craving after forced abstinence is associated with alterations in circuit-level directed connectivity and large-scale dynamic brain-state organization remains unknown. This is important because distinct circuit mechanisms underlie incubation of oxycodone craving after forced and voluntary abstinence. Here, we aimed to use resting-state functional magnetic resonance imaging (rs-fMRI) to examine circuit-level directed connectivity and dynamic brain-state alterations associated with incubation of oxycodone craving. We trained male rats to self-administer either saline or oxycodone (0.1 mg/kg, 6 h/d for 10 d) after baseline rs-fMRI scans (pre-training). All rats were then tested for cue-induced seeking on abstinence day (AD) 1 and 15, followed by rs-fMRI scans on AD2 and AD16, respectively. Behavioral analysis showed increased cue-induced oxycodone seeking on AD15 compared with AD1, confirming incubation of oxycodone craving occurred under our experimental conditions. Our rs-fMRI analysis included both static directed connectivity and dynamic brain state measures. The initial fMRI analysis focused on the orbitofrontal cortex (OFC) and dorsal striatum (DS) circuitry, given the recently demonstrated critical role of OFC-to-DS projections in this incubation after forced abstinence. Preliminary directed-connectivity analysis revealed decreased bidirectional OFC-DS connectivity on AD16 compared with AD2, with a slightly greater reduction in DS-to-OFC connectivity than in the reverse direction, and no changes between pre-training and AD2. Ongoing work is expanding our analysis to OFC-associated circuits and dynamic brain-state measures to identify broader neural signatures associated with oxycodone craving after forced abstinence.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

Title: Exploring the Cerebellar Role in Opioid Signaling and Drug-Associated Behavior

Authors: *C. CLARK[1], P. G. MERMELSTEIN[4], M. CVETANOVIC[2], E. LABRADA[3];
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Abstract: Opioids are a leading cause of overdose deaths worldwide, presenting a major health crisis that costs many lives and financially burdens health care systems. At the center of this crisis is Opioid Use Disorder (OUD), a chronic drug disorder that is associated with high rates of drug relapse, presenting a challenge to treatment and recovery. Opioids have garnered significant research interest, but most studies investigate traditional reward-associated pathways and circuitry. Notably, deep cerebellar nuclei (DCN) have direct glutamatergic connections with the ventral tegmental area (VTA), a midbrain structure closely tied to reward processing. Evidence has shown DCN-VTA activity to modulate reinforcement learning, indicating a possible role in modulating opioid-associated behaviors. Considering the cerebellar role in opioid-associated behaviors is not well understood, we sought to further explore cerebellar signaling during morphine administration. Using an inhibitory DREADD expressed within the DCN of mice, we inhibited DCN activity during morphine conditioned place preference (CPP) to determine the effect on morphine-associated behavior. We hypothesize that cerebellar signaling will modulate morphine-associated preference and behavior. These results suggest that the cerebellum likely plays a powerful role in opioid-associated reinforcement learning and subsequent drug-seeking behavior.

Disclosures: C. Clark: None. **P.G. Mermelstein:** None. **M. Cvetanovic:** None. **E. Labrada:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Modulation of morphine-activated brain reward circuitry by the galanin receptor agonist, galnon, in female mice

Authors: *E. FOSTER, B. S. PATE, D. WEINSHENKER;
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Abstract: Opioid use disorder (OUD) is a chronic, relapsing condition characterized by compulsive opioid use despite harmful consequences. It is driven in part by opioid-induced activation of mesolimbic reward circuitry, including the rostromedial tegmental nucleus (RMTg), ventral tegmental area (VTA), and nucleus accumbens shell (NAc). OUD remains a major public health concern in the United States, with increasing prevalence and overdose-related mortality. Females exhibit heightened vulnerability to OUD, including faster progression to dependence, greater withdrawal severity, and higher relapse rates, yet remain underrepresented in preclinical and clinical research. The neuropeptide galanin has emerged as a potential modulator of opioid reward, but its clinical utility is limited by poor blood-brain barrier permeability. This study investigates whether systemic administration of the galanin receptor agonist, galnon, attenuates morphine-induced neuronal activation in key reward-related brain regions in female mice. Female C57BL/6J mice were used to assess morphine-evoked neuronal activation. Brain sections were processed using immunohistochemistry to label c-Fos as a marker of neuronal activation and tyrosine hydroxylase (TH) to identify dopaminergic neurons. A dose response experiment determined the optimal morphine (3 mg/kg) dose for inducing c-Fos expression in the RMTg, VTA, and NAc shell. Mice were pretreated with galnon or vehicle prior to morphine administration. Neuronal activation was quantified as the percentage of c-Fos+ cells in the RMTg and NAc shell, and c-Fos+/TH+ neurons in the VTA. Data were analyzed using two-way ANOVA. Morphine produced robust increases in c-Fos expression across the RMTg, VTA and NAc shell. Galnon pretreatment did not significantly alter morphine-induced neuronal activation in the RMTg or VTA. In contrast, galnon significantly reduced c-Fos expression in the NAc shell at baseline and following morphine administration, indicating a region-specific effect. Systemic galnon selectively attenuates neuronal activation in the NAc without altering upstream regions, suggesting that galanin signaling modulates opioid reward potentially through local NAc effects or broader network interactions. These findings provide insight into opioid reward processing in females and support the galanin system as a potential therapeutic target.

Disclosures: E. Foster: None. **B.S. Pate:** None. **D. Weinshenker:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant 1ZIADA000566-12

Title: Brain oxygen responses induced by arousing stimuli and fentanyl: generalized or structure-specific?

Authors: *A. ARCE[1], E. A. KIYATKIN[2], F. LIMIAC[3];
[2]Behavioral Neurosci Br., [1]NIH, Natl. Inst. On Drug Abuse, Baltimore, MD; [3]NIDA, Baltimore, MD

Abstract: Brain oxygen levels fluctuate with changes in neural activity and systemic physiology, yet it remains unclear whether oxygen responses to salient stimuli are structure-specific or reflect generalized brain activation. Using oxygen sensors coupled with high-speed amperometry in freely moving rats, we compared oxygen dynamics in three structures with markedly different neuronal firing properties: nucleus accumbens, medial thalamus, and substantia nigra pars reticulata, along with simultaneous measurements in the subcutaneous space. Natural arousing stimuli produced rapid oxygen increases in all brain sites coupled with robust SC oxygen decreases, though there are minor differences in magnitude. In contrast, intravenous fentanyl (30 μg/kg) induced uniform hypoxic responses in all brain sites, consisting of a rapid and strong decrease followed by a weaker post-hypoxic rebound, with low between-site variability. These findings show that physiological oxygen increases during arousal are largely generalized and likely dominated by systemic mechanisms such as peripheral vasoconstriction, cerebral vasodilation, and global increases in cerebral blood flow, whereas fentanyl-induced hypoxia reflects purely systemic effect induced by respiratory depression. Overall, these results indicate that brain oxygen dynamics are shaped predominantly by systemic physiology rather than local neuronal firing properties, highlighting important constraints on interpreting oxygen-based signals as markers of neuronal activity.

Disclosures: A. Arce: None. **E.A. Kiyatkin:** None. **F. Limiac:** None.

Poster

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Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant HL168211

Title: Lower Airway Mechanics and the Neural Control of Fentanyl-Induced Airway Disruption

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Abstract: The leading cause of death following opioid overdose is opioid-induced respiratory depression (OIRD). Fentanyl uniquely causes airway obstruction and thoracic rigidity in addition to suppressed respiratory rhythm generation leading to ineffective ventilation and resuscitation. While the effect(s) of opioids on central rhythm-generation has been well documented, airway obstruction and the mechanisms behind it remain poorly understood. We investigated the role of enhanced vagal parasympathetic output as well as the contribution of the lower airways to fentanyl-induced airway disruption. Bilateral vagotomy, atropine administration, and intracisternal naloxone administration were used to evaluate the contribution of the vagus and central opioid receptor mechanisms. In urethane-anesthetized mice, diaphragm electromyography (EMG), respiratory airflow, and vagus activity were recorded in-vivo before

and after intraperitoneal fentanyl (500 μg/kg). Mechanical ventilation was used to study lower airway mechanics and was further evaluated through atropine and salbutamol administration. We found fentanyl caused a characteristic slowing of respiratory rate accompanied by a compensatory increase in tidal volume. Fentanyl also produced a transient delay between diaphragm activation and airflow onset, consistent with airway obstruction. This delay was prevented with bilateral vagotomy or atropine administration and was reversed by intracisternal naloxone, implicating central vagal mechanisms. Vagal electroneurograms showed increased tonic multiunit activity and enhanced large-amplitude single-unit firing, particularly within efferent fibers, as well as a loss of normal inspiratory phase-locking following fentanyl. The magnitude of tonic vagal activity as well as the activity from a majority of the large-amplitude single units were strongly positively correlated with the severity of airway disruption. We also found an increase in airway resistance and a decrease in lung compliance following fentanyl and naloxone administration suggesting a lower airway component. Salbutamol and atropine administration abolished these deteriorations in lung mechanics. From this we conclude that fentanyl disrupts respiratory-autonomic integration by enhancing parasympathetic vagal drive, producing a central, opioid receptor-mediated mechanism of airway constriction. Targeting vagal pathways as well as the lower airways and the muscle tissue surrounding it may therefore represent a promising adjunctive strategy to improve airway patency and increase the effectiveness of ventilatory recovery during opioid overdose reversal.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Neuropharmacology of the illicit opioid ortho-methylfentanyl in comparison to its meta and para positional isomers

Authors: *M. H. BAUMANN[1], D. WALTHER[1], N. GONZALEZ[1], J. MCCORVY[2], G. GLATFELTER[1];
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Abstract: Illicitly-manufactured fentanyl is a main contributor to the current opioid crisis, but a variety of fentanyl analogs continue to appear in non-medical drug markets. *Ortho*-methylfentanyl (OMF) is a phenyl ring-substituted fentanyl analog being detected in confiscated opioid products and human overdose cases. OMF is reported to be a mu-opioid receptor (MOR) agonist *in vitro*, yet little is known about its potency and efficacy *in vivo*. Here, we characterized

the pharmacology of OMF and its positional isomers, *meta*-methylfentanyl (MMF) and *para*-methylfentanyl (PMF), using *in vitro* and *in vivo* pharmacological methods. Radioligand binding at MOR, delta-opioid receptors (DOR), and kappa-opioid receptors (KOR) was carried out in rat brain membranes. Functional activities at MOR, DOR, and KOR were determined using BRET assays in cells expressing a single human opioid receptor subtype and GoA. The antinociceptive (52^{o}C hot plate test), locomotor, and body temperature effects of subcutaneously administered drugs were determined in C57BL/6J mice. Naloxone reversal studies were carried out to gauge sensitivity to MOR antagonism. Radioligand binding results showed that methylfentanyl isomers have affinities at MOR (K_i range = 6.6 - 22.0 nM) that are slightly weaker than that of fentanyl (K_i = 3.7 nM). Moving the methyl group from *ortho*, to *meta*, to *para* ring-position yielded a stepwise decrease in MOR affinity and an increase in KOR affinity. BRET assays showed the compounds were potent and efficacious MOR agonists, and moving the methyl group from *ortho*, to *meta*, to *para* engendered a decrease in MOR potency with an increase in KOR potency. The mouse experiments revealed that methylfentanyl isomers produce dose-dependent antinociception (ED_{50} range=0.29 -1.75 mg/kg), locomotor stimulation, and hypothermia, with OMF being the most potent compound. Interestingly, PMF displayed reduced efficacy in producing locomotor effects but enhanced efficacy in producing hypothermia. Naloxone administration (0.3 mg/kg, s.c.) attenuated the effects of all methylfentanyl analogs, suggesting MOR involvement. Overall, our findings demonstrate that methylfentanyl isomers are potent MOR ligands that produce opioid-like effects in mice. OMF displays about 1/3 the potency of fentanyl across *in vivo* measures, suggesting this compound may pose risk to people who use illicit opioids. Notably, PMF displays an unusual profile of fully efficacious antinociception, weak motor stimulation, and marked hypothermia, which may be related to its co-activation of both MOR and KOR.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

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Title: The 'peripherally restricted' opioid antagonist naloxone-methiodide reverses fentanyl-induced brain hypoxia via central mechanisms

Authors: *E. A. KIYATKIN[1], F. LIMIAC[2], Y. SHAHAM[3];
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Abstract: Brain hypoxia is a critical consequence of opioid overdose, traditionally attributed to the activation of central opioid receptors. However, peripheral receptors have also been implicated, as studies using naloxone-methiodide, a peripherally restricted opioid antagonist, show that it can reverse fentanyl-induced respiratory depression. This interpretation assumes naloxone-methiodide does not enter the brain, yet our previous mass spectrometry data revealed that it crosses the blood-brain barrier at a ~1:50 ratio compared to naloxone-HCl. In this study, we used amperometric oxygen sensors in freely moving rats to assess the role of central versus peripheral opioid receptors in fentanyl-induced (30 μg/kg IV) brain hypoxia. We compared the effects of naloxone-methiodide (2.0 mg/kg IV) and naloxone-HCl and found that while naloxone-methiodide significantly reduced hypoxia. However, naloxone-methiodide was less potent and its effects were shorter than a ten-fold lower dose of naloxone-HCl. Furthermore, naloxone-HCl at 50- and 250-times lower doses (50 and 8 μg/kg), but not at 1000-fold lower dose (2 μg/kg), mimicked the effects of naloxone-methiodide. These results suggest that the ability of naloxone-methiodide to block fentanyl-induced brain hypoxia is at least partially mediated by central opioid receptor antagonism. This challenges its designation as a strictly peripherally acting compound and emphasizes the need to reevaluate its use in mechanistic studies, particularly in distinguishing central from peripheral contributions to opioid-induced hypoxia.

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Poster

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Support: The Dan and Diane Riccio Fund for Neuroscience at UMass Chan Medical School.

Title: ASSESSING OPIOID-INDUCED DNA DAMAGE RESPONSES in POSTMORTEM HUMAN BRAINS and INDUCED PLURIPOTENT STEM CELL (iPSC)-DERIVED NEURONS

Authors: *E. SIRCAR[1], T. DELORME[2], J. ZIEGENFUSS[3], M. L. SENEY[6], C. WALSS-BASS[7], M. LODATO[4], R. W. LOGAN[5];
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Abstract: Our prior work using snRNA-sequencing found an enrichment of DNA damage genes in the striatal neurons of subjects with opioid use disorder (OUD) and in rhesus macaques following chronic opioid administration. However, the molecular drivers of DNA damage in OUD, its impact on neuronal physiology, and whether existing therapies can mitigate these effects remain unknown. This project thus tests the ***hypothesis*** that OUD induces DNA damage in the human dorsal striatum and that mu-opioid receptor (MOR) activation contributes to this damage and to opioid-induced changes in neuronal excitability. It also assesses whether these effects can be mitigated by naloxone (a MOR blocker) and DNA repair enhancers. **Aim 1:** Quantify levels and day-night variation of DNA damage markers in dorsal striatal neurons of OUD and control subjects. **Aim 2:** Determine whether MOR signaling drives neuronal DNA damage and alters neuronal physiology, and whether naloxone or DNA repair enhancers mitigate these effects. **Methods:** DNA damage markers 8-oxoguanine (8-oxoG), 8-oxoG glycosylase (OGG1), and MutT Homolog 1 (MTH1) were quantified by immunofluorescence (IF) in postmortem dorsal striatal tissue (n = 12; OUD: 6, control: 6; 3/sex/group). Nuclear signal (mean gray value minus background) was quantified using Fiji (~100 neurons/subject). Neurogenin-2 iPSC-derived human neurons were treated with fentanyl across doses and time points; 8-oxoG, OGG1, and γH2AX were quantified by IF (~50 cells/condition/replicate; N = 3 biological replicates), transcriptomic analysis was performed using 3′ poly(A) sequencing, and biophysical properties were measured by whole-cell patch clamp (n = 10 neurons/condition). **Results:** OUD increased 8-oxoG, OGG1, and MTH1 in striatal neurons (*P < 0.05), without significant day-night differences. In NGN2 neurons, acute and chronic fentanyl elevated 8-oxoG, OGG1, and γH2AX; chronic fentanyl induced stress and early-response genes and increased neuronal excitability. These effects were attenuated by naloxone and DNA repair enhancers, which also partially restored chronic fentanyl-induced changes in resting membrane potential and rheobase. **Conclusion:** OUD is associated with increased neuronal DNA damage in the dorsal striatum without significant day-night variation. MOR activation contributed to both DNA damage and altered excitability, which was mitigated by naloxone and DNA repair enhancers. This suggests that long-term biophysical changes in OUD neurons may be driven by opioid-induced DNA damage and highlights the potential of DNA repair enhancers as a therapy. **Supported by:** The Dan and Diane Riccio Fund for Neuroscience at UMass Chan Medical School.

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Poster

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Topic: H.08. Drugs of Abuse and Addiction

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Title: Single-cell multiomic and single chromatin fiber profiling of opioid use disorder in human frontal pole

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Abstract: Opioid overdose, the most severe consequence of opioid use disorder (OUD), remains the leading cause of accidental death in the United States. To detail OUD-sensitive changes in frontal pole (FP), a brain region implicated in addiction circuitry, we generated single-cell multiomic profiles from 41 human postmortem brains, including 18 with OUD. We additionally profiled chromatin architecture at nucleosome resolution along extended 10-kb chromatin fibers using single-molecule chromatin fiber sequencing (Fiber-seq) in a subset of FP tissues (control n=16, OUD n=20). We profiled 34,356 nuclei and identified distinct cell types including glutamatergic (vGlut$^+$) and GABAergic neurons and glial cells. Across cell types, we identified 336 differentially expressed genes (DEGs) and 3,854 differentially accessible regions (DARs). While OUD-sensitive transcription and chromatin accessibility were largely cell type-specific, DEGs were consistently enriched for processes governing synaptic organization and plasticity. DARs were commonly enriched for genetic variants associated with risk taking traits and depression, conditions frequently comorbid with OUD. Among all cell types, vGlut$^+$ exhibited the strongest OUD-sensitive changes, including differential expression of KCNJ3, GABRA2 and PDE10A. vGlut$^+$-DEGs were enriched in pathways such as morphine addiction and MAPK signaling pathway, highlighting their role in addiction pathology.Fiber-seq enables single-molecule identification of regulatory elements but is currently limited to bulk tissue profiling. Consequently, differential Fiber-seq inferred regulatory elements (FIREs) identified from bulk tissue likely underestimate OUD-sensitive changes. Thus, we developed a novel computational framework to deconvolute the cellular origin of individual chromatin fibers. Using cell type-specific ATAC profiles, we quantified active chromatin signals per fiber and applied a Shannon entropy-based probabilistic model to assign fibers to specific cell types. We assigned approximately six million fibers to vGlut$^+$ with high confidence. Analysis of vGlut$^+$-derived fibers identified 25,047 FIREs exhibiting chromatin accessibility uniquely enriched in vGlut$^+$. Furthermore, we identified 1,159 OUD-sensitive vGlut$^+$-FIREs, whose putative target genes were enriched for neuronal projection, axon guidance and addiction pathways.Together, these findings demonstrate the power of integrating large-scale single-cell and single-fiber multiomic approaches to dissect complex gene regulation in the human brain, which has implications beyond the addiction studies.

Disclosures: Y. Huang: None. **A. Harnett:** None. **A. Agarwal:** None. **B. Jiang:** None. **D. Mash:** None. **O. Corradin:** None. **S. Akbarian:** None.

Poster

PSTR152: Neural Substrates of Opioid Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.24/JJ8

Topic: H.08. Drugs of Abuse and Addiction

Support: Center for Medicinal Cannabis Research Project P64-05-002

Title: Evaluating the effects of cannabidiol on stress-induced reinstatement in fentanyl dependent mice

Authors: *E. C. WHITEHOUSE[1], W. GREENE[1], C. M. CAHILL[2];
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Abstract: Introduction
Recently, cannabis has garnered attention as a possible pharmacotherapy for alleviating negative symptoms associated with opioid craving and withdrawal. In particular, the phytocannabinoid cannabidiol (CBD) has emerged as a candidate drug for the reduction of cue-induced craving and withdrawal-associated anxiety. However, the majority of research in this field has focused on stimulant use disorders, and the effects of CBD on stress-induced reinstatement remain unclear. To address these gaps, we used the conditioned place preference (CPP) assay to analyze the effects of CBD on restraint stress-induced reinstatement of fentanyl seeking.
Methods
Adult male and female C57BL/6J mice underwent conditioning training to develop a dependence on fentanyl (0.1mg/kg), and were verified to have developed a context-drug association. They next underwent extinction training to remove this learned association. After it was confirmed that preference for the drug-associated context had been ablated, mice underwent brief restraint stress to induce reinstatement. To assess the potential of CBD to attenuate stress-induced reinstatement, mice were orally administered a CBD-containing (~10mg/kg) or vehicle gelatin daily one hour before each extinction training session and prior to the stressor. A within-subject, counterbalanced design was used across treatment days.
Results
Mice developed a significant preference for the fentanyl-associated context following conditioning training, and successfully extinguished this preference following extinction training. CBD was found to have no effect on extinction when measured after four days of extinction training. Restraint stress was found to induce reinstatement of fentanyl-context preference in mice that received vehicle gelatins. Mice that received CBD-containing gelatins failed to significantly reinstate, implying a potential protective effect of CBD against drug-seeking behaviors.
Conclusions
These findings support the hypothesis that CBD can reduce stress-induced reinstatement in a model of fentanyl conditioned place preference. This work expands the current CBD literature to more thoroughly include opioid reinstatement, and validates a novel method of CBD administration in murine models. These results provide insight into the potential uses of CBD as a therapeutic for drug-reinstatement, serving as a possible treatment for people with opioid use disorders.

Disclosures: E.C. Whitehouse: None. **W. Greene:** None. **C.M. Cahill:** None.

Poster

PSTR152: Neural Substrates of Opioid Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR152.25/JJ9

Topic: H.08. Drugs of Abuse and Addiction

Support: R01DA053070

Title: Region- and Contingency-Specific Adaptation of Potassium channels in Fentanyl Use Behavior in the Rat

Authors: *F. WU[1], J. SHAYKIN[2], E. PRANTZALOS[3], M. T. BARDO[2], J. R. TURNER[3], P. I. ORTINSKI[4];
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Abstract: Fentanyl abuse has become a severe public health crisis in the United States over the past decade. Opioid-induced cellular adaptations involve potassium (K^+) channels. However, fentanyl self-administration effects on the activity of specific K^+ channel subtypes remain poorly understood. This study investigates how escalated fentanyl self-administration alters subtype-specific potassium (K+) channel signaling and thereby impacts neuronal excitability within the infralimbic cortex (IL) and the nucleus accumbens shell (NAc), two brain regions implicated in escalation of drug use. Young adult Sprague-Dawley rats were trained to self-administer fentanyl in triads. In each triad, one rat received fentanyl contingent upon active lever press while the other two received non-contingent infusions of fentanyl or saline upon lever press by the contingent animals. Following 3 weeks of fentanyl or saline administration in long-access (6 hrs) daily sessions, animals were sacrificed for brain extraction and brain slice preparation. *Ex vivo* whole-cell patch-clamp techniques were used to isolate activities of six distinct groups of K^+ channels in the IL and the NAc neurons: GIRK channels, BK channels, SK channels, delayed rectifiers, A-type channels, and two-pore domain K^+ channels. Single-nucleus RNA sequencing (snRNA seq) was used to evaluate single genes and gene pathways impacted by fentanyl exposure. Our results showed that Contingent fentanyl rats exhibited an increase in baclofen-induced GIRK currents compared to both non-contingent fentanyl and non-contingent saline groups. Additionally, fentanyl-exposed rats showed increased amplitude of calcium-activated, BK, channel-mediated current in the IL, compared to saline controls. Conversely, NAc showed no activity changes for any of the six K^+ channel subtypes examined. snRNA Seq identified L5/6 neurons in the IL as enriched with GIRK subunit genes as well as potential GIRK regulators in the tyrosine kinase and PIP signaling pathways. Together, these findings reveal that fentanyl use produces selective, subtype-specific adaptations of K^+ channel. Such neurophysiological alterations may represent therapeutic targets for the development of future interventions for opioid use disorders.

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Poster

PSTR152: Neural Substrates of Opioid Seeking

Location: WCC Halls A-C

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Program #/Poster #: PSTR152.26/JJ10

Topic: H.08. Drugs of Abuse and Addiction

Support: NIDA P01DA047233
NIDA R01DA014133

Title: Multi-omic profiling of synthetic and non-synthetic opioid withdrawal reveals sex-specific epigenetic reprogramming of the nucleus accumbens

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Abstract: Fentanyl drives the majority of overdose deaths, yet its long-term molecular effects remain poorly understood. Using bulk RNA-sequencing of the nucleus accumbens (NAc) in male and female mice following chronic fentanyl or morphine exposure, we found that fentanyl produces a partly distinct transcriptional signature from morphine at 24 hours post-cessation in males, while females showed high convergence at both timepoints. By 30 days of withdrawal, male profiles converged dramatically, suggesting shared long-term NAc adaptations regardless of opioid. To interrogate the epigenetic basis of these persistent adaptations, we performed bulk ATAC-seq on NAc following chronic fentanyl exposure and 30-day withdrawal. Differentially accessible regions were largely non-overlapping between sexes, yet gene ontology converged on shared themes of synapse structure, activity, and organization in both, indicating distinct epigenetic programs driving common biological outcomes. Motif enrichment analysis revealed sex-specific regulatory programs. Females showed open chromatin enriched for steroid hormone receptor motifs, implicating endocrine and stress-responsive regulatory elements in female withdrawal. Males showed open chromatin enriched for AP-1 and circadian regulator motifs, and closed chromatin enriched for MEF2 family motifs, paralleling prior findings that MEF2 repression drives structural remodeling of NAc medium spiny neuron synapses after cocaine and implicating a convergent epigenetic mechanism across drugs of abuse. Integrating RNA-seq, ATAC-seq, and gene co-expression network analysis, we prioritized hub genes regulating transcriptional programs linked to relapse vulnerability. MEF2C emerged as a top candidate across all three analyses: a co-expression network hub in both sexes, with reduced chromatin accessibility and predicted upstream regulatory activity specifically in males after withdrawal. Molecular validation of MEF2C and additional prioritized targets is ongoing. These findings

reveal sex-specific epigenetic responses to fentanyl withdrawal converging on MEF2-dependent synaptic remodeling as a candidate mechanism sustaining neuroadaptation in opioid addiction.

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Poster

PSTR153: GLP-1 Receptor Influences on Drug Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.01/JJ11

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant DA047413
Baylor University Ronald E. McNair Scholars Research Fund
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Nu Rho Psi Undergraduate Research Grant

Title: Effects of semaglutide on acquisition and expression of intravenous fentanyl self-administration and on neuroinflammation

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Abstract: Existing treatments for opioid use disorder (OUD) retain barriers to access. Therefore, finding new potential therapies for OUD is of importance to public health. Previous work implicated glucagon-like peptide-1 receptor agonists, such as semaglutide, in decreasing use of addictive substances. In this study, female Wistar rats were surgically implanted with jugular catheters and trained to self-administer fentanyl (2.5 µg/kg/inf, i.v.) at fixed-ratio 1 (FR1) for 21 sessions under short- (ShA; 1-hour) or long-access (LgA; 8-hours) conditions. Prior to the start of an additional FR1 session, animals received injections of semaglutide (0.1 mg/kg, s.c.) or saline (0.9% NaCl, s.c.). Then, the animals completed 4 sessions at a progressive ratio (PR) where they self-administered fentanyl (0-10 µg/kg/inf, i.v.) while receiving semaglutide (0.1 mg/kg, s.c.) or saline (s.c.). Next, the semaglutide-experienced rats underwent a dose response procedure where they received escalating doses of semaglutide (0-0.1 mg/kg, s.c.) while self-administering fentanyl (2.5 µg/kg/inf, i.v.) at a FR1. Following drug discontinuation, spontaneous locomotor activity and withdrawal-like behavior were measured. Following behavioral measures, rats were sacrificed and their tissue fixed with paraformaldehyde. Their brains were cryopreserved frozen, cryosectioned, stained for TNF-alpha, imaged with a fluorescent microscope, and quantified. Semaglutide dose-dependently decreased fentanyl rewards under ShA and LgA conditions ($p<0.05$) without altering lever discrimination, and semaglutide decreased breakpoint ($p<0.05$) under PR, suggesting semaglutide decreased

motivation to self-administer fentanyl. Furthermore, semaglutide decreased spontaneous locomotion and withdrawal-like behavior in ShA ($p<0.05$) but not LgA animals. In a follow-up study, rats were trained to self-administer fentanyl (2.5 µg/kg/inf, i.v.) for 21 FR1 sessions while receiving saline (s.c.) or semaglutide (0.03 or 0.1 mg/kg, s.c.). Then, animals completed a PR challenge as described above while continuing to receive saline or semaglutide. Finally, the rats completed another FR1 session. Our findings suggest semaglutide decreases motivation to seek opioid reward and may be useful in the development of therapies for OUD.

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Poster

PSTR153: GLP-1 Receptor Influences on Drug Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.02/JJ12

Topic: H.08. Drugs of Abuse and Addiction

Support: NIH Grant R01 DA037897
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Title: Activating GLP-1 Receptors in Interpeduncular Circuits Decreases Drug Seeking and Negative Affective States in Fentanyl-Experienced Rats

Authors: *R. HERMAN[1], A. POTHIKAMJORN[2], A. CAFFREY[2], V. CHINAKA[2], H. D. SCHMIDT[3];
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Abstract: While emerging studies support repurposing glucagon-like peptide-1 receptor (GLP-1R) agonists for treating opioid use disorder, the neurobiological mechanisms underlying these effects remain unknown. We showed that infusions of the GLP-1R agonist exendin-4 (Ex-4) directly into the interpeduncular nucleus (IPN) attenuated opioid-seeking behavior during abstinence at doses that were well-tolerated in fentanyl-experienced rats. Pharmacological activation of GLP-1Rs in the IPN during fentanyl abstinence did not induce avoidance-like behaviors but did produce sex-specific anxiolytic-like effects, highlighting a complex role for IPN GLP-1R signaling in modulating affective states during opioid withdrawal. Next, we identified a subset of GABAergic IPN neurons that project to the laterodorsal tegmental nucleus (LDTg) and express GLP-1Rs. This microcircuitry suggests that activation of inhibitory IPN->LDTg projections mediates the behavioral effects of GLP-1R agonists. Consistent with this hypothesis, systemic administration of a GLP-1R agonist increased Ca^{2+} dynamics in GABAergic IPN neurons during fentanyl abstinence. Selectively activating IPN->LDTg

projections attenuated fentanyl seeking, while chemogenetic inhibition of this GABAergic midbrain circuit blocked the suppressive effects of a GLP-1R agonist on fentanyl seeking. These findings highlight a translationally relevant GLP1-R-expressing neural circuit that could be targeted to reduce opioid seeking and negative affective states during fentanyl withdrawal.

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Poster

PSTR153: GLP-1 Receptor Influences on Drug Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.03/JJ13

Topic: H.08. Drugs of Abuse and Addiction

Support: UH3 DA050325

Title: Chronic Semaglutide Treatment Leads to Tolerance to the Protective Effect of Semaglutide on Cue-Induced Fentanyl Seeking in rats.

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Abstract: Acute administration of glucagon-like peptide-1 receptor agonists (GLP-1RAs) reduces drug seeking in preclinical models of substance use disorder (SUD). While acute administration may be of therapeutic value, the need for long-term treatment for the chronic disease of SUD is clear. Here, we investigated the effects of chronic semaglutide treatment on cue-induced fentanyl seeking following abstinence, body weight, food intake, water intake and, in a separate study, pharmacokinetics and circulating blood glucose. Male Sprague Dawley rats (n=48) self-administered saline or fentanyl (1.85 µg/infusion, FR10, 6 h/day,14 days), followed by a 14 days abstinence period with daily or every other day vehicle or semaglutide treatment (0.026, 0.056, and 0.078 mg/kg, SC). Cue-induced fentanyl seeking was then assessed under extinction conditions. Following behavioral testing rats were sacrificed and the Ventral Tegmental Area (VTA) was collected for single-nucleus RNA sequencing (snRNA-seq). The

results showed that chronic treatment with semaglutide (daily or every other day) failed to reduce cue-induced responding at any dose tested, indicating tolerance to the protective effects of semaglutide. Semaglutide initially suppressed body weight gain, but this effect attenuated with repeated dosing, with weight trajectories converging toward those of vehicle-treated controls at later time points. When administered acutely, semaglutide initially reduced circulating blood glucose, followed by a short period of hyperglycemia for the two higher doses of semaglutide. Ongoing snRNA-seq analyses of the VTA will identify cell-type-specific transcriptional adaptations associated with chronic semaglutide exposure and behavioral tolerance. These findings indicate that the effects of semaglutide on opioid seeking and energy balance evolve across repeated exposures and highlight the importance of treatment strategy in determining the most effective ongoing dose regimen for the treatment of obesity and SUD. Understanding the neurobiological mechanisms underlying tolerance may inform the development of GLP-1RA-based therapies for opioid use disorder (OUD). This work was supported by UH3 DA050325.

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Poster

PSTR153: GLP-1 Receptor Influences on Drug Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.04/JJ14

Topic: H.08. Drugs of Abuse and Addiction

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São Paulo Research Foundation (FAPESP)

Title: Tirzepatide reduces fentanyl taking and seeking in male and female rats

Authors: *X. ZHANG[1,2], C. E. EDVARDSSON[3], M. DALALO[2], M. FORD[2], E. JERLHAG[4], H. D. SCHMIDT[2];
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Abstract: Globally, an estimated 60 million people engage in non-medical opioid use, contributing to roughly 450,000 of the 600,000 drug-related deaths recorded annually by the WHO. Relapse rates associated with current medications for opioid use disorder (MOUD) are high, underscoring a persistent clinical gap that existing medications have not adequately resolved. Emerging preclinical studies indicate that glucagon-like peptide-1 receptor (GLP-1R), agonists attenuate opioid-seeking in rodents. However, the clinical utility of GLP-1R agonists can be limited by adverse gastrointestinal effects, such as nausea and emesis. Glucose-dependent insulinotropic polypeptide (GIP) agonists exert antiemetic effects and, when combined with GLP-1R agonists, may improve both efficacy and tolerability. This study tested the hypothesis that tirzepatide, a dual GLP-1R/GIPR agonist, would reduce voluntary fentanyl taking- and seeking-behaviors at doses that do not produce malaise-like effects in rats. Male and female Sprague-Dawley rats were trained to self-administer fentanyl (1.25 μg/kg, i.v.) under a fixed-ratio 5 (FR5) schedule of reinforcement. Once intake had stabilized, rats were pretreated with vehicle or tirzepatide (3.0 or 30.0 nmol/kg, s.c.) prior to a self-administration test session. Tirzepatide dose-dependently attenuated fentanyl self-administration in both sexes. Following extinction of opioid self-administration, we screened the efficacy of tirzepatide to reduce the reinstatement of fentanyl-seeking behavior, an animal model of relapse. Systemic tirzepatide (3.0 or 30.0 nmol/kg, s.c.) attenuated fentanyl reinstatement in both male and female rats. Doses of tirzepatide that reduced opioid taking and seeking also attenuated food intake, but did not increase kaolin consumption, a measure of malaise-like effects, in fentanyl-experienced rats. Collectively, these findings support further studies of GLP-1R/GIPR dual agonists like tirzepatide for reducing opioid-mediated behaviors.

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Poster

PSTR153: GLP-1 Receptor Influences on Drug Seeking

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR153.05/JJ15

Topic: H.08. Drugs of Abuse and Addiction

Support: ZIA-DA000602
ZIA-DA000644

Title: Tirzepatide reduces motivation for fentanyl in mice

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Abstract: Opioid use disorder is characterized by compulsive opioid seeking, loss of control over intake, and high rates of relapse. Although medications for opioid use disorder are available, including methadone, buprenorphine, and naltrexone, many patients discontinue treatment or continue to experience craving and relapse. Therefore, developing new treatments that target the motivational processes sustaining opioid use is critical for addressing the ongoing opioid crisis. Glucagon-like peptide-1 (GLP-1) receptor agonists reduce alcohol, nicotine, opioid, and stimulant self-administration in preclinical models, and their prescription has been associated with a reduced risk of opioid overdose in humans. Recently, dual GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptor agonists, such as tirzepatide, have been identified as superior to GLP-1 receptor agonists alone in the treatment of metabolic disorders. However, whether and to what extent they reduce opioid use remains to be determined. Therefore, we tested tirzepatide in male and female C57BL/6J mice in a fentanyl vapor self-administration model that captures key features of opioid addiction. Mice were tested either under short-access (1 hour) conditions that model nondependent intake or extended (6 hours) conditions that model drug-dependent intake. The effect of tirzepatide (0.01, 0.03, 0.1, and 0.3 mg/kg, i.p.) on the number of fentanyl vapor deliveries earned during these sessions was assessed under a fixed-ratio 1 (FR1) schedule of reinforcement and using a within-session behavioral economic demand procedure, in which response requirements increased hourly (FR1, 2, 4, 8, 16, 32) during a 6-hour session. Drug-dependent mice escalated fentanyl vapor self-administration over time. Tirzepatide dose-dependently reduced fentanyl vapor self-administration in both nondependent and dependent male and female mice. Tirzepatide increased demand elasticity without affecting demand intensity, indicating reduced essential value and decreased motivation to work for fentanyl across sexes and dependence conditions. These findings identify dual GLP-1/GIP receptor agonists as a promising and readily repurposable pharmacological strategy for selectively reducing opioid motivation, supporting rapid clinical evaluation of tirzepatide for opioid use disorder.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.01/JJ16

Topic: I.03. Decision Making

Support: NHLBI T32HL160507

Title: Synaptic organization and corticostriatal dynamics of value coding in the retrosplenial cortex

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Abstract: The retrosplenial cortex (RSC) persistently encodes the relative value of available actions (ΔQ) during value-based decision-making (Hattori et al., 2019). However, the mechanisms underlying this persistent value code and the RSC's broader role in guiding behavior remain unknown, specifically regarding synaptic organization and downstream communication of value-related information. We addressed these gaps using high-density extracellular recordings, obtained with a novel probe we developed, in mice performing a dynamic foraging task. Consistent with prior results with calcium imaging, ~28% of RSC units were significantly ΔQ-modulated during the pre-choice ready period. To ask whether value coding has a distinct synaptic architecture, we computed jitter-corrected cross-correlograms (CCGs) for all simultaneously recorded pairs (6418 pairs from 10 sessions, 3 mice) and classified putative monosynaptic connections by a significant peak (>5 SD) at 1-10 ms lag. 97% of connections were excitatory, and ΔQ-modulated pairs showed higher monosynaptic connectivity than non-modulated pairs (Fisher's exact test); this relationship persisted after controlling for unit isolation and firing rate. To ask how RSC value coding relates to downstream action-selection circuitry, we performed simultaneous RSC two-photon calcium imaging and dorsomedial striatum (DMS) electrophysiology (8 sessions, 2 mice) and used reduced-rank regression (RRR) to estimate a low-dimensional RSC-DMS subspace. RSC population activity predicted DMS activity above a trial-shuffled null in all sessions (cross-validated $R^2 = 0.139 \pm 0.023$; z vs null = 23.0 ± 1.6, mean ± s.e.m.). This shared subspace was distinct from the dominant modes of RSC activity and carried both choice identity and reward outcome in separable dimensions. Together, these results show that ΔQ-coding RSC neurons form a preferentially interconnected excitatory subnetwork whose activity is coupled to DMS through a low-dimensional subspace encoding choice and reward. These findings place the RSC value code within a defined local circuit and link it to striatal activity, motivating causal and directional tests of whether RSC reports value to the striatum to support action selection.

Disclosures: C. Rowell: None. **M. Ramezani:** None. **D. Kuzum:** None. **T. Komiyama:** None.

Poster

PSTR154: Decision-Making: Value and Risk Representations

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.02/JJ17

Topic: I.03. Decision Making

Title: Frontal cortex mechanisms underlying effort-reward integration and belief updating in naturalistic motivated behavior

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Abstract: Acting to achieve goals is a fundamental behavior, requiring continuous decisions on whether to persist in goal pursuit or disengage. Such dynamic decision-making requires inferring both the effort cost and the goal value. These variables have largely been examined separately, often in tasks relying on sensory cues to signal value in highly trained animals. However, in naturalistic settings, effort and reward contingencies are rarely signaled explicitly, and often persist over extended periods. Animals must therefore infer latent effort-reward states from experience, accumulating evidence over time to update beliefs and motivational states. How effort-reward signals are integrated and accumulated over long timescales to shape goal value and motivational states, and which circuit mechanisms govern flexible motivational state transitions, remains unknown. Here, we propose that motivated behavior can be understood as a problem of belief updating over latent effort-reward states. We developed a novel, naturalistic paradigm, requiring no training, allowing to study 'innate' motivational strategies and individual differences. Mice dynamically infer changing latent states varying in their physical effort for goal and reward size, to decide whether to engage ("goal pursuit"), disengage ("giving up"), or re-engage ("try again"). Following a state transition, belief updating of the new goal value unfolded over several trials before mice converged to a new motivational state 'set point'. High-density recordings across the frontal cortex revealed distinct functional dynamics across regions. A large population of orbitofrontal cortex (OFC) neurons robustly integrated inferred effort-reward contingencies, whereas a subpopulation of anterior lateral motor cortex (ALM) neurons exhibited state-dependent graded persistent activity. Both populations tracked the subjective value of inferred states, and state identity could be reliably decoded from single-trial population activity during the inter-trial interval, suggesting sustained encoding of the state value. Following transient unilateral optogenetic perturbation of ALM, sustained activity rapidly returned to a state-specific graded set point, consistent with continuous attractor dynamics. Taken together, our findings suggest that innate motivational states in naive animals emerge from belief updating over latent effort-reward states, with frontal cortical networks track and update state value to shape motivated behavior.

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Poster

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Program #/Poster #: PSTR154.03/JJ18

Topic: I.03. Decision Making

Support: R01MH123446

Title: Time-evolving Value Signals in the Anterior Cingulate Cortex and Secondary Motor Cortex

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Abstract: During foraging, animals must continuously decide whether to remain engaged with a current reward source or switch to alternative opportunities. Such decisions require integrating information about elapsed time and recent reward history to estimate the value of waiting. Previous studies have implicated the anterior cingulate cortex (ACC) in foraging and value-based decision making, and secondary motor cortex (M2) in action planning. However, how reward history is integrated across trials and represented in ACC-M2 circuits to guide next decisions remains elusive. To address this question, we designed a head fixed task to gauge mice's ability to time behavior in their effort to maximize reward rate. Following an enforced inter-trial-interval, mice entered a time-investment period over which they were free to initiate licking for the chance of a water reward. The probability of receiving reward increased with the delay to initiate licking, though at a diminishing rate, posing the challenge of how much time to invest. Two cohorts of mice were trained on different reward-over-time functions where probability of reward increased at different rates, leading to different reward-rate optimal lick initiation times. Neuropixels 2.0 probes were acutely inserted into ACC and M2 following stable task acquisition. Behaviorally, mice adapted their waiting strategies to the reward structure of the task, resulting in significantly different wait-time distributions across cohorts. Trial-by-trial behavior was influenced by reward history and could be captured by models incorporating decaying effects of past outcomes and time-investment histories. Neurally, single-neuron activity was modulated by variables including reward outcome, environmental reward rate, elapsed time, and behavioral performance. Generalized linear models revealed contributions of both temporal and value-related variables to neuronal activity. Population decoding analyses further showed that neural ensembles contain information about recent outcomes, invested time, and upcoming time-investment decisions. Together, these results suggest that ACC and M2 encode both temporal and reward-history information relevant for adaptive timing behavior. Ongoing work aims to develop reinforcement-learning models of behavior and use model-derived value variables to further characterize the neural representations underlying timing decisions.

Disclosures: Z. Guo: None. **M.G. Shuler:** None.

Poster

PSTR154: Decision-Making: Value and Risk Representations

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Program #/Poster #: PSTR154.04/JJ19

Topic: I.03. Decision Making

Support: R01AA031609

Title: Rat medial prefrontal cortex encodes dynamic preference across a satiety-induced switch in reward choice

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Abstract: Adaptive reward seeking requires agents to alternate favoring one reward over another across different contexts. We can observe this experimentally in real-time by leveraging a satiety-driven shift in reward preference—when offering water-restricted rats a free choice between a large water reward and a small sucrose reward, initially the rat chooses the large water option. However, as rats perform more trials and begin to satiate, they switch choice preference to the smaller sucrose option. The activity in the medial wall of rat frontal cortex is critical for some types of context-mediated shifts in value-guided decision making, but how it might guide a satiety-driven shift in reward preference is not well understood. Electrophysiological recordings using neuropixels probes in the medial wall allow us to obtain simultaneous recordings from Anterior Cingulate (ACC), PreLimbic (PL), and Infralimbic (IL) cortices in freely-moving rats across a reward preference shift. As expected, phasic activity aligns to task events such as reward delivery and the operant responses. In order to assess the behavioral correlates of neural activity across every time point of the trial, we fit a lasso-regularized generalized linear model (GLM) with predictors for events, trial parameters, and spike history, to 202 recorded neurons. Most neurons had more than one significant predictor (96%), with large proportions significantly modulated by active lever presses for sucrose (71%) and latency to respond (64%). Using a GLM focused on the time of outcome, we identified a subset of cells whose reward identity encoding is significantly modulated by shifting preference at the time of a surprise reward delivery. Altogether, we found that the responses of neurons in the medial wall encode task-relevant parameters in this procedure, including current subjective reward value, supporting a role for rat medial frontal cortex in real-time encoding of reward preference.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

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Topic: I.03. Decision Making

Support: NIH Grant R01-MH128177
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Title: Representations of context-dependent usefulness during sequential decision-making in macaques

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Abstract: Sequential decision-making requires evaluating not only immediate reward outcomes, but also how present choices shape the future viability of goal-directed behavior. Functional properties of an option such as usefulness have been proposed to contribute to these future evaluations, yet their computational structure and neural representations remain unclear. Previous work has largely examined usefulness as goal-dependent, where the usefulness of an object or action varies across different task goals. However, in many real-world decision-making situations, goals remain stable while contexts evolve in response to previous choices. We leverage a Tetris task to examine context-dependent usefulness, in which a piece's usefulness varies as a function of the current board state under the fixed goal of maximizing line completion. We operationalize usefulness as the extent to which a placement preserves future board viability, quantified using a weighted cost function over resulting board states. The cost function extracts structural features of the board including holes, bumpiness, aggregate height, and landing height which combined influence future line completion success. In our Tetris task, filled lines do not clear until the end of a trial and the trial lengths vary (2-7 pieces), allowing dissociation between immediate reward opportunities and future board viability. Consequently, two placements may yield identical immediate rewards (e.g. fill two lines), but the resulting board states have different future costs. Rhesus macaques (n=3) preferentially chose lower cost placements in these situations, indicating sensitivity to context-dependent usefulness beyond immediate rewards. We further compared behavior against optimal sequence-planning models that minimized final trial cost under conditions with deterministic and uncertain sequence length. Macaque behavior was better predicted by a planning model with unpredictable sequence length, suggesting incorporation of sequence uncertainty into decision-making strategies. Finally, using Neuropixels recordings, choices with equivalent immediate reward but varying usefulness elicited distinct neural responses within the dlPFC, OFC, and ACC, consistent with tracking future board viability during long term expected value computations.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

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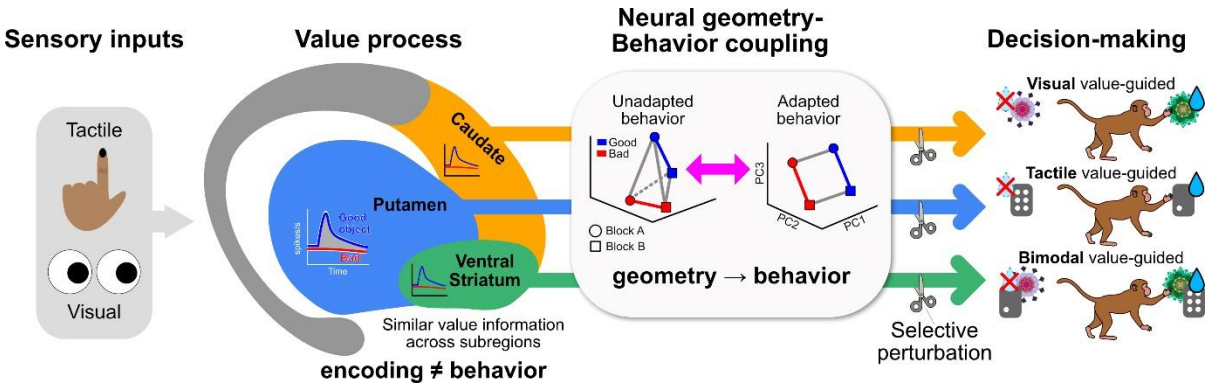
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Title: Functional and causal specialization of striatal subregions during tactile and visual value-guided decision in primates

Authors: *J.-W. LEE[1], M. KIM[2], S. HWANG[4,3], H. F. KIM[3];
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Abstract: A key question in neuroscience is how the brain integrates different types of information to guide specific actions. Although traditional views suggest that brain structures have strictly separate functions, recent studies show that different subregions often display highly overlapping neural responses to the same inputs. This raises a critical question: do these subregions process redundant information, or do they have unique behavioral roles? To address this, we investigated the computational and causal roles of three striatal subregions: the putamen, caudate, and ventral striatum. Monkeys were trained to discriminate the values of tactile (braille) and visual (fractal) stimuli. We found bimodal, tactile-selective, and visual-selective value neurons in similar proportions across all three subregions. However, regional differences emerged in how population-level value representations couple with behavior: the putamen was primarily involved in tactile-value decisions, the caudate in visual decisions, and the ventral striatum in both. To test causality, we selectively inactivated each subregion using muscimol. The results revealed distinct roles in value updating versus maintenance across the subregions. The caudate was specialized for visual updating and maintenance; the putamen for tactile updating and cross-modal maintenance; and the ventral striatum contributed to both functions across both modalities. Together, these results indicate that each striatal subregion differentially controls value-based behavior depending on the sensory modality. This is demonstrated by the coupling between neural population activity and behavior, and further confirmed by our inactivation results. Our findings suggest that distinct downstream readouts are driven by regional differences in neural geometry, showing how the striatum transforms shared inputs into modality-specific actions.



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Poster

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Title: Input modality organizes value coding in primate dopamine neurons

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Abstract: Primates, unlike rodents, learn value through fine fingertip touch and vision. Midbrain dopamine (DA) neurons classically broadcast a single reward prediction error common to all senses (Schultz et al., 1997), yet they are functionally heterogeneous, conveying value, salience, and sensory signals (Engelhard et al., 2019). This heterogeneity has so far been characterized mainly by projection target and response type, rather than by input modality. It remains unknown whether substantia nigra pars compacta (SNc) DA neurons encode value as a single shared signal or as signals organized by input modality. Answering this is central to understanding how the brain assigns value to each sense during multisensory learning. To address this, we trained a macaque monkey on visual (fractal) and tactile (braille) value reversal tasks to compare value coding across modalities. In each task, two stimuli of a single modality were paired with reward or no reward, and these contingencies reversed between blocks (Hwang et al., 2024). The monkey responded faster to high-valued than to low-valued stimuli in both modalities (reaction time differences: tactile 362 ± 9 ms; visual 418 ± 6 ms), demonstrating that it had learned stimulus value. To examine how value is encoded, we recorded SNc neurons using single-unit electrophysiology during both tasks. Of 201 neurons, 84 responded to unpredicted free reward and were classified as putative DA neurons following Matsumoto & Hikosaka (2009). Of these, 35 (42%) coded stimulus value. Most were modality-selective (27/35, 77%), coding value in only one modality (tactile, 11; visual, 16), whereas bimodal value neurons (8/35, 23%) coded value in both. The bimodal value neurons showed correlated value preferences across modalities ($r \approx 0.80$), indicating convergence. Across the value population, most coded positive value (28/35). These results reveal that modality-specific and bimodal value neurons coexist in the SNc. Together, these findings indicate that the primate SNc organizes value coding according to input modality rather than relaying a single shared signal. We therefore propose parallel, modality-defined channels that partially converge, conveying both modality-specific and integrated value to downstream structures.

Disclosures: Y. Kim: None. **H.F. Kim:** None.

Poster

PSTR154: Decision-Making: Value and Risk Representations

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Topic: I.03. Decision Making

Title: Striatal neurons represent dynamically changing expected values through multiplexed representations of reward and time

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Abstract: Adaptive behavior requires predicting the value of future rewards whose magnitude changes dynamically over time. Such predictions are thought to rely on neural representations of both reward magnitude and temporal information. Although the striatum plays a central role in reward-guided learning and decision-making, it remains unclear how reward and temporal information are jointly encoded at the neuronal level. Here, we recorded neuronal activity from the striatum of macaque monkeys during three classical conditioning paradigms in which reward magnitude evolved systematically over time. In all conditions, a bar stimulus served as a conditioned stimulus (CS), and its length indicated the amount of liquid reward. Longer bars corresponded to larger reward magnitudes. In the first condition (value-increase condition), the bar length started at a minimum and gradually increased, indicating a gradual increase in expected reward value. This increase stopped at a random time within 2450 ms after CS onset. In the second condition (value-decrease condition), the bar length started at a maximum and gradually decreased, indicating a gradual decrease in expected reward value. This decrease also stopped at a random time within 2450 ms after CS onset. In the third condition (value-fixed condition), the bar length remained constant throughout the trial and was fixed at either the minimum, intermediate, or maximum value. In all conditions, monkeys received the reward indicated by the final bar length immediately after CS offset. We found that the activity of some striatal neurons systematically changed as the expected reward magnitude evolved over time. To determine whether these neuronal responses reflected dynamically changing reward value, temporal progression, or both, we performed a model-comparison analysis. Specifically, the firing rate of each neuron was fitted with models incorporating reward value changing over time and/or a temporal template associated with the temporal progression. We found that the activity of some neurons was best explained by reward value alone, whereas others by a combination of both factors. Thus, the striatum contains distinct neuronal populations that represent reward value alone or combine reward information with temporal context. Such multiplexed representations may provide a neural substrate for tracking dynamically changing reward expectations and support adaptive learning and decision-making in environments where reward values evolve over time.

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Poster

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Title: Social interaction shapes choice policy and mSTS coding during macaque market decisions

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Abstract: Economic choices in social markets are shaped by immediate outcomes, accumulated market state, and the visible choices of other agents. We tested how these factors interact in a sequential stock-market task in macaques and humans. Two adult macaques performed the task by choosing among three actions: Buy, Hold, and Sell. They completed the task under four social-context conditions: Computer, Replay, Decoy, and Live. In all conditions, the subject monkey always initiated the task. We recorded single-unit activity from the medial superior temporal sulcus (mSTS) of the two subject monkeys across Baseline, oxytocin (OT), and saline control sessions. We also tested 232 human participants in an analogous Computer, Replay, and Live version of the task. Live interaction produced two behavioral signatures. Repeated Live exposure shifted macaque choice policy toward more Buy choices, consistent with increased portfolio-building behavior. In addition, Live trials produced social following: opponent monkeys were more likely to align their choices with the subject monkey's immediately observed action than expected from shuffled controls or from their own previous choices. Human participants showed a convergent Live following effect, suggesting a cross-species behavioral signature of real-time social market influence. mSTS activity was organized around the subject monkey's own market state and outcomes. Population activity distinguished Live from non-Live conditions during subject reward epochs. Buy-related activity was temporally structured: a general pre-choice Buy signal was present across task contexts, whereas a reward-aligned Buy signal emerged selectively during Live interaction. In parallel, mSTS activity tracked the subject monkey's current portfolio state across choices during Live sessions. Behaviorally, giving the subject OT reduced the partner's Live social following; at the neural level, OT attenuated reward-aligned portfolio-related mSTS activity without producing a broad shift in overall choice policy. These findings suggest that mSTS represents portfolio-based decision signals in real-time social interaction. Rather than simply encoding immediate reward magnitude or action identity,

mSTS represented Buy choices in relation to the subject's current portfolio state and longer-term dividend value, identifying an OT-sensitive modulation of social modulation of market decisions.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

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Program #/Poster #: PSTR154.10/KK1

Topic: I.03. Decision Making

Support: R01MH137085

Title: Reversible cryogenic cooling dissociates local computation from afferent input in supplementary eye field LFPs

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Abstract: Cortical local field potentials (LFPs) reflect signals generated within local circuits and inputs arriving from other brain regions, making their functional origins difficult to distinguish. We used reversible cryogenic cooling to perturb local processing in the supplementary eye field (SEF) while leaving action potential conduction along afferent axons comparatively intact. LFPs and multiunit activity were recorded simultaneously from two rhesus monkeys performing an oculomotor gambling task during interleaved control and bilateral cooling blocks. Time-frequency power was estimated using matching pursuit and analyzed during the decision, uncertainty, and outcome periods. Task-variable encoding was measured primarily with mutual information, which captures both linear and nonlinear statistical relationships, and was complemented by regression analyses of linear associations. Cooling strongly suppressed local spiking and produced frequency- and depth-dependent effects on LFP power. Beta-band power decreased during cooling regardless of electrode depth, consistent with disruption of local SEF circuitry. In contrast, the cooling-induced change in high-gamma power was negatively correlated with electrode depth. At deeper recording sites, high-gamma power was greater during cooling than during control despite reduced local spiking. This spike-LFP dissociation indicates that high-gamma activity is not generated exclusively by nearby neuronal firing and suggests contributions from afferent inputs or spatially distributed activity. Cooling also affected two groups of task variables differently, further distinguishing their likely signal sources. Encoding of chosen saccade direction, chosen-option attributes, risk, and subjective value was reduced or abolished, particularly in lower-frequency bands, including the beta band. These effects support the dependence of these signals on intact local SEF circuitry. Conversely, high-gamma encoding of reaction time, reward magnitude, signed and unsigned reward prediction errors, and gamble

outcome often persisted during cooling, consistent with a substantial afferent contribution. Together, these findings suggest a frequency-specific dissociation between cooling-sensitive local computation and cooling-resistant input-related activity in SEF. Local circuits preferentially contribute to choice, value, and risk computations, whereas motivational and outcome-related signals are more consistent with afferent or spatially distributed sources.

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Poster

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Support: DFG EXC 307
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DAAD

Title: Neurocomputational correlates of value-based decision-making in macaques and humans

Authors: *J. LEE[1,2,3,4], E. ZEZELIC[1,2,3,4], M. SIEGEL[1,2,3,4];
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Abstract: Value-based decision-making requires subjects to integrate reward and choice history, internal subjective value, and changing environmental contingencies. We combined behavioral modeling with electrophysiology to identify neural correlates of internal decision variables during a dynamic value-based decision-making task, and tested whether computational models generalize across macaques and humans.Two macaques performed a value-based decision task in which the reward probabilities of two choice objects switched unpredictably across blocks. We fit a spectrum of behavioral models, including win-stay/lose-switch (WSLS), recursive logistic regression (rLogReg), and Q-learning with forgetting (FQ), using leave-one-block-out cross-validation. In the same animals, we recorded 64-channel electroencephalography (EEG) and decoded task and latent variables at each time point using cross-validated multivariate analysis of variance (cvMANOVA). Human participants completed an online version of the task as a pilot for ongoing magnetoencephalography (MEG) recordings.Choice behavior tracked relative reward history and followed Herrnstein's matching law. rLogReg and FQ outperformed the heuristic WSLS model, indicating that upcoming choices were better explained by graded reward-history integration than by simple stay/switch rules, with value estimates largely consistent across the rLogReg and FQ models. EEG decoding showed reliable task-variable representations: object position and current choice emerged around stimulus and saccade periods,

and reward-outcome signals emerged at feedback for both rewarded and unrewarded trials. Beyond current-trial information, EEG also encoded previous-trial choice and reward, demonstrating that recent behavioral history persists in the non-invasive neural signal. Moreover, model-derived variables were decodable from EEG. Because these regressors were only weakly correlated, they index largely separable neural signals rather than a single reward-history axis. In human participants, choice behavior was also captured by FQ and rLogReg, supporting the cross-species behavioral validity of the task and models.Behavioral models thus provide a trial-by-trial readout of valuation, reward history, and strategy that is reflected in non-invasive neural signals. This framework links separable computational signals to adaptive choice strategies, and shows that a shared modeling account captures behavior across monkeys and humans, providing a cross-species approach to study the neural dynamics of value-based decision-making.

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Poster

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Topic: I.03. Decision Making

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Wellcome Trust 206207/Z/17/Z
Wellcome Trust 206207/Z/17/A

Title: Social monitoring during reciprocal value-based decisions in macaques

Authors: *S. FERRARI-TONIOLO[1], M. KADOHISA[2], M. KUSUNOKI[2], M. J. BUCKLEY[3], F. GRABENHORST[2];
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Abstract: Introduction. In social contexts, choices can affect both the decision maker and other individuals. This requires not only to evaluate available rewards, but also to monitor the actions and potential outcomes of social partners. Characterizing gaze patterns during social choices can reveal which information is sampled when evaluating self- and other-relevant outcomes, and can provide behavioural markers for identifying distinct components of social decision-making. Here, we developed a dyadic macaque touchscreen task to characterize how gaze is structured by task context, actor-observer role, and reward value during reciprocal social decision-making. **Methods.** Two macaques sat facing each other across a horizontal touchscreen and alternated between making choices and observing the partner's choices. On each trial, a central cue indicated the task context: choose for self, choose for other, or choose for both (n = 94 total sessions). Two lateral cues then indicated the offered reward types and amounts, followed by two choice targets presented beside the acting animal. Gaze was monitored throughout the trial, and

rewards consisted of fuit smoothies (apple, blackcurrant, orange). Value-based choices provided a quantitative readout of each animal's subjective evaluation of the choice options, allowing self- and partner-specific subjective reward values to be related to gaze patterns.**Results.** Psychometric choice curves revealed stable reward preferences across sessions in both animals, quantifying subject-specific evaluations for different reward types and amounts. Gaze was structured by task events: animals looked at the central cue, sampled the lateral reward cues, and then looked toward the choice targets. At the choice epoch, gaze was directed to the acting hand, with animals looking at their own hand when choosing and at the partner's hand when observing. Animals also looked at the partner's face, especially before trial onset and around reward delivery, suggesting that gaze was not limited to instrumental screen sampling but also included social monitoring. Ongoing analyses test whether gaze reflects self-value, partner-value, or conflict between the two, particularly during observation and shared-outcome trials.**Conclusions.** These results establish a dyadic macaque paradigm for dissociating reward valuation, action monitoring, and social gaze during reciprocal economic decision-making. The resulting behavioural metrics provide a foundation for targeted neurophysiological investigations into the brain mechanisms of social monitoring and other-regarding choice.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.13/KK4

Topic: I.03. Decision Making

Support: NIH Grant MH130374

Title: Mapping regional variation in the parametric form of reward responses using the Monetary Incentive Delay (MID) task

Authors: *L. BAKST, Y. ONIPEDE, Y. LI, S. LING, J. T. MCGUIRE;
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Abstract: Preparing a speeded response to gain a reward or avoid a loss, as operationalized in the Monetary Incentive Delay (MID) task, drives robust anticipatory BOLD activity in regions such as the striatum, insula, thalamus, and precentral gyrus. However, the pattern of response amplitudes across a continuous range of prospective outcomes, from large potential losses to large potential gains, has been underexplored. Whether activity in value-sensitive regions scales linearly with signed value, follows a V-shaped function akin to absolute value or salience, or shows saturating nonlinearities - or some combination of the three - has not been fully investigated. Here, human participants (N=25) performed the MID task while undergoing fMRI. Unlike prior work, we parametrically varied the prospective gain or loss amount in 10 uniformly

spaced increments. With this finer sampling, we were able to draw from approaches to modeling the visual contrast response function to characterize the form of the value response. In keeping with previous findings, the ventral striatum showed a non-monotonic and asymmetrical response: larger incentive magnitudes evoked larger responses, more steeply for potential gains than losses. Anterior insula showed more a symmetrical response that appeared to reflect the absolute magnitude of the prospective outcome. Precentral gyrus demonstrated a non-monotonic response similar to striatum, with stronger responses for gains compared to losses. In addition to examining cue-related brain responses, we also investigated motor preparation activity during the cue-target interval and observed large effects, both in widespread BOLD activity and systemic physiology (cardiac deceleration) that scaled with the randomized duration of the interval. In summary, we use a parametric variant of the MID task to map the functional form of anticipatory valuation effects across the brain. The findings have potential to facilitate more accurate modeling of valuation effects in BOLD activity in future studies and to suggest new individual differences metrics based on features of the shape of the valuation function.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.14/KK5

Topic: I.03. Decision Making

Support: NIH Grant R01MH119086

Title: Task Difficulty as a Cost in Effort-Based Decision-Making

Authors: *Y. WANG[1,2], A. CASAMENTO MORAN[1,2], J. LEE[1,2], V. S. CHIB[1,2];
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Abstract: Effort and difficulty shape everyday decisions, influencing whether we pursue tasks that require intense exertion or precise performance. Despite their importance, little is known about how these two costs are jointly evaluated and represented in the brain. Here, we investigated how individuals weigh effort and difficulty during decision-making at both behavioral and neural levels. Participants first performed a motor task in which effort and difficulty were manipulated independently. Effort was varied by changing the grip force required to complete the task, whereas difficulty was varied by changing the precision required. Specifically, participants squeezed a hand-grip dynamometer to move a cursor into a target on a screen; target position determined the required force level, and target size determined task difficulty. Participants then completed an fMRI decision-making task in which they chose between options that varied in effort, difficulty, and monetary reward. Behaviorally, participants treated difficulty as a quantifiable cost, trading it against both effort and reward. Neurally,

activity in the ventromedial prefrontal cortex (vmPFC) increased as effort costs decreased, whereas activity in the anterior cingulate cortex (ACC) increased as difficulty costs decreased. Both regions also encoded reward magnitude and integrated effort, difficulty, and reward into a subjective value signal. Together, these findings demonstrate that difficulty functions as a distinct cost in effort-based decision-making and reveal how the brain combines multiple task demands to guide choice.

Disclosures: Y. Wang: None. **A. Casamento Moran:** None. **J. Lee:** None. **V.S. Chib:** None.

Poster

PSTR154: Decision-Making: Value and Risk Representations

Location: WCC Halls A-C

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Program #/Poster #: PSTR154.15/KK6

Topic: I.03. Decision Making

Support: NIH Grant R01-MH130374

Title: Neural signatures of flexible time-dependent valuation

Authors: *Y. LI[1], M. ARMSTRONG[1], L. BAKST[1], Y. CHEN[1], J. GUO[2], Y. ONIPEDE[1], M. P. PASCALE[1], J. T. MCGUIRE[1];
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Abstract: Adaptive decision making requires learning environmental structure and using it to infer the value of available options. Value can sometimes depend on temporal information retrieved from memory. For instance, the quality of the milk in your fridge depends on how long ago you bought it. The medial temporal lobe (MTL) is thought to interact with valuation systems to support such memory-guided value-based decisions. Here, we present neuroimaging findings examining the neural mechanisms implicated in this kind of flexible valuation based on temporal recency. Participants (N=32) completed a four-session fMRI study designed to investigate context-dependent memory-guided valuation. Participants encountered a series of unique visual items and were periodically asked to accept or decline a previously encountered item. The value of the item depended both on the amount of time since it was first encountered as well as the decision context. In the value-appreciation context, an item's value increased with time since it was originally encountered, whereas in the value-depreciation context, its value decreased. Because the value-appreciation and value-depreciation contexts jointly dissociated expected reward from temporal recency and task difficulty, we were able to separately examine whole-brain signatures of each factor. Behavioral results showed that participants on average were successful at learning through experience to make value-maximizing choices by preferentially engaging with more temporally remote items in one context and more recent items in the other. In fMRI BOLD data acquired after successful learning, expected value was positively associated with activity in vmPFC and left occipital cortex. Temporal remoteness was positively associated with activity in retrosplenial, hippocampal, and parahippocampal cortex, while task difficulty

was negatively associated with activity in vmPFC and positively associated with activity in dorsal anterior cingulate cortex and bilateral anterior insula (all cluster corrected at $z > 3.9$, $p < .001$, $\alpha < 0.05$). Together, these findings support the hypothesis that flexible memory-guided valuation emerges from interactions between MTL and valuation systems.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR154.16/KK7

Topic: I.03. Decision Making

Support: Canon Medical System

Title: Causal modulation of human value-based decision-making with transcranial focused ultrasound

Authors: *S. ZHENG;
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Abstract: The ventromedial prefrontal cortex (vmPFC) is consistently implicated in subjective valuation, but most human evidence is correlational. Here we tested whether low-intensity transcranial focused ultrasound (TUS) can causally modulate value-based choice and value-based learning by targeting vmPFC. Participants **(n = 10)** completed a participant-blind, within-subject design with active vmPFC TUS and sham sessions separated by at least 7 days and counterbalanced in order. Structural MRI was used for subject-specific targeting and acoustic planning to focus stimulation on vmPFC while avoiding the frontal sinus. Active stimulation used an offline theta-burst TUS protocol: 265 kHz fundamental frequency, 20 ms pulses delivered at 5 Hz for 80 s, yielding 400 pulses total, with free-field ISppa = 28.8 W/cm². Sham controlled for auditory confounds using TUS-like sounds delivered through bone-conduction headphones. Behavior was assessed with three tasks. First, a Becker-DeGroot-Marschak auction measured willingness-to-pay for 75 items across food, trinket, and lottery categories. Second, 24 items near each participant's median bids were selected for a 276-trial pairwise preference task to quantify choice consistency and transitivity errors. Third, a 170-trial probabilistic reversal-learning task measured value updating under changing reward contingencies. Preliminary results suggest that vmPFC TUS affects specific components of value-guided behavior rather than global task performance. In the preference task, stimulation appeared to disrupt choice consistency, with stronger effects for bid-based transitivity errors than for preference-derived rankings. In reversal learning, stimulation modulated learning dynamics, especially the stability of choices around the currently high-probability option before reversal and the tendency to regress after switching. These findings provide initial causal evidence that human vmPFC

contributes not only to representing subjective value, but also to maintaining and updating value-guided choices. More broadly, this work demonstrates the feasibility of using TUS to perturb deep ventral decision circuits non-invasively during human decision neuroscience experiments.

Disclosures: S. Zheng: None.

Poster

PSTR154: Decision-Making: Value and Risk Representations

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Topic: I.03. Decision Making

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Title: Fast Affective, Slow Cognitive: Distributed Neural Signatures of Value and Risk-based Decision-Making

Authors: *G. DENG[1,3], X. MENG[4], Y. CUI[3], G. ZHOU[5], J. ZHOU[6], Y. LUO[3], H. AI[7], C. ZELANO[8], F. CHEN[9], V. MENON[2], P. XU[3];
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Abstract: Value- and risk-based decisions are often framed as interactions between fast affective and slower cognitive processes, yet their millisecond-scale neural implementation remains unclear. We recorded intracranial EEG from 39 human epilepsy patients (16 males, 16-49 years; 308 ROI contacts) during a 256-trial mixed-gamble task manipulating expected value (EV) and outcome variance (OV). We combined behavioral analysis, hierarchical Bayesian prospect-theory modeling, profile analysis, intracranial event-related potentials (iERPs), time-frequency cluster-based permutation testing, and nonlinear causal relationship estimation by artificial neural network (nCREANN) across amygdala, ventral anterior insula (vAI), dorsal anterior insula (dAI), dorsal anterior cingulate cortex (dACC), and dorsolateral prefrontal cortex (dlPFC). Behaviorally, choices were driven by EV but not OV: participants accepted positive-EV gambles

more often than negative-EV gambles ($t_{(38)} = 12.79$, $p < 0.001$), whereas OV had no significant effect. Rejecting gambles was slower than accepting them ($t_{(38)} = 2.16$, $p = 0.037$), and reaction times followed an inverted-U function of EV, indicating maximal conflict near indifference. Computational modeling favored a three-parameter model including risk aversion, loss aversion, and choice consistency, revealing substantial individual heterogeneity. Neurally, affective and cognitive systems showed distinct polarities and timing. Amygdala and vAI exhibited negative-going responses and early broadband oscillatory differentiation within ~200 ms, whereas dAI, dACC, and dlPFC showed positive-going and later beta/gamma responses after ~300 ms. Peak latencies followed an affective-to-cognitive gradient from vAI/amygdala to dAI/dlPFC and finally dACC. Model-based neural analyses showed that risk aversion was encoded early in vAI (33-320 ms) and later in dAI (565-678 ms), whereas loss aversion required late coordination across amygdala, dAI, and dlPFC (>500 ms). nCREANN identified vAI as a central causal hub during value evaluation, with sustained vAI→dAI influence and later vAI→amygdala/vAI→dlPFC interactions. Critically, risky and safe choices emerged from distinct causal pathways converging on dACC: gambling was supported by an intra-insular cascade (vAI→dAI→dACC), whereas rejection recruited an amygdala-to-prefrontal control pathway (amygdala→dlPFC→dACC). These findings provide direct human neurophysiological evidence that risky decisions are implemented through temporally ordered, dynamically reconfigurable affective-cognitive circuits rather than a single common valuation pathway.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

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Topic: I.03. Decision Making

Support: APF F.J. McGuigan Dissertation Award

Title: Social Modulation of Anticipatory CNV-Like Activity During Decision-Making

Authors: *E. DOUGLAS;
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Abstract: Social context influences decision-making, yet its effects on anticipatory neural activity preceding risky choices remain poorly understood. The contingent negative variation (CNV) is thought to reflect anticipatory attention and cognitive preparation. This study investigated whether social presence modulates CNV-like activity preceding risky decisions. We compared pre-decision ERP activity during decisions made alone versus in the presence of observers to characterize social modulation of cognitive control and decision preparation.

Participants (N= 118, ages 18-76) completed a 250-trial decision-making task in which they chose between foraging for berries while risking bear attack or leaving a patch while risking starvation. Following preprocessing and artifact rejection, analyses included 68 participants. Trials were performed either alone or in the presence of unfamiliar observers, creating the two conditions. EEG was recorded throughout the task. ERP analyses focused on the 500-ms pre-response window preceding each decision. Data were sampled at 500 Hz using a 32-channel EEG system. Analyses focused on electrodes Fz and Cz, where CNV-like activity is observed. Trials exceeding ±100 μV were excluded. Mean pre-decision ERP amplitude served as the primary outcome measure. Repeated-measures ANOVAs were used to examine the effects of condition and electrode site on anticipatory ERP amplitudes. Paired t-tests compared conditions at each electrode. A repeated-measures ANOVA revealed a significant main effect of condition ($F(1,67) = 24.58$, $p < .001$, $\eta^2G = 0.122$), indicating that anticipatory ERP amplitudes were more negative during Presence than Alone trials. Follow-up paired t-tests confirmed greater anticipatory negativity during Presence trials at both Fz (mean difference = 1.07 μV, $t(67) = 4.83$, $p < .001$) and Cz (mean difference = 0.99 μV, $t(67) = 4.82$, $p < .001$). The present findings support the hypothesis that social presence modulates anticipatory neural processes during risky decision-making. Greater CNV-like negativity in the Presence condition suggests enhanced cognitive preparation and control allocation before choice, indicating that even simulated social observation can modulate the neural mechanisms underlying decision-making. Future research should examine whether these effects generalize to real-world social interactions involving physically present observers.

Disclosures: E. Douglas: None.

Poster

PSTR154: Decision-Making: Value and Risk Representations

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Topic: I.03. Decision Making

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Title: Dissociable Neural and Computational Mechanisms of Ambiguity Sensitivity and Management in Decision-Making Under Uncertainty

Authors: *F. GÓMEZ-IBARRA[1], R. HENRÍQUEZ-CH[1], P. BILLEKE[2], F. ABOITIZ[1];
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Abstract: Most research on intolerance of uncertainty has focused on initial responses to ambiguity, leaving open whether behavior after engagement with uncertainty relies on distinct mechanisms. To investigate the behavioral, computational, and neural basis of this distinction, 40

healthy adults (18 female, mean age 26.2 ± 5.90) completed the Ambiguity Avoidance and Management (AAM) task during electroencephalographic (EEG) recording and measures of psychopathology symptoms and personality traits. The task dissociates an initial choice between a certain reward and an ambiguous gamble (Stage 1, capturing ambiguity-related behavior) from a subsequent probability-guided decision following partial information (Stage 2, capturing subsequent decision behavior). Hierarchical Bayesian modeling estimated ambiguity sensitivity (AS; difference in safe choice probability between ambiguous and risky conditions in Stage 1) and ambiguity distortion (AD; latent subjective estimation of uncertainty in Stage 2), while behavioral shift was quantified using a shift-rate index capturing sensitivity to ambiguity during Stage 2 choices (BS). AS was associated with BS ($\rho = -0.41$, $p = 0.009$), and BS was associated with AD ($\rho = -0.59$, $p < 0.001$), while AS and AD were not correlated ($\rho = 0.12$, $p = 0.453$). AS was positively associated with obsessive-compulsive symptoms measured by the Obsessive-Compulsive Inventory-Revised (OCI-R; $\rho = 0.43$, $p = 0.006$) and neuroticism ($\rho = 0.32$, $p = 0.042$), whereas AD and BS showed no associations with either trait (all $p > 0.15$). All correlations were assessed using Spearman's rank correlation coefficients. EEG analyses, conducted using Wilcoxon signed-rank tests with multiple-comparison correction, revealed distinct frontoparietal dynamics across Stage 1 and Stage 2 in GLMM-derived neural activity estimates. In Stage 1, ambiguity-related betting was associated with predecisional parietal 8-24 Hz activity ($p = 0.0003$) and postdecisional frontal 0-7 Hz activity ($p = 0.0001$). In Stage 2, adaptive high-probability choices under ambiguity engaged frontal and parietal clusters spanning 5.5-25 Hz (all $p < 0.02$), with neuroticism positively associated with parietal activity during ambiguity management ($\rho = 0.31$, $p = 0.049$). Together, these results demonstrate that early ambiguity sensitivity and later ambiguity management reflect partially dissociable computational and neural processes. Early sensitivity is selectively linked to trait-level affective vulnerability, whereas later-stage adaptation is supported by frontoparietal dynamics tracking behavioral adjustment under sustained uncertainty independently of personality traits.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

Location: WCC Halls A-C

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Program #/Poster #: PSTR154.20/KK11

Topic: I.03. Decision Making

Title: Subjective value, uncertainty, and confidence representations during preference-based decision making in human intracranial recordings

Authors: *C. L. BRANDON[1,2], C.-H. KAO[3], O. E. FRUCHET[1], K. A. ZAGHLOUL[1], S. LOPEZ-GUZMAN[3];
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Abstract: Most real-life decisions involve uncertainty, and adaptive decision-making requires comparing the uncertain value of possible options. The sources of uncertainty can be external or internal. External uncertainty in decision making is determined by outcome probability which may be fully known (risk) or unknown (ambiguity). Internal uncertainty requires introspection and may reflect individuals' belief about the reliability of their decisions, expressed as decision confidence. Imaging studies have shown that insula and orbitofrontal cortex (OFC) represent value, uncertainty, and confidence during decision making, but limited spaciotemporal resolution has constrained our understanding of how these features are segregated. In this study, we recorded human intracranial EEG activity across multiple areas including OFC and insula to further elucidate how these areas construct and maintain these representations. Participants (n=8) performed a decision-making task with intracranial EEG coverage that included depth electrodes in the insula and OFC. In the task, participants chose between a sure gain (i.e., 100% probability of receiving a small reward) and playing a lottery (a larger, probabilistic gain). Risk and ambiguity varied with each trial. Exact reward probability was fully known on risk trials and partially known on ambiguity trials. After each choice, participants then rated their decision confidence. Computational modeling showed that participants computed subjective values (SVs) for the two options and were more likely to choose the lottery as its SV exceeded that of the sure option. Decision confidence increased as the absolute difference between the SVs grew. Preliminary analysis of the power spectral density of signals from the insula and OFC during this task show modulation, particularly in the theta and alpha bands, that correlates with the varying levels of risk, ambiguity, and confidence identified in the behavioral data. These results suggest the presence of external and internal uncertainty representation in OFC and insula. Recruitment is ongoing, and future analyses will examine temporal differences in encoding between external and internal uncertainty within this network.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

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Topic: I.03. Decision Making

Support: NIGMS 5P20GM103645
Brainstorm Program at the Robert J. & Nancy D. Carney Institute for Brain Science at Brown University

Title: Cardiac influences on value-based decision-making in chronic pain

Authors: *P. PEI[1], C. WILLIAMS[2], C. ZIMMERMAN[1], P. MEADER YETTER[1], L. L. OWEN[3], M. R. NASSAR[1], F. PETZSCHNER[1];
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Abstract: Interoceptive signals are closely tied to value-based decision-making with homeostatic states dynamically reweighting the subjective value of available options (Weber et al., 2025). Cortical processing of cardiac activity preceding choice presentations, indexed by heartbeat-evoked potentials (HEPs), has been linked to subjective value encoding (Azzalini et al., 2021), suggesting that the heart-brain axis actively shapes how we learn and decide. Chronic pain, a condition characterized by profound alterations in bodily perception, has been demonstrated to be associated with shifted reinforcement learning strategies, from global, context-independent value representations toward locally learned, context-dependent values (Williams et al., 2025). The present study investigates whether the shifted reinforcement learning strategies can be partly explained by aberrant interoceptive processing across varied chronic pain conditions. Chronic back pain (CBP, N = 33) and fibromyalgia (FM, N = 23) patients, and healthy controls (HC, N = 27) completed a reinforcement learning task with simultaneous EEG recordings. Behaviorally, overall learning performance was comparable across groups ($\chi^2(2, 72) = 3.56$, $p = 0.168$), but decision-making strategies were significantly different ($\chi^2(8, 72) = 17.32$, $p = 0.027$). Computational model parameters revealed that only CBP, not FM or HC, preferred local context-dependent valuation to global value integration. Preliminary EEG analysis showed that the contrast of pre-decision HEPs between incorrect and correct responses was larger in HC and FM in comparison to CBP, in line with the behavioral and modeling results. We are currently examining the interaction between HEPs and choice consistency; we predict that larger HEP amplitudes are associated with higher choice consistency in accordance with the learned value across contexts. These findings will illuminate how interoceptive processing shapes learning strategy selection in chronic pain, and how heart-brain communication may contribute to the formation of value representations.

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Poster

PSTR154: Decision-Making: Value and Risk Representations

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Program #/Poster #: PSTR154.22/KK13

Topic: I.03. Decision Making

Title: Examining the role of agency-related beliefs in betting decisions under uncertainty

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Abstract: Humans routinely make decisions under uncertainty, even when outcome probabilities are partially known or opaque. Although risky choice is often modeled as a function of outcome probability and reward magnitude, choosing itself may carry subjective value through agency-related beliefs. These include beliefs about free will, despite longstanding debates about its causal role in behavior, and trait sense of agency, the generalized sense of being the author of one's actions and outcomes. Here, we examine whether agency-related beliefs predict action selection under uncertainty using betting behavior in gambling-like tasks as a controlled behavioral assay. To this end, we employ two tasks: (1) a positive/negative expected-value (EV) task and (2) a single/four-box task. In the positive/negative-EV task, participants choose whether to pay a cost to bet on a box; depending on the condition, betting is either advantageous or disadvantageous in terms of EV. Prior data from this task showed near-ceiling betting in the positive-value condition but substantial individual differences in betting under negative expected value. In the single/four-box task, participants choose whether to bet or pass on a single box with a 25% winning probability, whereas in four-box trials they select one of four boxes or pass. In four-box trials, one box contains a reward, yielding the same 25% winning probability and zero EV as the single-box condition. Nevertheless, prior data showed higher betting in the four-box condition. These betting patterns deviate from EV maximization, suggesting that action selection itself carries subjective value. We hypothesized that these deviations reflect individual differences in free will beliefs and trait sense of agency. To measure these constructs, we use the Japanese version of the Free Will and Determinism-Plus Scale (FAD+) and the Japanese version of the Sense of Agency Scale (J-SoAS). We also use the Domain-Specific Risk-Taking Scale (DOSPERT) to account for general risk preference. Participants first complete both tasks to quantify deviations from EV maximization. Subsequently, they complete the FAD+, J-SoAS, and DOSPERT to assess free will and determinism beliefs, trait sense of agency, and risk preference. We then test whether agency-related beliefs explain individual differences in negative-EV betting and the four-box betting increase beyond general risk preference. Together, these analyses address how agency-related beliefs may contribute to behavioral differences under uncertainty.

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Poster

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Topic: I.03. Decision Making

Title: The explicit and implicit in delegation of agency

Authors: *K. MOGI;
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Abstract: Conditions and contexts in which an agent like a human delegates part of its judgement, choice, and selection to systems supported by modern technologies such as artificial intelligence is becoming an important issue both scientifically and technologically. Delegation involves elements of cognition, including visual and auditory perception, language, embodied cognition, and emotion. When a human subject makes a decision, he or she is not necessarily aware of all the cognitive elements involved. In vision, there is in general more information in the visual field than can be handled by the cognitive system (Block 2011). The superfluous nature of visual information makes implicit as well as explicit elements in visual field as important denominators of in the handling of visual perception. The exact nature of the division of labor between implicit and explicit systems is still debated (Lau and Rosenthal 2011, O'Regan 2011, Brown 2012, Brown et al. 2019, Kozuch 2024). In embodied cognition, tools might be processed as part of the extended body (Iriki et al. 1996, Farnè and Làdavas 2000). Emotion can be understood as an adaptive strategy to the uncertainties involved in the interaction with the environment (Barrett 2017, Seth and Friston 2016). The cognitive system making judgements about the visual field is affected even when the cognitive system is unable to handle all the relevant information available in the visual field. In some cases, the implicitly processed information has more effect on the subjects' emotive judgments than the explicitly processed information.Here I investigate the roles played by the explicitly and implicitly processed elements in the visual environment in the subjects' cognitive and emotional judgments. Scenarios were presented simulating situations in self-driving cars, where various information concerning the algorithm (e.g., values of evaluation function assigned to elements related to the possible alternative maneuvers of the automobile) were either explicitly presented or absent, affecting the subjects' judgments. The stimuli included houses, trees, pedestrians, etc., occurring frequently in the daily lives. The subjects were given alternative scenarios as to how the visual scenes were generated and presented, with varying degrees of explicit and implicit information.Based on the results, I analyze the cognitive factors handling implicit and explicit information affecting the delegation of agency.

Disclosures: K. Mogi: None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.01/KK15

Topic: I.06. Social Cognition

Support: NIH R01DC019653
NIH U01NS121616

Title: Dynamic Population Coding of Semantic Structure in Primate Prefrontal Cortex

Authors: *S. LEE[1], B. MASH[1], C. AYUBCHA[2], I. CAPRARA[3], R. BÁEZ-MENDOZA[4], M. JAMALI[1], Z. WILLIAMS[1];
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Abstract: Semantic knowledge enables humans and non-human primates (NHPs) to interpret socially and behaviorally relevant information in complex environments. Although the prefrontal cortex (PFC) plays a central role in higher-order cognition and social behavior, it remains unclear how structured semantic information is represented in evolving neural population states, how reliably stimulus-evoked responses are expressed across species, and how semantic and visual stimulus features are encoded at the level of individual neurons. We recorded single-unit activity from homologous PFC regions in humans and rhesus macaques during passive viewing of brief image sequences. Stimuli were characterized using two 13-dimensional feature spaces: a high-level semantic (HS) space capturing socially and behaviorally relevant attributes and a low-level visual (LL) space derived from image statistics.We combined three complementary analyses. First, to assess population dynamics, we quantified time-resolved neural trajectories associated with stimulus clusters and compared their geometry, dimensional structure, and pairwise trajectory distances across species. Second, to determine whether cross-species differences in representational structure could be explained by differences in neural responsiveness, we measured active trial fractions, evoked firing rates (FR), mean FR, and inhibitory and excitatory trial fractions during the stimulus-viewing epoch. Third, as a separate feature-encoding analysis, we applied feature-based generalized linear models to estimate how semantic and visual feature dimensions were represented in neural activity.Population trajectories in both species showed structured temporal evolution during stimulus viewing rather than static cluster separation. Cluster-based trajectories occupied low-dimensional neural-state spaces and continued to evolve throughout the one-second viewing period. Pairwise trajectory-distance analyses further showed separable cluster trajectories, with species- and feature-space-dependent differences in trajectory geometry. Cross-species responsiveness analyses showed broadly comparable levels of stimulus engagement, with only modest species-dependent trends in FR magnitude and response polarity. Feature-encoding analyses further showed that individual neurons carried information about both semantic and visual stimulus dimensions. Together, these findings suggest that PFC representations of semantic and visual structure are expressed through dynamic population trajectories supported by largely conserved patterns of stimulus engagement across primate species.

Disclosures: S. Lee: None. **B. Mash:** None. **C. Ayubcha:** None. **I. Caprara:** None. **R. Báez-Mendoza:** None. **M. Jamali:** None. **Z. Williams:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Topic: I.06. Social Cognition

Support: NIH Grant U01NS108680
NIH Grant 1F31MH125451

Title: Social learning refines social neural representations by selectively recruiting context-informative neurons

Authors: *J. KIM[1], M. FRANCH[2], M. SLAPIK[3], V. DRAGOI[4];
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Abstract: The brain has a remarkable ability to assign different meanings to the same visual input depending on context. For example, during social cooperation, sensory information from an individual may be encoded as a cue for cooperation, whereas the same input may carry a different meaning in a non-social context. Although such context-dependent visual processing is essential for flexible social decision-making, it remains unclear how prefrontal neural populations represent and refine social context as animals become familiar with it.
To investigate this, we wirelessly recorded population activity from visual cortical area V4 and dorsolateral prefrontal cortex (dlPFC) in freely moving macaques as they learned a social cooperation task. Using wireless eye tracking and receptive field mapping, we extracted neural activity during fixations on task-relevant objects, including the partner and reward, when these objects fell within neurons' receptive fields. We defined the trial period as the social context and the inter-trial interval as the non-social context, and examined how neural populations encoded context while the monkey viewed the same object.
Using linear discriminant analysis (LDA), we decoded social versus non-social context from population activity during fixations on the partner and reward. Context decoding accuracy increased in dlPFC as animals became more familiar with the cooperative context, whereas V4 neurons showed weaker and less consistent learning-related changes. Decoder weight analysis further revealed that a subset of high-contribution dlPFC neurons became increasingly dominant in context decoding over learning, suggesting that social experience sharpens prefrontal context representations by selectively recruiting context-informative neurons.
Together, these findings show that social experience sharpens dlPFC representations of social context during naturalistic cooperation. Rather than simply encoding visual objects, dlPFC increasingly represents the context-dependent relevance of the same visual input, providing a potential neural mechanism for flexible, context-driven decision-making in freely interacting macaques.

Disclosures: J. Kim: None. **M. Franch:** None. **M. Slapik:** None. **V. Dragoi:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Topic: I.06. Social Cognition

Support: National Institute of Aging Grant R56 AG071486

Title: Social Context Modulates Cortical Responses to Affective Touch Differently in Young and Elderly Macaques

Authors: *S. MARCHAND[1], J. A. CHARBONNEAU[1], A. ARMITANO[1], J. BENNETT[1,2], G. MOADAB[1,2], E. BLISS-MOREAU[1,2];
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Abstract: Loneliness has dire health consequences and elderly people are particularly vulnerable to loneliness as their social circles shrink. Studies on loneliness conducted in nonhuman primate models have revealed many of the same biological effects as those in humans, suggesting the existence of conserved mechanisms common to all primates and allowing for mechanistic studies. Social interactions provide the nervous system with a wealth of information, particularly regarding the perception of affective touch. Among primates, grooming plays an important role in social interactions; however, although we have previously demonstrated age-related differences in how touch is processed in animals living in social groups, a causal link between the cortical response to affective touch, age, and the availability of social partners has yet to be established. To investigate how the neural mechanisms for affective touch change across the lifespan relative to social environment, 16 anesthetized rhesus monkeys (8 young and 8 elderly) who came from robust social groups, went through our standardized affective touch paradigm after two experimental social conditions. The first functional MRI session was conducted ~2 years after they had been moved into new small social groups and the second session was conducted after they had been living in a restricted social environment for 14 weeks. The touch paradigm contrasted affective touch (slow, 3 cm/s), which preferentially activates C-tactile afferents, with discriminative touch (fast, 15 cm/s), which primarily engages mechanoreceptors. MRI data analysis using nonparametric permutation testing enabled the assessment of differences between the two social contexts and between the two age groups. Replicating previous findings from our group, all animals evidenced strong cortical activation in response to affective touch, particularly in the somatosensory, parietal, motor/premotor, and, surprisingly, visual cortices. Social context modulated these activations, with the motor/premotor cortex more active during group-housing and the visual cortex during social restriction. Young adults' multimodal sensory regions differentiated between touch speeds to a greater extent than did elderly adults. Only in elderly subjects did social context modulate responses to both touch conditions in the somatosensory cortex, parietal regions, and anterior cingulate cortex. These results suggest that with age, the somatosensory cortex becomes increasingly sensitive to social context, strengthening the relevance of the macaque model for understanding the neural mechanisms linking social environment to health outcomes in humans.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Program #/Poster #: PSTR155.04/KK18

Topic: I.06. Social Cognition

Support: NIH Grant R01MH121009

Title: Estimating the relative status of others depends on perceived status of self

Authors: *M. H. LYNCH[1], M. A. KRAUSE[2], K. M. GOTHARD[3];
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Abstract: Higher social status is coveted by both humans and non-human primates as it ensures access to valuable resources such as food, mates, and shelter. Rhesus macaques are ideal to explore status-related behaviors, as their society is organized in a strict linear dominance hierarchy. For males, the hierarchy is fluid and is established through competition, therefore males often rise and fall in status. Our previous work demonstrated that macaque third-party observers of dominant-subordinate interactions learned the status of individuals in a four-member virtual hierarchy. Here, we asked if they could integrate themselves into such a hierarchy. We hypothesized that two male observers would be able to infer their own status in the hierarchy if dominant or subordinate displays were directed toward them. Further, we examined whether a change in self-status shifted visual allocation of attention towards the other members of the hierarchy, expecting a looking preference for individuals of neighboring status. In third-party observers, gaze pattern analysis revealed increased attention on subordinate animals, measured by cumulative looking time and frequency of joint-attention saccades (paired t-tests, $p < .001$). This looking preference was maintained by one viewer monkey as he watched videos of the same individuals with directed gaze and neutral expression. To integrate the viewer into the hierarchy, each video monkey was shown displaying facial expressions directed at the viewer. Threatening and appeasing expressions establish the dominant or subordinate status of the video monkeys relative to the viewer. Viewers were assigned three separate ranks (in order): middle rank (two video monkeys displayed threats and two displayed appeasement), top rank (all video monkeys displayed appeasement), and bottom rank (all video monkeys displayed threats). When viewers were assigned the middle rank, both monkeys looked longest at the dominant or subordinate monkey immediately above or below them (ANOVA, $p < .05$). When shifted to the top, they both looked longest at the video monkey immediately subordinate to them (ANOVA, $p < .001$). Similarly, in the bottom rank, one viewer looked longest at the monkey immediately dominant to them (ANOVA, $p < .001$). Bonferroni correction was performed for all repeated comparisons. Taken together, these data confirm our hypothesis, indicating that viewers can integrate themselves into an artificial hierarchy and shift gaze patterns according to perceived self-status relative to others. Further analysis will determine the neural correlates of status shifts in the amygdala and hippocampus.

Disclosures: M.H. Lynch: None. **M.A. Krause:** None. **K.M. Gothard:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Program #/Poster #: PSTR155.05/KK19

Topic: I.06. Social Cognition

Support: NIH Grant R01MH121009

Title: Neural representation of social hierarchy in the primate hippocampus

Authors: *M. A. KRAUSE[1], M. H. LYNCH[2], S. LEE[3], M. T. KABIR[2], K. M. GOTHARD[4]; [1]Neurosci., [2]Physiol., Univ. of Arizona, Tucson, AZ; [3]Neurosurg., Harvard Med. Sch. / Massachusetts Gen. Hosp., Boston, MA; [4]Physiol., Univ. Arizona, Col. Med., Tucson, AZ

Abstract: To successfully integrate into a hierarchically organized social group, rhesus macaques learn their own position in the hierarchy as well as those of others. Previous work demonstrated that when monkeys viewed simulated interactions between dominant and subordinate animals, the dominant animal receives more visual attention, while the social status of both individuals emerges as a latent variable in the viewer's amygdala. As both the amygdala and the hippocampus are involved in gaze-mediated social learning, we hypothesized that neurons in the hippocampus also respond to social status. To test this hypothesis, we recorded eye movements and hippocampal single-unit activity from 2 macaques in response to videos containing exchanges of threatening facial expressions from dominant individuals and appeasing facial expressions from subordinate individuals. The videos depicted all possible pairwise interactions among five unfamiliar monkeys, providing information about each monkey's rank within the social hierarchy. We also presented videos of dominant-subordinate pairs with neutral facial expressions to assess whether social status was associated with each monkey's identity in the absence of overt hierarchical behaviors. Of the 51 isolated hippocampal cells analyzed to date, 9 neurons (18%) responded to at least one of the social features of the videos. Of these responsive neurons, 22% were tuned to only social status, as determined by a two-sample *t*-test performed for each cell which compared firing rate during fixations on the dominant versus subordinate monkey. 33% of cells responded differently to expression versus neutral videos, determined by a two-sample *t*-test comparing firing rates during fixations on any monkey during the two types of videos. 33% of neurons were tuned to the identity of one of the video monkeys, which was determined by a one-way ANOVA with a main effect of identity on firing rate. The remaining 11% of neurons demonstrated multimodal tuning to at least two of the factors. All statistical tests were followed up with a FDR correction for multiple comparisons. Upcoming analyses will determine whether expression-responsive cells encode facial expressions specifically or broader identity- or status-related information in neutral videos. Additionally, population dynamics will assess the evolution of social hierarchy representations and differences in temporal trajectories in populations of hippocampal neurons. This work may uncover neural mechanisms underlying how social status is encoded in the hippocampus, and the relative contribution of the amygdala and hippocampus to the overall social circuit of the primate brain.

Disclosures: M.A. Krause: None. **M.H. Lynch:** None. **S. Lee:** None. **M.T. Kabir:** None. **K.M. Gothard:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Program #/Poster #: PSTR155.06/KK20

Topic: I.06. Social Cognition

Support: R01MH121009

Title: Primate Hippocampal Subregions Exhibit Distinct Saccade-Related Power Transients During Viewing of Social Interactions

Authors: *M. T. KABIR[1], M. A. KRAUSE[2], S. LEE[3], Z. NADASDY[4], K. M. GOTHARD[5]; [1]Univ. of Arizona, Chandler, AZ; [2]Univ. of Arizona, Tucson, AZ; [3]Neurosurg., Harvard Med. Sch. / Massachusetts Gen. Hosp., Boston, MA; [4]Univ. of Texas at Austin, Austin, TX; [5]Physiol., Univ. Arizona, Col. Med., Tucson, AZ

Abstract: In hierarchical social groups, individuals often use information about their own and others' social status to guide behavior. Rhesus macaques are well suited for studying status-related learning, because they organize into linear social hierarchies. Our current work demonstrates that macaque third-party observers of dominant-subordinate pairwise interactions can learn the status of individuals in a five-member virtual hierarchy. Observers perform socially meaningful joint attention (JA) saccades, which originate significantly more from the subordinate individuals. Here, we preliminarily examine LFP power transients across hippocampal subregions CA1, CA3, CA4, dentate gyrus (DG), and subicular complex (SC). We defined three analysis windows relative to saccade onset: pre-saccadic (-100-0 ms), peri-saccadic (0-50 ms), and post-saccadic (50-250 ms). Comparing subordinate JA saccades to subordinate-to-dominant (S-D) non-JA saccades revealed significant beta band differences in CA1 during the pre- and peri-saccadic windows and gamma band differences across all three windows (Welch's t-test, $p < .05$). In CA1 gamma, dominant and subordinate JA saccades also differed during the peri-saccadic window. Dominant JA versus dominant-to-subordinate (D-S) non-JA comparisons showed post-saccadic gamma differences in CA3 and DG (Welch's t-test, $p < .05$). In SC, beta-band comparisons showed a post-saccadic difference for dominant JA versus D-S non-JA saccades, while gamma-band comparisons showed a peri-saccadic difference for subordinate JA versus S-D non-JA saccades (Welch's t-test, $p < .05$). Additional analyses showed CA3 exhibited a significantly higher post-saccadic beta band power peak for dominant JA saccades compared to all non-JA saccades (Monte Carlo permutation test, $p < .05$). We also found status-related differences in beta band power during JA saccades in CA1, CA4, and SC. In CA1, there was greater power for the subordinate JA compared to the dominant JA saccades both pre- and post-saccade (Kruskal-Wallis, $p < .05$). In CA4, we found two post-saccadic peaks of increased subordinate JA saccade power relative to the dominant JA (Kruskal-Wallis, $p < .05$). Lastly, SC

showed a higher subordinate JA power peak post-saccade, although this may be fixation-related (Kruskal-Wallis, $p < .05$). Together, this data indicates that macaque hippocampal subregions exhibit unique power transients correlated to gaze patterns during observations of social scenes. This suggests that an ideal observer of the hippocampal beta band modulation of LFP at the time of saccade can assert the social status of the monkey being watched by the individual in the experiment.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Topic: I.06. Social Cognition

Support: R01-MH-75702
OD-011107
F32-MH-087067

Title: Anterior cingulate cortex lesions impair the translation of social information into action and reduce social engagement.

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Abstract: The anterior cingulate cortex (ACC) is hypothesized to be critical for many socially motivated behaviors. To test this hypothesis, we bilaterally inactivated the ACC in nonhuman primates via ibonate (N=7) and compared their behavior to procedure matched neurologically intact cage mates (N=7) across a series of tasks to evaluate social processing. Subjects' social interactions were monitored in their home cages with their familiar partners and in large enclosures with novel animals. With familiar partners, there were no significant differences in the initiation of close social interactions. But with novel partners, the lesioned animals spent less time in proximity to those animals and initiated fewer close social interactions. These findings suggest that ACC lesions selectively disrupt social engagement in unfamiliar social conditions, rather than producing a global social deficits. We next examined whether reduction in social engagement could be explained by decreased motor activity. Motor activity was monitored in their home cages for 20 days via activity trackers. Lesioned animals had 24 hour activity profiles similar to those of the controls, but movement intensity and frequency was significantly reduced. In the context of evaluation with novel social partners, there were no significant group differences in activity suggesting that ACC lesioned animals retained their ability to generate

motivated actions in appropriate novel social contexts. Moreover, the reduced social engagement observed in novel social settings cannot be fully explained by a general inability to generate movement. To understand the source of variation in overt social behavior, animals were tested on an eye-tracking task in which they chose to view either social or nonsocial videos by fixating on a neutral stimulus (either a blue or yellow square). There were no significant group differences in the attention to social and nonsocial stimuli, indexed by viewing time and saccades on the stimuli, suggesting intact social attention. Lesioned animals completed significantly fewer trials during longer experimental sessions and evidenced longer durations to start each trial via fixation and longer decision times during the choice period, suggesting impairment in initiating or selecting task-relevant actions. These findings suggest that ACC may link social information to action selection. ACC lesions did not modulate familiar social interactions, general motor capacity, or visual attention to social stimuli. Instead, the lesions appeared to impair the translation of social information into appropriate motivated actions, particularly in unfamiliar or demanding social contexts.

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Poster

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Topic: I.06. Social Cognition

Support: KAKENHI JP 25K10618

Title: Altruistic behavior in macaques depends on the basolateral amygdala, as revealed by transcranial focused ultrasound stimulation

Authors: *K. ENOMOTO[1], R. BRETAS[1], K. WATANABE[2], M. HARUNO[1];
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Abstract: Many primates live in groups and form hierarchical societies. To avoid risks and conflicts while efficiently acquiring resources, individuals need to make appropriate decisions that take into account their own and others' social rank. Because behavioral adjustments based on social relationships are widely observed not only in humans but also in apes and monkeys, the neural mechanisms underlying rank-dependent decision-making and behavioral selection are likely shared across most primates. To elucidate this neural basis, we examined the social behavior of macaque monkeys using reward and aversive stimuli. First, we estimated the dominance hierarchy among three female Japanese macaques by automatically analyzing video footage of a food-grabbing competition between each pair of the three monkeys. Next, we trained socially subordinate monkeys to learn a choice task while facing a dominant monkey

across a transparent display and touch panel. The monkeys were required to select one of two options, each corresponding to a distinct combination of the amount of juice reward and the intensity of an aversive stimulus (air puff to the face) given to themselves or their opponent, in response to visual stimuli presented on the display. When both a reward and an aversive stimulus were delivered to themselves, the monkeys appropriately avoided risk and selected the higher-value option with a high probability (approximately 80%). Notably, when an aversive stimulus was delivered to a socially dominant partner, subordinate monkeys frequently selected the prosocial option, which resulted in less aversive stimulation for the partner (more than 50%). These prosocial choices were made more quickly than selfish choices and were observed even when they resulted in a reduction in their own reward (altruistic behavior). Subsequently, we used low-power transcranial focused ultrasound stimulation to modulate neural activity in the bilateral basolateral amygdala (BLA) estimated via MRI in awake, non-invasively head-restrained monkeys (stimulation frequency: 500 kHz; mean peak pulse intensity (I_{sppa}) in free field: 80 W/cm²; duty cycle: 30%; 60 seconds per hemisphere). Analysis of performance on the social choice task following stimulation revealed a decrease in the frequency of altruistic behavior. These findings suggest that macaques are capable of altruistic behavior, which may represent an evolutionary precursor to cooperative behavior in humans, and that the BLA plays an essential role as the neural basis underlying such prosocial behavior.

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Poster

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Topic: I.06. Social Cognition

Support: National Eye Institute Intramural Research Program at the National Institutes of Health (ZIA EY000511)

Title: Neuronal processing of facial expressions in the primate superior colliculus

Authors: *G. YU[1,2], L. N. KATZ[4], R. J. KRAUZLIS[3];
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Abstract: Rapid evaluation of emotionally salient facial expressions is important for primate social behavior and has long been proposed to involve a subcortical visual pathway linking the superior colliculus (SC), pulvinar and amygdala. Despite the prominence of this hypothesis, single-neuron evidence for facial-expression processing in the primate SC has been lacking. We recorded neuronal activity from visually responsive SC neurons in two macaques while presenting images of facial expressions, including images previously shown to evoke expression-selective activity in the amygdala. We found that facial-expression information was present in

the SC and was organized across time and visual-field location. At the single-neuron level, expression-related modulation emerged in two phases: an early threat-related component around 60 ms after image onset and a later fear-related component around 150 ms. These two components were carried by largely distinct sets of neurons. At the population level, linear decoders confirmed that threat-related information was strongest early, whereas fear-related information became stronger later, and the corresponding decoding axes were nearly orthogonal. Expression signals also differed across the visual field, with parafoveal neuronal activity carrying more sustained threat-related information and foveal neuronal activity carrying earlier fear-related information. These findings provide, to our knowledge, the first single-neuron evidence that facial-expression information is present in the primate SC. By demonstrating early and temporally structured expression-related signals within the SC, our results fill a critical missing link in the proposed subcortical pathway for rapid evaluation of emotionally salient faces and refine models of how subcortical circuits support fast social perception.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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SFARI 875855
Wu Tsai Institute at Yale University
T32 MH014276
P30 EY026878

Title: Effort Costs and Social Information Shape Cooperative Decisions in Marmosets

Authors: *W. SHI[1,2,3,4,5], M. P. JADI[2,4,5], A. S. NANDY[2,5,3,6], S. W. CHANG[3,2,5,6];
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Abstract: A central challenge in neuroscience is to understand how the brain guides complex social behaviors such as cooperation in naturalistic settings. While evidence accumulation is a well-established framework for simple decisions, it remains unclear whether similar principles govern real-world social interactions that unfold continuously and require active monitoring of others. Our research addresses this question by integrating naturalistic behavioral paradigms, quantitative analysis, and wireless neural recordings in freely moving marmosets (*Callithrix jacchus*). Marmosets provide a uniquely powerful primate model for this work due to their rich

repertoire of prosocial behaviors, high social tolerance, and compatibility with high-density neural recordings during unconstrained interaction. Using an automated cooperative pulling task, we decomposed continuous social behavior into self-paced cooperation episodes and identified a strategy in which animals selectively gather information about their partner during moments of social gaze. Behavioral analyses revealed that cooperative decisions depend on the gradual accumulation of socially relevant information, linking active social monitoring to coordinated action. Recordings from the dorsomedial prefrontal cortex (dmPFC) uncovered neural activity patterns consistent with this process: neurons exhibited gradual changes in activity prior to action that reflected the strength of social information and were shaped by recent cooperative outcomes. Both single-neuron signals and population-level activity patterns were reliably weakened on failed cooperative trials, directly linking dmPFC dynamics to cooperative success. To test whether these decision processes generalize beyond uncertainty about partner actions, we further examined cooperation under systematically manipulated effort costs. By increasing the physical effort required for one partner to act, we found that marmosets maintain cooperative success despite rising personal costs by flexibly adjusting the timing and structure of their coordination strategies due to the increased physical effort. These results indicate that cooperative decisions integrate both social information and effort costs rather than relying on fixed rules or reflexive responses.

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Poster

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NIH R01 EY032555

Title: Motivational asymmetries generate role-differentiated cooperative dynamics and neural representations in marmosets

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Abstract: Cooperative behavior requires individuals to coordinate actions while continuously monitoring and adapting to social partners. Although cooperative interactions often exhibit stable leader-follower relationships, the mechanisms generating these asymmetric roles remain poorly understood. Here, we combined behavior modeling of non-stationary partner interactions, and

simulated learning in computational models to identify a mechanistic basis of cooperative role differentiation in marmosets. Male-female marmoset dyads performed a cooperative lever-pulling task where rewards were delivered only when both animals pulled within a restricted temporal window. Although males and females achieved similar cooperative performance, females consistently exhibited higher rates of social gaze towards their partners. To characterize how interactions evolved during learning, we developed a Continuous Time-weighted Dynamic Bayesian Network (CTwDBN) that infers time-varying directed dependencies among gaze and pull behaviors across two animals. Across all dyads, cooperative learning was accompanied by a transition from weak, distributed interactions to increasingly specialized interaction networks. Gaze exhibited stronger behavioral dependencies and there was a greater tendency to adopt follower-like strategies, in a sex-dependent manner. To test a potential mechanism for these asymmetries, we developed a multi-agent reinforcement learning (MARL) model where agents, assisted by recurrent neural networks (RNN), learned both pull and gaze policies for effective cooperation. Remarkably, differences in reward sensitivity between agents - akin to sex-dependent reward motivation in marmosets - reproduced the major features observed in the animals, including asymmetric social gaze and follower tendency. Analysis of model population activity revealed distinct low-dimensional neural trajectories associated with leader- and follower-like behavioral roles, generating testable predictions for the cooperating animals, specifically the dorsomedial prefrontal cortex (dmPFC), an area implicated in social decision making. Together, these findings identify reward motivation as a minimal, interpretable variable linking social attention, cooperative role allocation, and neural population dynamics, providing a mechanistic framework for understanding how stable cooperative roles emerge during social interactions.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

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Topic: I.06. Social Cognition

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Title: Cholinergic control of vocal-emotional behavior in the developing marmoset (Callithrix jacchus)

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Abstract: Cholinergic neurons play an essential role in refining cognitive-emotional components of executive function by interacting with the activity of prefrontal-hippocampal networks. A major population of these neurons originate from the basal forebrain nuclei that lie as a continuum extending from the medial septum (MS), vertical and horizontal diagonal bands of broca, through the nucleus basalis of Meynert. During development, acetylcholine modulates neuronal proliferation, differentiation, and synaptic plasticity but its contribution to the development and maturation of cognitive, social and emotional processing remains unknown. In this study we show how early life degeneration of medial septal cholinergic projections in infant marmosets alters the normal development of vocal and social behavior. We targeted the MS-basal forebrain nuclei by injecting ME20.4-IgG-saporin (saporin) in 14-day old neonatal marmosets (n=6). Saporin is an immunotoxin that selectively destroys the p75-positive cholinergic cells projecting to the hippocampus. Another group of infant marmosets received sham control surgery (n=6). We first examined changes in isolation induced vocal calls before and after the MS-saporin lesion. Vocal calls such as phee, twitter, trill and tsik were preserved after the lesion. The infant specific cry-call that triggers parental feedback was also intact but there was a notable discontinuation of cry-calls by week 5. In addition, their cries were short in duration, low in frequency and they made fewer long distance social contact calls (muti-syllabic phees). We also assessed their emotional responses to a fear inducing object (i.e., a fake owl) or neutral objects (e.g., toy car, color blocks) that were not fear inducing. We noted that at 4, 8 and 12 weeks of age, neither controls nor the MS-lesioned group expressed fear emotion either through defensive behavior or vocalizations. At 9 weeks of age, we examined their social behavior towards a parent and a stranger. Control infants spent more time in close proximity to the parent and were equally social towards a stranger. Those with MS-saporin lesions appeared ambivalent in their behavior showing a mixture of approach, avoidance, and disinterest towards the parent, even when the parent tried to touch their infant. Histological analysis revealed that the MS-saporin lesion successfully denervated cholinergic neurons in the MS, as well as MS-projecting areas including the hippocampus and prefrontal cortex. Together, these data suggest that the normal development of MS-basal forebrain cholinergic projections are integral to the postnatal development of vocal-emotional and social behavior.

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Poster

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Topic: I.06. Social Cognition

Support: NIH Intramural Program
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Title: 3d tracking of prototypical facial behaviors in the marmoset

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Abstract: As in humans, marmosets are social animals and they display prototypical facial behaviors that may reflect their well-being and social interactions with conspecifics or investigators. Presently, these behaviors are quantified on the basis of expert observation and/or manual annotation. While there has been progress in related behavioral questions such as automatic tracking of gaze between animals and face detection, the ability of quantifying and decomposing 3d facial behavior in marmosets in the same fashion of what has been achieved in rodents is still lacking. In mice, dynamic facial behaviors and derived representations have been linked back to neural and physiological processes providing deeper insights in brain-behavior relationships. Here we propose to fill out this gap using off-the shelf face tracking technology originally designed to humans. We demonstrate that the technology can be adapted to handle videos of marmoset monkeys in real time yielding 3d timeseries of key facial landmarks. We then show that these timeseries can be organized into prototypical behaviors that can differ between populations of animals that underwent surgical interventions versus controls.

Disclosures: L. Claudino: None. **E. Lim:** None. **J. Scott:** None. **K. Marche:** None. **J.A. Bourne:** None.

Poster

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Topic: I.06. Social Cognition

Support: NIH Intramural Program
Brain Initiative U01NS136338-01

Title: Real-time tracking of identities and trajectories of freely behaving marmoset monkeys

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Abstract: Recent work has demonstrated that off-the-shelf general object detection and classification models originally trained on human faces perform well in videos of marmoset monkeys [1]. However, so far, they have only been tested on a small number of animals and less frequently when more than two animals are present in a video frame. Here we use the method proposed in [1] who fine-tuned a general object detection model to track more marmosets individually and in pairs from videos. First, we recorded videos of each individual animal in our colony using a tablet. Next, we trained a classification model to recognize individual marmosets and combined it with the detection module and a tracker to extract 2-d coordinates of individual animals solo or in groups. The resulting system was then integrated to our operant conditioning

platform ("CalliCog" [2]) yielding real-time identification and position information of marmosets while they performed behavioral tasks. Our results reproduced the findings in [1] using faces alone and at a larger scale therefore validating their proposed method as a useful tool to automatically identify and track behavior of marmoset monkeys as they freely move.
[1] Yang et al., A real-time, multi-animal model for automatic face detection and identification of freely moving common marmosets based on YOLOv8 algorithms. eLife 2025.
[2] Scott et al., CalliCog is an open-source cognitive neuroscience toolkit for freely behaving nonhuman primates. Cell Reports Methods, 2025.

Disclosures: E. Lim: None. **L. Claudino:** None. **J. Scott:** None. **K. Marche:** None. **J.A. Bourne:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Topic: I.06. Social Cognition

Support: NIH Grant R01MH120638
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Title: Validation of a non-restrained oxytocin administration paradigm in macaques: Pharmacokinetic and behavioral outcomes

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Abstract: Preclinical literature investigating oxytocin (OT) as a potential therapeutic intervention for impaired social behavior remains inconsistent. Variability in administration methods, dosing strategies, and behavioral paradigms likely contributes to these mixed findings in nonhuman primate models (Bauman et al., 2018). OT is most commonly administered as an aerosol mist via nebulizer in macaques, which typically requires physical restraint. This introduces potential stress-related confounds limiting translational relevance. Here, we designed an apparatus to administer OT via nebulizer in non-restrained pigtail macaques (Macaca nemestrina), and characterized associated pharmacokinetic and behavioral outcomes.
The custom-designed apparatus includes a nebulizer and a drinking port where animals voluntarily consume liquid reinforcement while OT (5 IU/kg and 7.5 IU/kg) is administered for 5 minutes. Five adult male pigtail macaques were included in behavioral assessments, with 3 animals receiving OT (experimental animals) and 2 serving as familiar social partners (partners) during testing. Behavioral observations were conducted 30 minutes following OT administration, or nebulized saline, performed on separate days. Behavioral assessments included two independent social behavioral paradigms: 1/ each experimental animal (n=3) was observed

together with its partner freely interacting in an enclosure and their interactions were subsequently quantified, 2/ each experimental animal (n=3) was allowed to approach, using a wire tunnel, its partner confined in an adjoining home cage quadrant, and their spatial relationship to each other was later evaluated.
We found significantly increased plasma OT concentrations following administration using the apparatus, peaking at 15 minutes following the 5 IU/kg dose and remaining elevated at both 15 and 30 minutes following the 7.5 IU/kg dose. Behavioral outcomes also demonstrated behavioral effects of OT administration, either increasing or decreasing social interactions depending on the animals' baseline behavior. Here we show the apparatus produced biologically relevant OT exposure associated with changes in social behavior, demonstrating the feasibility of non-restrained, minimally invasive, nebulized OT administration in macaques.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Topic: H.03. Motivation

Support: NIH Grant R01MH133456
KKI P50HD105328
JHU U54HD079123
KKI Goldstein Award
JHU Undergraduate Research Award
JHU Discovery Award

Title: Adversity Severity Gates Inhibitory Amygdala Circuit Engagement During Early Social Development in Rats

Authors: *C. LIM[1], I. MCKIE[1], A. SU[1], M. OPENDAK[2];
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Abstract: Early-life adversity (ELA) is a major transdiagnostic risk factor for psychiatric illness, yet its behavioral consequences are heterogeneous. Whether adversity severity scales linearly or instead crosses thresholds that reorganize developing limbic circuits remains unresolved. Although limited bedding paradigms in rats are widely used to model caregiving-related adversity, severity is typically treated as procedural rather than mechanistic. We calibrated adversity intensity by directly comparing canonical scarcity (100 cc bedding), moderate restriction (500 cc), and normative rearing (2000 cc) from postnatal day 8-12. Maternal caregiving trajectories were modeled using day-resolved generalized estimating equations, and pup social approach at P13 was analyzed with right-censored Cox survival models incorporating litter-level maternal stepping. c-Fos density was quantified in basolateral amygdala (BLA),

dorsal and ventral intercalated cell clusters (dITC, vITC), and lateral habenula (LHb). Scarcity did not operate as a graded continuum. Canonical scarcity drove progressive escalation of maternal stepping, robust delays in social approach, and stratified latency distributions, whereas moderate restriction produced intermediate caregiving disruption without reproducing the dITC-behavior coupling observed under canonical scarcity. Stepping emerged as the dominant environmental predictor of approach timing. Critically, dITC activity exhibited severity-gated coupling: higher dITC c-Fos predicted earlier approach selectively under canonical scarcity. Nested survival models identified dITC as the strongest incremental predictor of approach beyond caregiving exposure and other circuit nodes. Adversity severity therefore determines when inhibitory amygdala microcircuits become behaviorally engaged. By identifying a threshold-dependent circuit-behavior transition within developing salience circuitry, this work provides a mechanistic framework for understanding stratified vulnerability following ELA.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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KKI Goldstein Award
JHU U54HD079123
JHU Neuroscience Department Honors Thesis Award
JHU Discovery Award

Title: Postpartum adversity in rats creates a hypervigilant maternal state through selective salience-circuit recruitment

Authors: *I. MCKIE[1], M. SONG[1], A. SU[1], M. YAMAMOTO[1], P. BENDALE[1], K. FOGUS[2,1], M. OPENDAK[3];
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Abstract: Maternal caregiving is a central regulator of infant stress physiology and socioemotional development, yet surprisingly little is known about how early-life adversity reshapes the maternal organism itself. Here, we asked how postpartum resource scarcity alters maternal caregiving and the neural circuits engaged during the dam's social behavior outside the nest. Using a limited bedding (LB) manipulation during PN8-12, a window that reliably induces

fragmented caregiving, we found that dams remained highly present in the nest but exhibited degraded caregiving quality, including reduced efficient pup transport and increased rough handling. During a mild social challenge with an unfamiliar adult female, LB dams showed intact sociability but heightened locomotor arousal in a social context, accompanied by increased Fos activation in basolateral amygdala (BLA), paraventricular thalamus (PVT), and ventral hippocampus (vHPC). Brain-behavior correlations dissociated these functions: BLA Fos predicted arousal, vHPC Fos predicted exploratory strategies, and lateral habenula (LHb) Fos negatively predicted sociability bias. Network analyses revealed largely preserved global topology but selective reweighting toward lateral habenula (LHb)-centered organization, with LHb emerging as the only region showing increased node strength under LB. Together, these findings identify a hypervigilant maternal phenotype in conditions of resource scarcity, marked by degraded tactile caregiving, salience-biased neural recruitment, and LHb-centered network reorganization. This maternal state likely alters the early-life environment in ways that contribute to the intergenerational transmission of adversity.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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NIH BRAIN Initiative 3R00MH124434
BBRF NARSAD
Goldstein Innovation Award

Title: Impaired social behavior following early life adversity coincides with alterations in blood metabolome and genetic profile of Basolateral Amygdala

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Abstract: Early life adversity (ELA) is a major risk factor for neuropsychiatric disorders such as anxiety and depression. Previous work using the scarcity adversity via limited bedding (SAM-LB) mode of ELA suggests that the long-term behavior consequences of ELA, such as impaired social behavior and threat processing, involve dysfunction of the Basolateral Amygdala (BLA) and changes in peripheral signaling. However, the specific mechanisms translating early experience to social impairments remain poorly understood. Here, we use a novel model of ELA

called the Deconstructed Adversity Model (DAM) in combination with liquid chromatography tandem mass spectrometer (LC-MS/MS) of peripheral blood sera, bulk mRNA-sequencing of the BLA to identify the underlying mechanisms driving ELA-induced infant/adolescent social behavior disruption. We found that levels of analytes linked with bile acid (BA) synthesis are altered following social and non-social adversity. To explore the link between BA metabolism, social behavior, and ELA, we supplemented rat pups with the primary BAs cholic acid (CA) and chenodeoxycholic acid (CDCA) during SAM-LB before assessing social behavior at infancy (P13-P15) and adolescence (P45-P50). Our findings suggest that BA supplementation mitigates social deficits associated with ELA, highlighting BA metabolism as a novel therapeutic target.

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Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Program #/Poster #: PSTR155.19/KK33

Topic: H.03. Motivation

Title: Early-life adversity prematurely enhances social exploratory behavior and BLA engagement in juvenile rats

Authors: *S. E. SILVERSTEIN[1], I. NIKITAH[2], E. TESONE[4], I. MCKIE[5], K. FOGUS[6], C. LIM[5], M. OPENDAK[3];
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Abstract: Early-life adversity is a robust environmental risk factor for enduring social dysfunction, yet the developmental mechanisms by which caregiving experience reshapes social learning circuits remain poorly understood. The basolateral amygdala (BLA) assigns motivational value to social cues and undergoes prolonged maturation across development, suggesting that recruitment of the BLA into social circuitry emerges gradually over time and may be sensitive to early caregiving experience. Here, we modeled early life stress using the Scarcity-Adversity Limited Bedding (LB) model in infant rat pups (PN8-12) as well as developed a juvenile-adapted Social Conditioned Place Preference (SCPP) paradigm to examine the developmental recruitment of the BLA during social learning in juvenile and adolescent rats. We hypothesize that early caregiving adversity accelerates the developmental timing and structure of BLA ensemble recruitment during social learning. Animals underwent SCPP testing at juvenile (PN26) and adolescent (PN36) ages following normal or LB rearing. Behavioral measures included social-context exploration and locomotor activity. Neural recruitment was assessed using a Fos-TRAP/c-Fos immediate early gene expression and activity-dependent ensemble tagging approach at PN26 and PN36. Preliminary findings indicate robust BLA recruitment during social-context exploration in adolescents, whereas juveniles exhibit

comparatively sparse activation under normal rearing conditions. However, early caregiving adversity shifted juvenile behavioral responses toward an adolescent-like phenotype and was associated with increased recruitment of BLA neurons during social-context exploration. Ongoing studies are using longitudinal single-cell calcium imaging to determine how developmental stage and caregiving history influence ensemble organization and neural-behavioral coupling within the BLA. Together, these findings suggest that recruitment of the BLA into social learning circuitry emerges across development and may be accelerated by early caregiving adversity. These results identify developmental timing of amygdala engagement as a potential mechanism linking early experience to long-term alterations in social behavior.

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Poster

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Title: Disruption of social decision-making preferences via stress-induced affective dysregulation

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Abstract: Decision making in social contexts requires individuals to evaluate available options in relation to others and their potential social consequences. Disruptions in these processes are core features of neuropsychiatric disorders characterized by social dysfunctions, anxiety, and depression-like states. However, how adverse social experiences shape emotional states to modulate subsequent social decision-making remains unclear. Here, we examined the effects of social defeat on choice behavior in male mice using a two-choice social reward task, in which animals could choose either to deliver a reward to both themselves and a partner, or to obtain the reward only for themselves. Three-chamber sociability and sucrose preference assays demonstrated that our social defeat paradigm successfully induced robust social avoidance and anxiety-like phenotypes without producing general anhedonia. Based on baseline choice preferences, mice were classified as prosocial or selfish. Social defeat abolished these pre-

existing, stable choice patterns in both groups, indicating that adverse, stress-inducing experiences disrupt stable social decision-making preference. Concurrently, cFos analysis revealed significantly reduced neuronal activity in the nucleus accumbens. Together, these findings suggest that social defeat reshapes social decision-making by abolishing choice preferences and altering activity in brain regions involved in reward processing and emotional stability.

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Poster

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Topic: H.03. Motivation

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Title: Stress reshapes social motivation through altered anterior cingulate cortex dynamics

Authors: *R. L. FISHER-FOYE[1], T. DALY[3], R. DURAND-DE CUTTOLI[4], A. V. AUBRY[6], M. CAROLE[7], H.-Y. LIN[4], L. LI[8], H. OH[5], J. ALVAREZ[2], T. M. GYLES[9], S. J. RUSSO[10]; [2]Neurosci., [1]Icahn Sch. of Med. At Mount Sinai Grad. Training Program In Neurosci., New York, NY; [3]Icahn Sch. of Med. at Mount Sinai, Atlantic Beach, NY; [4]Neurosci., [5]Nash Family Dept. of Neurosci., Icahn Sch. of Med. at Mount Sinai, New York, NY; [6]Icahn Sch. of Med., New York, NY; [7]SUNY Downstate Hlth. Sci. Univ., New York, NY; [8]Dept. of Neurosci., [9]Friedman Brain Inst., Icahn Sch. of Med. At Mount Sinai, New York, NY; [10]Neurosci., Icahn school of medicine at mount sinai, New York, NY

Abstract: Diminished social interaction is a core feature of numerous psychiatric disorders, including major depressive disorder, yet the neurobiological mechanisms underlying altered prosocial behavior remain poorly defined. Using the chronic social defeat stress (CSDS) model, we investigated how stress reshapes the neural substrates of social motivation. Whole-brain c-Fos mapping combined with tissue clearing revealed stress-induced alterations in neural activity, with network analyses identifying the anterior cingulate cortex (ACC) as a key hub regulating social interaction and avoidance. We hypothesized that CSDS-induced changes in ACC neuronal dynamics impair social reinforcement and motivation.
To test this, we quantified social behavior using an operant social self-administration (SSA) paradigm, including progressive ratio testing, alongside the resident-intruder (RI) assay and free social interaction. We then measured ACC neuronal population activity associated with stress-induced social deficits using immunohistochemistry and in vivo Ca^{2+} imaging via fiber photometry during both RI and SSA tasks. Preliminary analyses indicate that CSDS alters ACC activity patterns during social engagement, consistent with disrupted encoding of social reward.

Behaviorally, CSDS-exposed male and female mice exhibit reduced social interaction in the RI assay and impaired SSA acquisition, indicating deficits in both social approach and social reward processing. Together, these findings identify ACC neuronal dynamics as a key mechanism underlying stress-induced social dysfunction and provide insight into the neural basis of transdiagnostic social deficits.

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Poster

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Title: Neural architecture of parenting circuit: from circuit dynamics to cell types

Authors: *M. RAHMAN[1], D. CIFTCI[1], M. TALAY[2], V. N. MURTHY[3], X. ZHUANG[4], C. G. DULAC[1];
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Abstract: Parenting is an essential social behavior that unfolds as semi-rigid sequences of actions, yet how brain circuits organize these sequences remains unclear. Here we show that the medial preoptic area (MPOA) of the hypothalamus comprises functionally modular neuronal ensembles that differentially track—and likely help orchestrate—distinct components of parenting. Using deep-brain in vivo calcium imaging in mothers, fathers, and virgin females engaged in pup-directed behavior, we identified temporally defined clusters of MPOA neurons whose activity aligned with specific behavioral elements. One module was selectively active during parenting motor actions, including pup grooming, retrieval, and investigation. A second module was recruited during pup contact and was also engaged during social interactions with adult male and female conspecifics, suggesting a shared “social contact” code. A third module was activated around parenting initiation. A fourth module exhibited sustained, state-like inhibition across parenting bouts, consistent with a neural representation of parental satiation. These modules were present across sex and parental state, but their segregation significantly differed between mothers, fathers, and virgins. To link function to molecular identity, we developed an approach named Molecular Identity with Dynamic Activity Signals (MIDAS),

which combines in vivo calcium imaging with ex vivo MERFISH-based spatial transcriptomics in the same tissue. Modules were enriched for distinct transcriptional clusters: the motor module in Gal/Calcr neurons, the pup/social contact module in Gal/Th neurons, the state-like module in Mc4r neurons, and the initiation module in Crh-enriched neurons. Together, these results reveal a modular, molecularly specified MPOA architecture coordinating parental behavior.

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Poster

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Program #/Poster #: PSTR155.23/KK37

Topic: H.03. Motivation

Title: Conditioned Taste Aversion in Parents and Response in Offspring

Authors: *C.-C. LEE[1], S. GOLDBERG[2], N. MIMOUNI[3], T. ARZUA[4], W. FOSTER[3], C. LIFF[4], B. J. MARLIN[5];
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Abstract: Conditioned taste aversion (CTA) allows animals to avoid palatable stimuli associated with visceral malaise, but whether such aversive learning shapes offspring responses remains unclear — a question with implications for the paternal inheritance of visceral and affective states. We used a lithium chloride (LiCl)-based CTA paradigm to examine intergenerational effects of paternal aversive taste learning. Male mice (F0) received saccharin paired with LiCl or PBS vehicle; LiCl-treated males developed robust aversion. High-speed video revealed that conditioned F0 males showed aversive orofacial responses resembling those of unconditioned mice exposed to bitter stimuli. F0 males were then mated with naïve females and removed before birth to minimize postnatal social transmission. F1 offspring did not show overt avoidance of the sweet tastant; however, during consumption they exhibited aversion-like behaviors and altered inflammatory markers, suggesting a covert aversive-like phenotype rather than simple avoidance. To test whether paternal CTA alters offspring neural processing during consumption, we combined lickometer analysis with central amygdala (CeA) fiber photometry aligned to lick-bout events. Preliminary data suggest that LiCl-F1 offspring show reduced CeA activity at lick-bout initiation relative to PBS-F1 controls, consistent with altered internal-state or taste-salience processing during consummatory behavior. Together, these findings suggest that paternal taste-aversion learning can transmit altered consummatory and internal-state processing to offspring in the absence of overt behavioral avoidance.

Disclosures: C. Lee: None. **S. Goldberg:** None. **N. Mimouni:** None. **T. Arzua:** None. **W. Foster:** None. **C. Liff:** None. **B.J. Marlin:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.24/KK38

Topic: H.03. Motivation

Support: NYAS Leon Levy Neuroscience Scholarship (to T.A.)
HHMI Freeman Hrabowski (to B.J.M)
Columbia Research Initiatives in Science and Engineering (to B.J.M)

Title: Fear learning intergenerationally impacts the cerulean-olfactory circuitry

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Abstract: Stressful experiences can leave an impact across generations. A powerful example of this phenomenon is seen in the descendants of survivors of the Dutch Famine, who, despite having never experienced starvation, are at a higher risk of cardiovascular and metabolic diseases. Animal models have also linked environmental stressors to transgenerational phenotypes in the endocrine, metabolic, and sensory systems. Using olfactory fear conditioning in mice models, our lab has also shown that this type of learning increases the number of sensory neurons specific to that odor, not only in conditioned mice but, notably, also in their naïve offspring.Produced by a pair of brainstem nuclei called the locus coeruleus (LC), noradrenaline (NE) is part of our innate fight-or-flight response. Building on previous work that has shown the influence of NE on auditory and visual plasticity, we have set out to characterize the role that this neuromodulator has on olfactory plasticity using a combination of *in vivo* fiber photometry, optogenetics, and whole tissue clearing. Using viral tracers and whole-brain clearing, we first show that, on average, 20% of the LC projects to the olfactory bulb across sexes. Measuring fluctuations in both LC activity via GCaMP8f and noradrenaline levels via $GRAB_{NE2h}$, we first show that the cerulean-olfactory circuitry dynamically changes over the conditioning period, reflecting the mice's ability to use the odor as a predictor of the foot shock. Furthermore, upon re-exposure to the same odor, we see an increase in NE levels, as well as an increase in LC activity. Using the inhibitory opsin eOPN3, we also show that suppressing LC activity during conditioning abolishes the re-exposure response. Excitedly, we also see an increase in noradrenaline in the olfactory bulb of conditioned mice and in their naïve offspring when exposed to the same odor. We will also soon determine if inhibition of LC in one generation impacts the noradrenaline release in the next generation.To understand the neurobiological implications of these findings, we are currently examining changes in both corticotropin-releasing factor receptor in LC, as well as adrenergic receptors in the olfactory bulb. Preliminary sequencing data has pointed towards an increase in the α1A receptor expression in the olfactory system, and we hypothesize that along changes in corticotropin-releasing factor receptors in LC,

these receptor changes may mediate the intergenerational effects we observe. Together, this work will provide crucial insights into the processing and representation of stressful experiences in the brain, across generations.

Disclosures: T. Arzua: None. **C. Parkin:** None. **A.V. Lewis:** None. **P. Davis:** None. **C. Liff:** None. **B.J. Marlin:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

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Program #/Poster #: PSTR155.25/KK39

Topic: H.03. Motivation

Support: NIH F31HD114466
HHMI Freeman Habrowski

Title: Fatherhood on the Brain: Characterizing Whole-Brain Oxytocin Circuitry

Authors: *L. SMITH[1], D.-L. K. D. FERGUSON[2], B. R. MCRAE[3], B. J. MARLIN[2];
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Abstract: While we know that the transition to motherhood is marked by vast changes in physiology, males do not undergo pregnancy or parturition, thus removing any obvious physiological event to induce potential changes in behavior. Yet in biparental species, the onset of fatherhood, like motherhood, is accompanied by behavioral changes that support offspring care. The neuropeptide oxytocin is involved in the onset of maternal behavior as virgin female mice, who similarly have never undergone pregnancy-associated changes, injected with oxytocin learn maternal behaviors more quickly. It has also been shown that hypothalamic oxytocinergic neurons are important for paternal behavior, but there remains a gap in characterizing oxytocinergic projections across the entire paternal mouse brain. Therefore, this project aims to characterize the whole-brain oxytocinergic circuitry of fathers and naive males to determine whether this circuitry changes with the onset of fatherhood. To achieve this, we have fathers who have raised two litters, to set a defined paternal experience that matches the work done in our lab on mothers, and age-matched naïve virgin males. Both groups were screened for pup retrieval to assess parental caregiving, and we found that fathers, like mothers, retrieve while naïve males do not. Alongside these males, we have included two-litter mothers and naïve females to enable a comparison between maternal and paternal oxytocin circuity. We will use the iDISCO+ method for whole-brain clearing and light-sheet microscopy at 5x resolution to visualize oxytocinergic projections across the entire mouse brain. We will then use a consolidated deep-learning pipeline developed in our lab to automatically preprocess, segment, and quantify these projections following alignment to the Allen Brain Atlas. Prior work done in our lab on females at a lower resolution of 1.6x found no significant differences in oxytocinergic circuitry with maternal experience. By imaging fathers, mothers, and naïve males and females at a higher resolution, we

will be able to definitively characterize whole-brain oxytocinergic projections across sex and parental experience.

Disclosures: L. Smith: None. **D.K.D. Ferguson:** None. **B.R. McRae:** None. **B.J. Marlin:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.26/KK40

Topic: H.03. Motivation

Title: From Nose to Nurture: Investigating olfactory plasticity during the transition to motherhood

Authors: *N. MIMOUNI[1], V. ANDREU[1], E. J. LEE[2], S. L. FULTON[1], R. SEN[1], C. LIFF[1], D.-L. K. FERGUSON[1], A. V. LEWIS[1], C.-C. LEE[1], B. R. MCRAE[1], I. ABDUS-SABOOR[3], B. J. MARLIN[4];
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Abstract: Motherhood is accompanied by profound physiological and neurobiological changes, including adaptations in sensory systems that support infant care. While the olfactory system plays a critical role in guiding maternal behaviors such as pup retrieval and nesting, Yet the specific molecular changes occurring within the main olfactory epithelium (MOE) during the peripartum period and how olfactory processing is itself reshaped during the peripartum period remains poorly understood.
To address this, we combined behavioral, transcriptomic, and hormonal approaches. To characterize olfactory-guided maternal behaviors, we used an odor preference assay with pup urine as a chemosensory cue. To investigate the molecular changes associated with motherhood in the MOE, we performed bulk RNA sequencing on MOE tissue from virgin females in Diestrus and Proestrus, pregnant females at E18.5, and postpartum mothers at PPD5. To capture the hormonal landscape across reproductive states we have measured circulating estradiol, progesterone, and oxytocin levels by ELISA. Our results indicate that PPD5 mothers show a robust and selective preference for pup urine, whereas virgin females, late-pregnant females, and post-weaning mothers at PPD30 showed no such preference. This transient, postpartum-specific attraction was not generalized to other social or non-social odors, indicating that motherhood drives a precise tuning of the olfactory system toward pup-derived cues rather than a broad increase in olfactory sensitivity. Our bulk RNAseq analysis revealed stage-specific remodeling of the MOE across the reproductive cycle, most pronounced at PPD5. Furthermore, gene enrichment analysis identified significant upregulation of pathways involved in hormone modulation, synaptic transmission, and odor processing, consistent with coordinated molecular

reprogramming in preparation for motherhood.
Together, these findings reveal a previously unrecognized postpartum-specific remodeling of olfactory-guided behavior and establish the MOE as a highly adaptable sensory tissue whose molecular landscape is dynamically shaped by reproductive and maternal state. This plasticity likely enables the olfactory system to optimize the detection and processing of pup-related odors, thereby supporting maternal adjustment and behavior

Disclosures: N. Mimouni: None. **V. Andreu:** None. **E.J. Lee:** None. **S.L. Fulton:** None. **R. Sen:** None. **C. Liff:** None. **D.K. Ferguson:** None. **A.V. Lewis:** None. **C. Lee:** None. **B.R. McRae:** None. **B.J. Marlin:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

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Program #/Poster #: PSTR155.27/KK41

Topic: H.03. Motivation

Support: NIH 1S10OD023587-01
Leon Levy Scholarship

Title: Noradrenaline modulation of intergenerational stress-induced olfactory plasticity

Authors: *C. PARKIN[1], T. ARZUA[2], A. V. LEWIS[3], B. J. MARLIN[4];
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Abstract: The ability to detect, respond, and adapt to a threat is essential for our survival. This adaptive process depends on tightly coordinated activation of sensory and neuromodulatory circuits. Chronic stress and trauma, however, can drive lasting circuit reorganization that contributes to post-traumatic stress disorder, panic disorder, and generalized anxiety. Our hindered ability to address this issue stems, in part, from the lack of knowledge of how stressful experiences are encoded in the brain. We aim to address this gap by investigating how stress responses emerge from sensory experiences and how the resulting changes in the brain can be passed down through generations.
Taking advantage of the unique plasticity of the mouse olfactory system, we show that olfactory fear conditioning increases the number of sensory neurons responsive to the learned aversive odor in both conditioned mice and their naive offspring. However, changes in olfactory sensory neuron representation alone are unlikely able to fully explain odor avoidance behavior. Noradrenaline is a key neuromodulator released by the locus coeruleus (LC) during stressful events and known to influence sensory plasticity in both the auditory and visual systems. This project will dissect the influence noradrenaline signaling in intergenerational stress-induced olfactory plasticity.
Using a combination of fiber photometry, optogenetics, and tissue clearing, we first show that

the noradrenergic system is active in releasing noradrenaline in the olfactory bulb, which increases during olfactory fear conditioning. This heightened noradrenergic activity is still present 3 weeks after conditioning. Second, we show that selective optogenetic inhibition of LC activity during fear conditioning abolishes noradrenaline-mediated plasticity as well as changes sensory neuron representation. Excitingly, we also see an increase in noradrenaline in the naïve offspring of conditioned mice when exposed to their parents' conditioned odor. We are currently exploring whether their offspring show changes in the amount of sensory neurons.
In efforts to disentangle the relationship between increased odor-specific olfactory receptor representation and noradrenaline signaling in driving aversive behavior, we plan to artificially increase the population of olfactory sensory neurons expressing the receptor for an aversively conditioned odor. We will then determine whether this enhanced sensory representation in the main olfactory epithelium modifies noradrenergic activity and axonal targeting to downstream circuits.

Disclosures: C. Parkin: None. **T. Arzua:** None. **A.V. Lewis:** None. **B.J. Marlin:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.28/KK42

Topic: H.03. Motivation

Support: HHMI Freeman Hrabowski Scholars
NIH T32MH126036

Title: Neuromodulation of maternal behavior by β-endorphin

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Abstract: Maternal care is crucial for mammalian offspring survival, yet costly to the mother: she must redirect significant energy, time, and resources to her offspring. What, then, motivates a mother to invest in offspring care? The Brain Opioid Theory of Social Attachment (BOTSA), first proposed in the 1980s, argues that social attachments are the result of endogenous opioid signaling in the brain. In the case of a mother, the theory predicts that offspring interactions lead to endogenous opioid release. Indeed, pharmacological studies in rats have implicated the endogenous opioid peptide β-endorphin and the μ-opioid receptor (μOR), in particular, as key mediators of maternal behavior. However, the neural circuit and circuit dynamics underlying these behavioral effects remain unknown. To address this knowledge gap, we utilize the genetic, viral, and in vivo imaging techniques available in mice to investigate how the circuit from β-endorphin neurons in the ARC (ARC^{POMC}) to μOR neurons in the MPOA ($MPOA^{\mu OR}$) participates in maternal care. First, we characterize this ARC^{POMC}-$MPOA^{\mu OR}$ circuit and

investigate whether pregnancy and the postpartum period result in changes to this circuit. Next, we characterize the natural dynamics of β-endorphin release in the MPOA during pup interactions. Altogether, this work provides novel insights into how endogenous opioid signaling contributes to the mother-infant attachment.

Disclosures: C. Liff: None. **B.J. Marlin:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

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Program #/Poster #: PSTR155.29/KK43

Topic: H.03. Motivation

Support: Washington Universiry St Lou's school of Medicine start up
JHU Bloomberg endowment

Title: Mothers shape how their offspring investigate objects

Authors: *K. OGASAWARA[1,4], G. TAVONI[4], I. E. MONOSOV[1,4,5,2,3];
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Abstract: Humans and many animals show an early-life tendency to explore and investigate novel stimuli. However, it remains unclear how this behavior develops across the lifespan and whether and how mothers contribute to it. We developed a longitudinal object-investigation paradigm in which mouse families (one dam and two offspring) were repeatedly exposed to either a novel or a familiar object during childhood (PD1–PD28). During development, they were tested either with the dam present (mother-present group) or in the dam's temporary absent (mother-absent group), allowing us to examine intrinsic behavioral responses to perceptual novelty and maternal influences. Once they became adults, offspring were again retested to determine how early-life experiences and maternal presence shaped their novelty-investigation behavior. To study exploratory object behavior, we concentrated on the animals' object-directed approaches previously established to reflect object investigation: approaches with the tail relatively exposed to the object (tail-exposed) and approaches in which the tail was kept behind the body while the mice faced the object (tail-behind). Prior work has linked the tail-behind approach to rodent cautious investigation and risk assessment (Grant & Mackintosh, 1963; van der Poel, 1979; Kaesermann, 1986; Blanchard et al., 1991; Akiti et al., 2022). Our behavioral analyses show that in childhood, offspring approached novel objects relatively more cautiously than familiar objects. And this was observed even when analyzing the results for the mother-absent group suggesting that this behavior was not mother-dependent. Overall, maternal presence increased the proportion of tail-behind cautious approaches across all experimental conditions.

Following maturation into adulthood, the mother-present group continued to exhibit relatively similar behavioral patterns to those that they exhibited in childhood, remaining more cautious toward novel objects. In contrast, the mother-absent group did not show consistent behavioral patterns across childhood and adulthood. And since the dams frequently retrieved their pups during experimental sessions, we investigated the impact of pup retrieval on offspring object-related behavior. We found that less cautious offspring became more cautious with more retrievals, suggesting that retrievals influenced offspring's behavior well beyond the retrieval period itself. Together, these findings suggest that mothers play an active role in the long-term development of their offspring's exploratory behaviors across the lifespan.

Disclosures: K. Ogasawara: None. **G. Tavoni:** None. **I.E. Monosov:** None.

Poster

PSTR155: Behavioral and Circuit Mechanisms of Social Behavior II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR155.30/KK44

Topic: I.06. Social Cognition

Support: NIA Grant U19-AG051426
NIA Grant P01-AG020166

Title: APOE Ɛ4 Carriers but not Ɛ2 Carriers are More Vulnerable to Adult Cognitive Decline After Childhood Physical Abuse

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Abstract: Background:
Apolipoprotein (*APOE*) genotype is known to differentially impact susceptibility to developing Alzheimer's disease (AD). It is generally considered that *APOE* Ɛ4 is neurodegenerative and *APOE* Ɛ2 is neuroprotective. Interestingly, environmental factors can also modify AD risk or cognitive decline. Specifically, an individual's childhood is considered one of the most critical points of brain development. Indeed, negative early life experiences, such as childhood physical abuse, is known to produce lasting health consequences in adulthood. As such, we hypothesized that childhood physical abuse would have differential impacts on *APOE* Ɛ4 and Ɛ2 carriers on cognitive function measured in adulthood.
Methods:
Data were analyzed from 1,446 participants, aged 26-86 years old, in the MIDUS (Midlife in the United States) longitudinal aging study. *APOE* sequencing was performed on whole blood samples. A composite score of childhood physical abuse encompassed five items within the Childhood Trauma Questionnaire. The composite score from the brief test of adult cognition by telephone (BTACT) was standardized and used to examine changes to adult cognitive function.

The BTACT composite score encompassed both executive functioning and episodic memory. Age and gender were held as covariates. To examine the impact of *APOE* carrier status and childhood physical abuse, moderation analysis was performed using SPSS version 30.0 PROCESS version 5.0.
Results:
APOE Ɛ4 carrier status significantly moderated the relationship between childhood physical abuse and BTACT performance (b = -0.09, p = .012). Specifically, we find that *APOE* Ɛ4 carriers compared to non-carriers had a stronger decline in BTACT performance with childhood physical abuse scores (b = -0.12, p < .001), (b = -0.04, p = .04) respectively. Interestingly, *APOE* Ɛ2 carrier status did not significantly moderate this relationship (b = -0.01, p = .65).
Conclusion: Our data indicate that *APOE* Ɛ4 carriers that experience early life adversity are more vulnerable to later cognitive decline compared to non-carriers. Furthermore, we find that childhood physical abuse did not moderate cognitive decline in *APOE* Ɛ2 carriers. This highlights that *APOE* Ɛ4 carriers, but not *APOE* Ɛ2 carriers, could have increased susceptibility to developing cognitive impairment later in life following adverse early life experiences.

Disclosures: A.K. Johnson: None. **A.P. Auger:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.01/KK45

Topic: I.08. Learning and Memory

Title: Closed-loop stimulation causally modulates entorhinal-hippocampal ripples and recognition memory in humans

Authors: *E. BARATZ[1], A. BORO[3], E. N. ESKANDAR[4], N. J. KILLIAN[2];
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Abstract: The precise mechanisms underlying memory formation remain some of the most elusive and critical questions of modern research — an urgent problem underscored by the millions of patients worldwide suffering from severe memory impairment in conditions of brain injury and neurodegeneration. Robust evidence across animal models has identified patterns of high-frequency “sharp-wave ripple” oscillations in the hippocampus and entorhinal cortex that strongly correlate with successful memory retrieval. Experimentally prolonging ripple events during encoding enhanced spatial memory in rodents, suggesting that ripples causally contribute to novel memory formation. However, to our knowledge, no study has selectively manipulated hippocampal ripples in humans to evaluate their contributions to memory formation. Here, we created and trained a machine learning model to identify patterns of entorhinal and hippocampal stimulation that would strongly evoke or suppress hippocampal ripples in epilepsy patients

implanted with intracranial depth electrodes. Stimulation patterns that evoked the highest (Ripple+) and lowest (Ripple-) ripple band activity relative to baseline were selected from 120 unique stimulation patterns during model training. Selected patterns were then used to modulate ripple activity during novel image encoding as patients performed a visual recognition memory task with interleaved stimulated and non-stimulated image trials. Ripple+ induced higher entorhinal-hippocampal ripple rates than Ripple− (Wilcoxon signed-rank test, $p = 0.004$, $n = 32$ channels). Strikingly, Ripple+ stimulation significantly increased discrimination performance for stimulated novel images ($\Delta d' = +0.52$, paired t-test $p = 0.002$), while Ripple- patterns reduced discrimination performance relative to baseline. These results suggest that hippocampal ripples causally contribute to memory encoding in humans and elucidate a novel method of enhancing ripple activity for the potential treatment of memory impairment.

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Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

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Program #/Poster #: PSTR156.02/KK46

Topic: I.08. Learning and Memory

Support: R01MH128344
R01MH110594
R01MH116937

Title: Sleep-Driven Oscillations and Reward-Prediction-Error Tagging Enable Selective Forgetting in Spiking Neural Networks

Authors: *A. HATAMI[1], R. AALISHAH[1], I. E. MONOSOV[2];
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Abstract: Biological systems forget continually, discarding irrelevant details while retaining task-relevant features, and this balance shifts as goals change. How neural circuits achieve this selective forgetting remains poorly understood, and artificial neural networks (ANNs) lack a principled mechanism for it; when asked to erase a category, they suppress it at the output while leaving the information recoverable from internal representations. This also makes the mechanisms of forgetting in biology harder to conceptualize. Here we asked whether selective forgetting can emerge from a small set of biologically grounded mechanisms. We built a spiking neural network (SNN) trained with spike-timing-dependent plasticity (STDP), with a reward signal propagated backward to all layers. During an online wake phase, the network learned to classify all stimulus categories. Each class was assigned a salience level through the reward signal, and forgetting was driven during an offline sleep phase by slow oscillatory modulation of spiking thresholds, which destabilized weakly reinforced traces while replay consolidated

strongly reinforced ones. The learning rule combined an STDP eligibility trace, a signed reward term scaled by absolute reward-prediction error (RPE), and a layer-specific factor that strengthened reward modulation in deeper layers. We tested two predictions. First, reducing the RPE for target classes before sleep selectively weakened those classes; after sleep, targets showed lower classification accuracy and weaker firing, while other classes remained stable across increasing novelty, indicating that retained representations resisted sleep-dependent weakening. Second, we tested whether the network could forget only the level of representation that was irrelevant to the current task while preserving the relevant one. To test this, we used a custom stimulus set that dissociates global silhouette from internal texture. When the silhouette defined the label, shape representations were preserved and texture representations were weakened after sleep, so that test-time texture changes did not impair classification but silhouette changes did; reversing the task so that texture defined the label produced the opposite pattern. Low-RPE target classes and features that were irrelevant to the current task were weakened more than other representations. These findings indicate that flexible, relevance-dependent forgetting can emerge from synaptic plasticity, reward-modulated tagging, and sleep-like oscillatory dynamics, offering a path toward efficient, principled unlearning in artificial systems.

Disclosures: A. Hatami: None. **R. Aalishah:** None. **I.E. Monosov:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.03/KK47

Topic: I.08. Learning and Memory

Title: Modulating voluntary retrieval of autobiographical emotional memories by 5 Hz tACS in insomnia sleepers: A double-blind, sham-controlled study

Authors: *X. HAN[1], D. CHEN[1], X. ZUO[1], S. MU[1], M. LEE[1], Y. YANG[2], M. SHEN[3], X. HU[1]; [1]Dept. of Psychology, The Univ. of Hong Kong, Hong Kong, China; [2]Sch. of Psychology, Shenzhen Univ., Shenzhen, China; [3]Fac. of Med. Sci., Univ. Col. London, London, United Kingdom

Abstract: Insomnia is characterized by sleep disturbance and impaired regulation of negative affect, which may be linked to difficulties controlling emotional memories. Prior research has shown that theta-band activity indexes successful memory control. However, individuals with insomnia appear to exhibit deficits in this neural mechanism. It remains unknown whether theta-band transcranial alternating current stimulation (tACS) can improve voluntary control over emotional memories in individuals with insomnia. Here, we addressed this question by applying 5 Hz tACS during an autobiographical Think/No-Think (aTNT) paradigm: Participants repeatedly retrieved positive autobiographical memories and suppressed negative ones while receiving either active or sham stimulation. Questionnaire measures were collected at baseline

(Day 1) and at a one-week follow-up (Day 15), corresponding to one week after stimulation. Fifty-seven participants with self-reported elevated insomnia severity (Insomnia Severity Index ≥ 15) and depressive symptoms (Beck Depression Index ≥ 14) were recruited and randomly assigned to active 5-Hz tACS (F4; n = 28; 24 females; age = 22.7 ± 2.28 years) or sham stimulation (n = 29; 25 females; age = 22.7 ± 2.54 years). Our results found that active stimulation reduced self-reported vividness of negative autobiographical memories in the No-Think condition compared with sham ($p = .033$), and thinking difficulty increased over time within the active group ($p < .001$), although this change did not significantly differ from sham. Active stimulation also reduced the self-reported frequency of recalling these memories compared with sham ($p = .017$) and improved accuracy in the speeded affective judgment task ($p = .013$). Taken together, these preliminary results suggest that concurrent theta-frequency tACS during the aTNT task may influence subjective and affective components of emotional memory control. This points to the potential of combining aTNT training with tACS stimulation as a possible intervention for insomnia.

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Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.04/KK48

Topic: I.08. Learning and Memory

Support: MOST

Title: Memory reactivation during slow oscillation up-state was associated with reduced sigma-band entropy

Authors: *Z. MU[1], S. MU[2], Z. YAO[3], T. XIA[5], J. LIU[6], D. CHEN[2], X. HU[4];
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Abstract: Targeted Memory Reactivation (TMR) during non-REM sleep strengthens memories, with its efficacy critically depending on precise timing relative to slow oscillation phases. Based on the systems consolidation account, slow oscillation (SO) up states are associated with high neural plasticity and can be an optimal time window for TMR. However, the empirical evidence is rather mixed, with the neural mechanism remains unclear. We hypothesized that successful memory reactivation, initiated during the SO up-state, would elicit a more synchronized neural response, reflected as lower signal complexity. To test this, we pooled two overnight EEG

datasets (Xia et al., 2024, $N = 37$; Chen et al., 2024, $N = 35$; total $N = 72$, 12,731 trials) employing similar TMR paradigms. We identified the instantaneous SO phase at cue onset during N3 sleep and quantified the complexity of the subsequent time-frequency-decomposed sigma-band response (12-16 Hz) using trial-level fuzzy entropy. Linear mixed-effects modelling revealed a robust phase-dependent modulation of sigma-band entropy (FDR-corrected $p_cos = .011$; $p_sin = .190$). Specifically, entropy was significantly lower when cues were presented during the SO up-state compared to the down-state ($t(71) = -2.50$, $p = .015$). The phase of minimal entropy occurred near the SO peak (~333°), a window known to be critical for memory consolidation. These results provide a mechanistic explanation for the time-dependency of TMR cueing: up-state cueing organizes sigma power into a more synchronous, lower-entropy pattern than the down state . This reduced complexity may reflect more regular neural dynamics underlying memory reactivation, providing a potential neural signature for why precise cue timing is crucial for effective sleep-based memory consolidation.

Disclosures: Z. Mu: None. **S. Mu:** None. **Z. Yao:** None. **T. Xia:** None. **J. Liu:** None. **D. Chen:** None. **X. Hu:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.05/KK49

Topic: I.08. Learning and Memory

Title: Targeted Memory Reactivation Locally Strengthens Event Content while Globally Reshaping Temporal Structure

Authors: *Y. ZHANG[1], X. HU[2];
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Abstract: Episodic memory preserves not only what we remember but also when it happened, allowing mental time travel to retrieve our past experiences. While post-encoding sleep contributes to memory consolidation and transformation, it remains unclear how sleep selectively transforms naturalistic event memories over time according to emotional valence and event boundaries. Here, participants encoded neutral and aversive image sequences structured with event boundaries. During post-encoding slow-wave sleep (SWS), we used auditory cueing to reactivate post-boundary subevents and delineate how exogenous reactivation reshaped memory for event content and temporal structure over time. Behaviorally, we found that reactivation facilitated access to cued content memories, but exerted opposing effects on temporal memory: it impaired temporal order memory immediately after sleep but better preserved it over the long term. Physiologically, cue-elicited theta activity showed dissociable relationships with subsequent memory. Theta power and theta-mediated cue-specific representations predicted

better recognition of cued neutral post-boundary items. In contrast, stronger theta activity was associated with poorer temporal memory: theta power was most predictive for neutral events, while cue-specific representations were most predictive for aversive events. These findings suggest that targeted memory reactivation can locally strengthen cued subevent content while globally reshaping the temporal structure of event memories.

Disclosures: Y. Zhang: None. **X. Hu:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.06/KK50

Topic: I.08. Learning and Memory

Support: Brain Science and Brain-like Intelligence Technology-National Science and Technology Major Project 2021ZD0203500
NSFC 32400853
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NSFC 32130043
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Title: Distributed cortical learning through LEC-mediated γ-synchrony

Authors: *D. YUN[1], F. HE[3], J. LU[4], Y. LI[2], H. XIE[5], J.-S. GUAN[1];
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Abstract: Abstract: Despite the well-established theoretical and experimental foundations of dopamine-driven reinforcement learning, how the reward prediction error (RPE) teaching signal modifies specific cortical memory networks remains unclear. Neural oscillations are crucial for the temporal binding of activities across distributed cell ensembles. Here, we identify that lateral entorhinal cortex layer 5 (LEC^5) mediated intercortical γ-synchrony is a neural correlate of the RPE signal derived from dopamine neurons in the ventral tegmental area (VTA^{DA}). The VTA^{DA}-LEC^5 circuit-based intercortical γ-synchrony facilitates both learning and memory retention, and at the single-cell level, entrains the activity of cortical latent Engrams. Human brain recordings also demonstrate a universal role of γ-synchrony in the processing of prediction errors. These findings suggest that LEC^5-mediated intercortical γ-synchrony serves as the nexus connecting reinforcement learning with the formation of cortical memory networks.

Disclosures: D. Yun: None. **F. He:** None. **J. Lu:** None. **Y. Li:** None. **H. Xie:** None. **J. Guan:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.07/KK51

Topic: I.08. Learning and Memory

Support: R01NS127954 (Liu)
R61DC022830 (Liu)

Title: The Relationship Between Hippocampal Spiking Activity, Ripples, and Peripheral Biomarkers of Autonomic Tone During a Naturalistic Learning Task in Humans

Authors: *J. ZHU[1], N. PALEOLOGOS[2], L. M. VETERE[3], F. VASHEGHANI FARAHANI[3], S. HENIN[4], G. BUZSAKI[5], A. A. LIU[6];
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Abstract: Hippocampal ripples are transient, high-frequency oscillations that are known to play a critical role in memory consolidation and recall during offline states such as non-REM sleep and quiet wakefulness. Human and rodent studies have shown that hippocampal ripples coordinate reactivation of recent experiences during rest and retrieval periods. However, the relationship between hippocampal spiking activity, ripples, and peripheral biosignals (such as pupil size and heart rate variability) has not been previously assessed in a naturalistic learning paradigm. For this study, we enrolled surgical epilepsy patients with hippocampal depth electrodes to participate in a naturalistic task consisting of periods of movie watching (30s - 5min per movie), eyes-closed rest (20s between each movie), free recall, and cued recall. Pupil size measurements were simultaneously collected via the Tobii eye-tracking system. Electrophysiological data used for ripple detection and single-unit recordings were collected from microwire contacts in the CA1 subregion, selected using co-registered pre-operative MRI and post-operative CT scans. Ripple events were detected after filtering for environmental and pathological noise and defined as 20ms-250ms events within the ripple frequency band (80-120 Hz) with a minimum of 3 cycles. We observed the highest ripple rates during the cued recall portion of the task, followed by free recall, across all patients. Ripple rates during movie watching and eyes-closed rest were significantly lower than either recall period. Ripple rates during movie-watching, whereby pupillary measurements were most reliable, were negatively correlated with acute changes in pupil diameter; that is, ripples tended to occur mostly during constricted pupillary states, associated with elevated parasympathetic activity. Putative hippocampal single unit firing rates demonstrated movie-specific tuning, suggesting that population activity in the hippocampus encodes content-specific information during long-term memory formation. After curation, hippocampal population activity was used to decode movie identity during recall with an accuracy substantially above chance. Preliminary results suggest a

precise interplay between ripple activity, autonomic tone, and possible reactivation of movie content by hippocampal units during recall. This framework can reveal more about the role of ripples in long-term memory consolidation and retrieval.

Disclosures: J. Zhu: None. **N. Paleologos:** None. **L.M. Vetere:** None. **F. Vasheghani Farahani:** None. **S. Henin:** None. **G. Buzsaki:** None. **A.A. Liu:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.08/KK52

Topic: I.08. Learning and Memory

Support: BIAL Foundation under Grant No 218/24.
ERC Advanced Grant under Grant No 101200478

Title: The effects of prolonged 40 Hz audio-visual stimulation on memory performance, EEG and structural MRI

Authors: *Y. LI[1], J. MCDIARMID[1], K. DASTAFSHAN[1], E. DUCKWORTH[1], K. CAPSTICK[1], E. SNELLING[1], J. GARDNER[1], E. MARCANTONI[1], V. NEUMAIER[1,2], D. SENGUPTA[1], B. KINNIE[1], I. AMANI[1], D. WANG[3], L. HAINKE[1,2], C. SAMPAIO-BAPTISTA[1], S. HANSLMAYR[1];
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Abstract: Multisensory rhythmic stimulation at gamma frequency (40 Hz) has been proposed as a tool to probe spike-timing-dependent plasticity mechanisms (Wang et al., 2023) and as a low-cost therapeutic approach for neurodegenerative disorders (Murdock et al., 2024). However, the effects of prolonged multisensory stimulation on brain function and behaviour in healthy humans remain poorly understood. In particular, the role of phase offset (i.e., temporal lag) between sensory modalities (visual and auditory) is underexplored.
In this study, we tested whether four days of multisensory 40 Hz stimulation modulates episodic memory performance, neural synchrony, and brain structure. Healthy participants (N = 10) completed an episodic memory task in which arbitrary sound-movie pairs were encoded while EEG and fMRI were recorded. T1-weighted MRI and diffusion MRI were also acquired. Participants then underwent a "treatment" consisting of viewing a documentary (BBC Planet Earth) in which visual luminance and auditory amplitude were modulated at 40 Hz. This stimulation was administered for 1 hour per day over four consecutive days. Following the intervention, all behavioural, electrophysiological, and imaging measures were repeated.
To test the impact of multisensory timing, we manipulated the phase offset between modalities. In the 0° phase lag condition, visual and auditory inputs were presented synchronously, whereas

in the 90° phase lag condition, the visual signal preceded the auditory signal by approximately 6 ms.
Our preliminary results show that episodic memory performance significantly improved from pre- to post-intervention, with no modulation by phase offset. In parallel, EEG analyses revealed a significant increase in inter-trial coherence in the 40 Hz range, most prominently over fronto-central electrodes, indicating enhanced neural synchronisation. No significant changes were observed in Diffusion Tensor Imaging (DTI)-derived metrics, such as Fractional Anisotropy or Mean Diffusivity, after correction for multiple comparisons.
Together, these findings suggest that prolonged multisensory 40 Hz stimulation may enhance memory performance and entrain neural activity in the gamma band, potentially reflecting plasticity-related mechanisms. However, the absence of phase-offset effects and the lack of a no-stimulation control condition limit causal interpretation, as improvements may reflect practice effects rather than stimulation-specific effects.

Disclosures: Y. Li: None. **J. McDiarmid:** None. **K. Dastafshan:** None. **E. Duckworth:** None. **K. Capstick:** None. **E. Snelling:** None. **J. Gardner:** None. **E. Marcantoni:** None. **V. Neumaier:** None. **D. Sengupta:** None. **B. Kinnie:** None. **I. Amani:** None. **D. Wang:** None. **L. Hainke:** None. **C. Sampaio-Baptista:** None. **S. Hanslmayr:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.09/KK53

Topic: I.08. Learning and Memory

Support: National Research Foundation of Korea (NRF) grants funded by the Korean government (MSIT) (Nos. NRF-2021M3E5D2A01019538)
Alchemist Brain to X (B2X) Project funded by the Ministry of Trade, Industry and Energy (No. 20012355, NTIS: 1415181023)

Title: Real-time theta-based alarm improves associative memory by reorganizing hippocampal theta phase consistency

Authors: *S. LEE[1], E. LEE[2], C. CHUNG[3];
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Abstract: Episodic memory requires the hippocampus to bind events within a spatiotemporal context. Theta theories propose that this binding depends not only on oscillatory power, but on when encoding events, inputs, spikes, and plasticity windows are aligned within the theta cycle. Human hippocampal theta is heterogeneous across slow and fast components and the longitudinal axis. We tested whether a real-time theta-based auditory alarm, triggered by low

hippocampal theta power, could dynamically reorganize memory-relevant theta phase consistency during associative encoding.
We analyzed intracranial EEG from eight patients performing a word-pair associative memory task under no alarm, random alarm, and theta-based alarm conditions. Pairwise phase consistency (PPC) was measured during the 3 s encoding period from hippocampal contacts with detectable theta oscillatory peaks. We first tested whether PPC was memory relevant. In the no alarm baseline, successful encoding showed greater PPC than failed encoding in fast theta (4-12 Hz), whereas slow theta (2-4 Hz) did not show a significant difference. We next tested whether theta-based alarm increased PPC. The alarm was delivered 1.2 s after word-pair onset when real-time hippocampal theta power fell below threshold. Theta-based alarm increased slow theta PPC relative to no alarm during late encoding (2.0-2.3 s) and increased fast theta PPC relative to random alarm during a late post-alarm window (1.8-2.0 s). Delta PPC, defined as post-alarm PPC minus pre-alarm PPC, was also larger after theta-based alarm than after control conditions. Slow theta Delta PPC reflected an alarm-related physiological increase, but was not linked to memory performance. In contrast, fast theta Delta PPC was significantly associated with recollection only in the theta-based alarm condition. Trial-level decomposition of theta-power state, alarm delivery, and subsequent memory showed that low theta power or auditory stimulation alone was insufficient; fast theta phase became aligned in the memory-favorable direction specifically when theta-based alarm was delivered.
These findings position theta power as a probabilistic online state marker, not a deterministic mechanism of memory success. The mechanism was expressed in fast theta phase consistency, a temporal organization marker that captures how encoding events align within hippocampal theta cycles. By showing that this timing structure can be reorganized by state-dependent auditory intervention, this study extends human hippocampal memory research from correlational theta markers to closed-loop modulation of memory-relevant temporal organization.

Disclosures: S. Lee: None. **E. Lee:** None. **C. Chung:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.10/KK54

Topic: I.08. Learning and Memory

Title: Oscillatory multiplexing supports directional communication in human thalamo-cortical networks

Authors: *D. CONCEICAO, R. F. HELFRICH;
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Abstract: The Papez circuit, a hippocampal-thalamo-cortical loop, underlies a broad range of cognitive functions, including attention, memory, and emotion regulation. To date, it remains

unclear how information is routed through this circuit in humans to support this diverse set of cognitive functions. Recent advances in clinical practice of human intracranial electroencephalography (iEEG) now provide the opportunity to begin to uncover these processes, providing unprecedented access to thalamic activity through simultaneous recordings from several key nodes of the circuit with high temporal precision. Here, we investigate the effective connectivity and spectral organization of thalamo-cortical pathways using combined iEEG and direct electrical brain stimulation. Specifically, we focus on bidirectional interactions between the thalamus, hippocampus, and neocortex, as well as their interactions with distributed cortical networks. Our results reveal a significant asymmetry in effective connectivity, with thalamic afferent pathways exhibiting significantly stronger responses than thalamic efferent pathways. We further show that these directional connections are characterized by direction-dependent frequency-specific interactions. Thalamo-cortical projections exhibit stronger theta-band (~3-8 Hz) rhythmicity than cortico-thalamic pathways. Likewise, hippocampal-thalamic projections are dominated by theta activity, whereas thalamo-hippocampal pathways were additionally characterized by increased alpha-band (~8-12 Hz) activity. These results reveal that oscillatory multiplexing mediates communication within key nodes of the Papez circuit. Lastly, we combined our electrophysiological analyses with MRI-derived functional and structural normative connectomics. This approach revealed a spatial segregation of frequency-specific thalamo-cortical networks: theta-band connectivity mainly linked the thalamus to anterior and midline cortical regions, while alpha-/beta-band (~8-30 Hz) connectivity reflected engagement of parieto-occipital areas. In sum, our findings demonstrate that frequency-specific thalamic connectivity supports engagement of distributed large-scale cortical networks and establishes oscillatory multiplexing as a key signature of directed information flow within thalamo-cortical networks.

Disclosures: D. Conceicao: None. **R.F. Helfrich:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.11/KK55

Topic: I.08. Learning and Memory

Support: NIH R21MH135232-01A1

Title: NMDAR GluN2 Signaling as a Modulator of the Hippocampal Theta and Gamma Oscillations Crucial for Spatial Navigation

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Abstract: N-methyl-D-aspartate receptor (NMDAR) hypofunction in the hippocampus is linked to impaired spatial and episodic memory in disorders such as schizophrenia and Alzheimer's disease. A shared feature of these disorders is aberrant hippocampal oscillations in the theta (4-12 Hz) and slow gamma (25-55 Hz) ranges. Normally, theta power increases during active exploration and regulates neuron discharge patterns to facilitate spatial learning. Slow gamma oscillations act to synchronize activity across hippocampal subregions to retrieve unified episodic memories. While GluN2A- and GluN2B-containing NMDARs are known to regulate theta and gamma oscillations, a knowledge gap remains regarding how NMDAR ionotropic and nonionotropic signaling differentially influence hippocampal network oscillations. We addressed this question by recording local field potentials from area CA3 or CA1 in transgenic mice expressing chimeric GluN2 subunits [intracellular carboxy-terminal domains (CTDs) swapped between GluN2A and GluN2B, GluN2A-B^{CTD} and GluN2B-A^{CTD}] as they performed a spatial reference memory task on the Barnes maze. On average, theta and gamma event rate and average power varied between training blocks and memory probes in both CA1 and CA3. In CA1, GluN2B-A^{CTD} animals showed trends for decreasing whole trial slow gamma event rate during the first training day, while GluN2A-B^{CTD} and WT animals remained relatively consistent per block. In CA3, GluN2A-B^{CTD} animals have trended towards greater whole trial slow gamma power during probes. Further analyses will assess alterations in theta and slow gamma power, event rate, and peak frequency as well as theta/slow gamma coupling during mobile and immobile epochs and in relation to behavioral performance. Results from this interdisciplinary study will clarify how NMDAR ionotropic and nonionotropic signaling regulate hippocampal oscillations to encode and retrieve spatial memories.

Disclosures: A. Boakye-Agyei: None. **D. Gonzalez:** None. **T.C. Dumas:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.12/KK56

Topic: I.08. Learning and Memory

Support: NIH R21MH135232-01A1

Title: Maturation of Human Sequence Memory in Relation to Cortical Oscillations from Five to Twenty One Years Old

Authors: *J. SHEIKH[1], D. HAMMOUDA[2], T. C. DUMAS[3];
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[3]Psychology, George Mason Univ., Fairfax, VA

Abstract: The maturation of episodic memory across childhood and adolescence reflects protracted development of cortical networks, yet the relationship between memory capacity and

oscillatory brain dynamics during this period remains poorly characterized. We leveraged the Healthy Brain Network (HBN) dataset, a large-scale open-access resource comprising cognitive assessments and resting-state and task-related EEG recordings from children and adolescents aged 5-21 years, to examine developmental trajectories of sequence memory and their neural correlates. Episodic sequence memory was assessed using 6-item and 8-item forward recall tasks. Accuracy on the 6-item task reached an age-related plateau between 8-9 years, while performance on the more demanding 8-item task continued to mature until 16-17 years, indicating that the developmental ceiling for sequence memory is load-dependent and extends into early adolescence for higher-capacity demands. These findings suggest that the neural substrates supporting sequential episodic encoding undergo a protracted maturation that scales with task complexity. Spectral analysis of resting-state and task-related EEG revealed individual differences in beta and theta event rate that correlated positively with sequence memory scores, especially in the 10-12 and 12-14 age range, implicating lower-frequency cortical oscillations in the functional maturation of episodic memory capacity. The convergence of resting-state and task-related oscillatory changes suggests that beta and theta dynamics reflect a tonic maturational state of cortical circuitry rather than purely task-evoked processes. Together, these findings establish a capacity-dependent developmental trajectory for episodic sequence memory in which higher memory loads require an extended maturational period and identify beta and theta oscillations as candidate neural indices of cognitive maturation. These results have implications for understanding atypical memory development in pediatric populations and for the use of EEG biomarkers in neurodevelopmental assessment. We are currently assessing the specific brain regions correlated with these results using inverse solution and cortical parcellation methods in order to better understand the mechanistic foundations for the differing abilities during development.

Disclosures: J. Sheikh: None. **D. Hammouda:** None. **T.C. Dumas:** None.

Poster

PSTR156: The Role of Neural Oscillations in Memory Formation, Reactivation, and Forgetting

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR156.13/KK57

Topic: I.08. Learning and Memory

Support: OPUS 28 LAP no. 2024/55/I/NZ4/02203

Title: Global coincident bursts of low- and high-frequency oscillations orchestrate large-scale human memory processing

Authors: *J. S. GARCIA SALINAS[1], S. PRATHAPAGIRI[1], L. JURKOVICOVA[3], P. DANIEL[4], M. KOJAN[5], R. ROMAN[6], W. FORTUNA[7], P. TABAKOW[7], J. CIMBALNIK[8], M. T. KUCEWICZ[2];
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Republic; [4]Brno Epilepsy Center, Dept. of Neurol. and Neurosurgery, St. Anne's Univ. Hosp. and Med. Fac. of Masaryk Univ., Brno, Czech Republic; [5]Dept. of Neurol., Brno Epilepsy Ctr., Brno, Czech Republic; [6]Masaryk University, Brno Epilepsy Center, Dept. of Neurology, St. Anne's Univ. Hospital, Fac. of Med., Brno, Czech Republic; [7]Clin. Dept. of Neurosurgery, Fac. of Medicine, Wroclaw Med. Univ., Wroclaw, Poland; [8]ICRC, Intl. Clin. Res. Center, St. Anne's Univ. Hospital, Brno, Brno, Czech Republic

Abstract: High-frequency oscillations (HFOs), encompassing high gamma and ripple activity (>60 Hz) from intracranial EEG, are characterized by brief, spatially confined bursts of synchronized neuronal firing. Low-frequency oscillations (LFOs; <30 Hz), by contrast, persist longer and involve larger, more distributed neural populations. Despite their differences in temporal and spatial properties, both participate in electrophysiological events reflecting a shared organizational framework for neural information processing.To investigate their relationship, we examined individual LFO and HFO bursts in intracranial recordings from patients with drug-resistant epilepsy during memory encoding and retrieval of common nouns. Oscillatory events were detected across predefined frequency bands (theta, alpha, beta, gamma, and HFO) using z-scored amplitude envelopes from the Hilbert transform, with conservative thresholds for amplitude and duration.Both low- and high-frequency activities appeared as discrete events lasting approximately four oscillatory cycles. Their occurrence increased during stimulus presentation in encoding and around vocal response initiation during retrieval. Although activation timing varied across cortical regions, LFOs and HFOs frequently co-occurred within ±100 ms across frequencies and anatomical locations, suggesting consistent temporal correlations and reciprocal interactions.The observed temporal sequence indicates that low-frequency activity generally precedes high-frequency events, supporting a model in which widespread low-frequency dynamics establish a preparatory network state that facilitates localized high-frequency processing. Lobe-level coactivation analyses revealed strong intra- and cross-frequency interactions involving frontal, temporal, and limbic regions during both memory phases. The most pronounced patterns were associated with gamma and HFO activity within temporal lobe networks, and cross-frequency coupling analyses confirmed that localized high-frequency events are embedded within broader low-frequency network configurations.These findings support a spatio-temporal model of brain functional organization in which widespread low-frequency oscillations coordinate distributed local high-frequency activities, a general mechanism proposed to orchestrate large-scale neural processes underlying memory formation, recall, and possibly other cognitive functions.

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Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.01/KK58

Topic: I.10. Human Learning and Cognition

Title: Grid-like codes scaffold the construction of complex conceptual knowledge from simpler relational structures

Authors: *X. HUANG[1], S. A. PARK[2];
[1]Psychology, Virginia Tech., Blacksburg, VA; [2]Psychology, Virgina Tech., Blacksburg, VA

Abstract: How do people build new knowledge structure? Instead of learning from scratch, the brain may use learned structure as a scaffold for organizing new information. Recent computational models suggest that structure generalization may be achieved by factorizing abstract relational information and sensory information. We hypothesize that grid-like representations in the entorhinal and medial prefrontal cortex are potential mechanisms for abstract relational knowledge. To test this hypothesis, we design a novel experiment, where participants directly learned Map1, a 3×3 structure, followed by transfer learning for Map2, a more complex 4×4 structure learned during fMRI. Participants first learn Map1 through freely exploring all transitions in the structure with abstract actions. In Map2, participants learn relations among new items by applying relations of the given Map1 pairs on Map2 pairs. Importantly, Map2 learning dissociates learning sequence from transition in the structure: participants observe only selected item pairs, whose relations do not correspond to transitions in the structure. Successful learning therefore requires using Map1 to generalize Map2 structure and integrate relational information. During testing, participants need to recall learned relation and make inference on unobserved relations, which allow us to quantify transfer-learning performance. We found that participants were able to learn Map2 structure from Map1-derived relation without direct Map2 transition experience and used this structure to infer unobserved Map2 relations. Among participants who showed evidence of structural learning, inference time and accuracy for novel pairs did not depend on the number of Map1 links between corresponding items, suggesting that they represented direct relational vectors rather than relying on step-by-step transitive inference. Preliminary fMRI results suggest that successful learners began to form map-like representations of Map2 as learning progressed. Moreover, grid-like representations encoding Map2 vectors showed increasing alignment with Map1 vectors, suggesting a potential mechanism by which abstract relational structure is transferred across maps. We also examined how neural representations reorganize before and after structure learning using repetition suppression effect. Together, these findings suggest that grid-like codes may provide a mechanism by which the brain scaffolds new conceptual knowledge from previously learned structures, supporting flexible generalization beyond direct experience.

Disclosures: X. Huang: None. **S.A. Park:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.02/KK59

Topic: I.10. Human Learning and Cognition

Support: NIH Grant 2R01NS076856-11A1

Title: The space-time continuum: domain-general and domain-specific neural representations of spatial distance and temporal duration

Authors: *L. ZHENG[1], A. D. EKSTROM[2];
[1]Univ. of Arizona, TUCSON, AZ; [2]Psychology, Univ. of Arizona, Tucson, AZ

Abstract: Background: Spatial and temporal contexts are important dimensions of episodic memory. A central theoretical debate remains whether the brain utilizes a shared magnitude system or domain-specific modules to represent these dimensions. Furthermore, it is unknown whether the neural representation of a distance depends jointly on its metric identity and its behavioral role during a decision.
Methods: Twenty-seven participants completed an fMRI study learning and retrieving spatial distances and temporal durations across three virtual environments that decoupled these dimensions. During scanning, participants made forced-choice relational judgments comparing spatial distances or temporal intervals between virtual store locations.
Results: SVM classifiers reliably decoded both spatial distance and temporal duration from distributed cortical networks, including lateral occipital cortex (LOC), parietal cortex, precuneus, and prefrontal regions, whereas no MTL subregion exceeded chance-level decoding for either domain. Cross-domain generalization decoding identified shared representations in frontal and sensorimotor cortices (precentral and postcentral gyri), where classifiers trained on one domain successfully decoded the other. This suggests at least partially overlapping neural codes for spatial and temporal magnitude. Domain-specific specialization was also evident: LOC selectively decoded spatial distance without temporal generalization, while the superior frontal gyrus showed the converse pattern. In addition, multivariate pattern similarity analyses revealed that parahippocampal cortex maintained separable representational patterns for chosen and unchosen distances: pattern similarity was systematically higher when a distance matched the participant's chosen response rather than unchosen response, and this decision-status modulation was preserved independently for both alternatives. These representations reflected conjunctive coding, jointly tracking objective distance magnitude and subjective decision relevance.
Conclusion: Together, these findings reveal a hybrid neural architecture in which distributed neocortical networks encode spatial and temporal magnitudes through both domain-general and domain-specific systems. The lack of MTL decoding suggests neocortical networks carry the primary representational burden during explicit retrieval. Parahippocampal conjunctive representations track both objective distance and decision role, showing the brain preserves a complete comparison structure—including unchosen alternatives—to support flexible, goal-directed retrieval.

Disclosures: L. Zheng: None. **A.D. Ekstrom:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.03/KK60

Topic: I.10. Human Learning and Cognition

Title: Generalization of structural representations across physical and abstract task spaces supports continual task learning

Authors: *L. SHU[1,2], Q. YU[1];
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Abstract: Continual learning benefits from generalization, the ability to extract shared task structure and apply existing task knowledge to new problems. Growing evidence has revealed neural codes for both physical (spatial and temporal/ordinal) and abstract (relational) structures. Yet how these structural representations relate remains poorly understood. Here, we directly tested whether humans leverage physical structures to aid learning of more abstract task structures, and whether individuals differ in their reliance on specific physical structures. Participants first acquired object lists organized by spatial or temporal ordinal structures. During MEG scanning, their neural responses to the learned spatial and ordinal lists were collected, followed by the learning and testing of new object lists defined by transitive inferential relationships. Time-resolved multivariate pattern analysis identified neural representations of spatial, ordinal, and inferential structures across broadband signals. Source localization further revealed that these representations originated from parietal regions and later spread throughout the brain, suggesting a common cortical origin for structural representations across task spaces. Despite this commonality, behavioral similarity analyses showed distinct individual reliance on physical structures for inferential representations. Critically, the extent of neural representational similarity between each physical structure and inferential structure significantly correlated with behavioral reliance. Together, these findings demonstrate that physical structures can be generalized to support abstract structure learning, providing evidence for a direct correspondence between physical and abstract structural maps.

Disclosures: L. Shu: None. **Q. Yu:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.04/KK61

Topic: I.10. Human Learning and Cognition

Support: R01MH136214

Title: Sparse cognitive graphs in human goal-directed behavior

Authors: *P. SEPULVEDA, A. GUNGI, I. AITSAHALIA, K. IIGAYA;
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Abstract: Flexible behavior depends on internal world models that support goal-directed action. Although humans learn statistical regularities in complex environments, how this knowledge is transformed into compact structures for decision making remains poorly understood. Learning dynamics are highly variable across individuals, but what drives this variability at a mechanistic level — and how it produces qualitatively distinct behavioral outcomes — remains unclear. Here, we introduce the Sparse Cognitive Graph (SCG), a reinforcement learning framework in which transition knowledge is transformed into sparse, structured representations that support goal-directed decision making. A key feature of the SCG is that transition knowledge accumulates continuously in a dense predictive representation, but only relationships that exceed a threshold are expressed as edges in a sparse directed graph that guides action. This separation allows gradual learning to produce abrupt reorganization of graph structure and sudden shifts in behavior. We validate the SCG using behavioral data from two experiments, focusing on discrete, qualitative changes in behavior as model benchmarks. First, we show that individual differences in sparse graph construction capture the diversity of human behavior observed in reward and transition revaluation tasks (Mommenejad et al., 2017). Second, we demonstrate that canonical reward-by-transition interactions in the two-step task (Daw et al., 2011; Kool et al., 2016) can be reproduced without invoking multiple competing control systems, but rather by constructing dynamic sparse graphs. Further, discrete patterns in two-step task behavior across participants are also reflected in distinct graph learning dynamics. Together, these findings establish threshold-based graph construction as a unifying principle by which statistical learning is converted into structured representations that support efficient, flexible, and goal-directed behavior.

Disclosures: P. Sepulveda: None. **A. Gungi:** None. **I. Aitsahalia:** None. **K. Iigaya:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

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Program #/Poster #: PSTR157.05/KK62

Topic: I.10. Human Learning and Cognition

Title: Goal-dependent readout of hierarchical and map-like conceptual relations in the hippocampal-entorhinal system

Authors: *I. BARNAVELI[1], S. VIGANÒ[1,2], P. HAGGARD[3], C. F. DOELLER[4,5,6];
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Abstract: Organising conceptual knowledge requires more than storing features of individual items. It requires building relational representations that make concepts available for mental operations, such as ordering along a dimension and set inclusion within a hierarchy. Concepts can be organised as graded distances in a map-like space or as nested categorical relations. Although hippocampal representations have been linked to both map-like and hierarchical organisation, there is less evidence for hippocampal involvement in concept hierarchies specifically. We therefore asked whether the hippocampal-entorhinal system flexibly reads out map-like and hierarchical relational structures over the same learned concepts. To test this, we developed a paradigm in which the same stimulus set supported two different relational structures. Adult participants learned 16 monster stimuli and their features through short narratives over three days. Monsters' skeleton, composition, and habitat formed a hidden hierarchy, whereas their speed and vision defined a decorrelated two-dimensional (2D) ability map. Thus, the same monsters could be organised by nested categorical relations or by metric distance in a 2D map. Crucially, participants were trained only on individual monster-feature associations and never on inter-monster relations. This tested whether participants could infer relational structure from feature learning alone. To examine the neural readout of these relational structures, participants performed feature-recall and goal-directed selection tasks while brain activity was recorded with 7-Tesla functional magnetic resonance imaging (fMRI). Preliminary findings provide evidence for representations of both map-like and hierarchical relational structures in the hippocampal-entorhinal system. Importantly, the neural responses to the same learned concepts showed a dissociation depending on whether task goals emphasised dimensional or hierarchical relations. These findings suggest that the hippocampal-entorhinal system may support flexible cognition by representing multiple relational structures over the same concepts and selectively reading out the format most relevant for the task at hand.

Disclosures: I. Barnaveli: None. **S. Viganò:** None. **P. Haggard:** None. **C.F. Doeller:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.06/KK63

Topic: I.03. Decision Making

Title: Rolling-window regressions show that a dividend hot-potato game precedes bubble peaks in lab asset markets: A potential behavioral target for studying timing in the neuroeconomics of asset-price bubbles

Authors: *J. L. HARACZ;
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Abstract: Objective: Excessive demand was recently defined as demand that promotes disequilibria in asset or goods markets and drives prices above fundamental values (e.g., an asset-price bubble [Haracz, 2024]). In a lab asset-market study, a market-level excessive demand

measure, calculated from summed subject-level desired share holdings, outperformed other demand proxies in explaining asset-price changes (Haracz, 2024). This result led to the question of what motivates subjects' desired holdings. A regression analysis of 7 potential motivating factors against the desired change in share holdings revealed that subjects' number of shares held in the current period was best able to explain the desired change in holdings for the next period (Haracz, 2025). If this shares-held variable is to have a causative role in forming the observed asset-price bubbles, then the variable should significantly affect the desired change in holdings before the bubbles peak, so the present study tests for this timing. Methods: In a classic lab asset-market design, 9 experiments each included 9 subjects. Experiments included 15 2.5-minute periods of trading an asset with a dividend-based fundamental value that declined across periods. To capture desired holdings, the end of each Period 1-14 was followed by a survey that elicited each subject's number of asset shares that they want to hold at the end of the next period. The influence of the shares-held variable on the desired change in holdings was analyzed with a regression equation of the form $DS_{i,t+1} - S_{i,t}$ (i.e., subject i's desired change in share holdings, calculated as the desired number of shares in upcoming Period t+1 minus the number of shares held in the current Period t) = $b_0 + b_1(S_{i,t})$. Rolling-window regressions (e.g., Chocobar and Claeys, 2026) were used to determine the timing of significant results ($p < 0.05$) relative to bubble peaks. The peaks rarely occurred before Period 6, so the 6 regression windows included Periods 3-5 and each of the 5 following pairs of periods. Results: Regression analyses in each of the 6 windows showed significant relationships between share holdings and desired change in holdings (adj. R^2 values ranged from 0.05 to 0.21). Conclusions: The pre-peak first window's (i.e., Periods 3-5) significant effect is consistent with a causal effect for the shares-held variable on bubble formation. The shares-held coefficient's negative sign means that subjects tended to hold dividend-yielding shares for a limited time before selling. This game of dividend hot potato exemplifies a bubble-related behavior that could be targeted in neuroimaging studies to further elucidate the neuroeconomics of asset-price bubbles.

Disclosures: J.L. Haracz: None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.07/KK64

Topic: I.10. Human Learning and Cognition

Title: Stability of movement by a multi-element system: Drifts and random walk within and orthogonal to the uncontrolled manifold

Authors: *S. D. DE[1], M. L. LATASH[2];
[1]Pennsylvania State Univ., State College, PA; [2]Dept. of Kinesiology, Penn State Univ., University Park, PA

Abstract: We tested one of the central assumptions of the uncontrolled manifold (UCM) hypothesis that stability within and orthogonal to the UCM differ in a task-specific was. This was done by exploring effects of visual feedback on the fast random walk (RW) and slow drifts during multi-finger force production. Healthy participants used the index and middle fingers of both hands to produce accurate total force magnitude with different initial sharing of the force between the hands. After 5 s, visual feedback was manipulated - kept for both force and sharing, for only one of those variables, or turned off. The subjects tried to keep their performance unchanged for 55 s. Trajectories both along and orthogonal to the UCM for total force showed fast RW and slow drifts. The diffusion plots confirmed persistent RW within the first 0.2 s and anti-persistent RW after 0.5 s. Persistent RW was similar across visual feedback conditions and larger orthogonal to the UCM. Its Hurst index correlated between the UCM and orthogonal to the UCM direction across participants. Anti-persistent RW depended strongly on visual feedback. Drift magnitude and characteristic time depended strongly on visual feedback, being similar along and orthogonal to the UCM. We conclude that RW destabilizes the state of the system thus encouraging exploration of nearby states over short time intervals and contributes to its stability over larger time intervals. Visual feedback plays a more important role in structuring stability of performance compared to the explicit task formulation. RW and drift exploration promises new insights into the organization of stability in abundant systems and a potential biomarker for clinical studies.

Disclosures: S.D. De: None. **M.L. Latash:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

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Program #/Poster #: PSTR157.08/KK65

Topic: I.03. Decision Making

Title: Subjective time perception shapes the neurocomputational architecture of intertemporal choice across adulthood

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Abstract: Intertemporal choice, the trade-off between immediate and delayed rewards, is shaped by subjective time perception, yet the latent computational mechanisms through which perceived time influences impulsive choice across adulthood remain unclear. This study combined functional magnetic resonance imaging (fMRI) with hierarchical drift-diffusion model (HDDM) to examine how time perception and aging jointly modulate delay discounting and financial risk-taking. A lifespan sample of 169 adults aged 18-81 years completed a delay discounting task during fMRI. To capture individual differences in temporal perception, we incorporated Stevens' power-law scaling into the drift-diffusion framework and tested whether subjective time altered specific value attributes or broader decision dynamics. Bayesian regressions linked latent model

parameters to self-reported financial risk preferences, while whole-brain general linear models and age-stratified analyses identified neural responses associated with subjective temporal scaling. Model comparison indicated that subjective time functions as a general amplifier of decision dynamics, modulating drift rate, starting-point bias, and decision threshold. Behaviorally, stronger initial bias toward immediate rewards and lower decision thresholds, reflecting reduced caution, predicted greater financial risk-taking. However, Bayesian age-moderation analyses revealed a non-linear, inverted-U-shaped developmental pattern: the association between these computational signatures and financial risk-taking was strong in young adults and significantly attenuated in middle age. Neurally, whole-brain analyses identified activation in the left precuneus and calcarine fissure associated with temporal perception. Age-stratified analyses further revealed a midlife-specific neural-computational mechanism: only among middle-aged adults did precuneus reactivity significantly correlate with higher delay discounting rates. This coupling was absent in younger and older adults. Together, these findings suggest that the neurocomputational basis of risk-taking changes across the adult lifespan. Whereas financial risk-taking in young adults is primarily associated with a general computational phenotype characterized by low caution and immediate bias, midlife impulsivity appears to depend more specifically on how the precuneus, a key default-mode-network region, represents future time. These results identify midlife as a critical transitional period in which subjective temporal perception becomes a central neural driver of intertemporal decision-making.

Disclosures: L. Dai: None. **L. Liu:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.09/LL1

Topic: I.10. Human Learning and Cognition

Title: Lost in time without an anchor: cerebellar dysfunction distorts cortical neural dynamics of subjective temporal judgments

Authors: *C. ZANONATO[1,2], R. IVRY[3], A. BRESKA[1];
[1]Max Planck Inst. for Biol. Cybernetics, Tübingen, Germany; [2]Grad. Training Ctr. of Neurosci., Univ. of Tübingen, Tübingen, Germany; [3]Psychology, Univ. of California, Berkeley, Berkely, CA

Abstract: The ability to estimate temporal intervals, known as explicit timing, has been associated with neural adjustments in cortico-striatal circuits, such as ramping activity. However, lesion studies suggest that the cerebellum also plays a key role, yet its impact on cortical dynamics of explicit timing, especially the affected stage of temporal information processing, remains unexplored. Here, we addressed this using scalp electroencephalography (EEG) in cerebellar ataxia (CA) patients (N=15) and neurotypical controls (N=10) performing a temporal

discrimination task. Participants judged whether the duration of a variable comparison interval (spanning from 700 and 1200 ms) matched or differed from that of a preceding standard interval, which was either 700 or 1200 ms block-wise. This design allowed us to dissociate temporal decision-making strategies based on the encoding of the standard vs. comparison set's midpoint (i.e. bisection point, BP). Behaviorally, patients had lower temporal sensitivity. Neurally, during the comparison interval, controls showed ramping activity that peaked at the BP of the comparison distribution and resolved thereafter, rather than a standard-based adjustment. In contrast, in CA patients ramping extended negatively beyond the BP, indicating a lack of sensitivity to this temporal anchor. Analysis of delta-band activity in the same time period revealed that controls showed a stronger phase alignment before the earliest possible comparison than patients, suggesting cerebellar involvement in supporting temporally consistent ramping from this early stage. Importantly, evoked responses to standard onset and delta phase dynamics during standard encoding were comparable between groups, ruling out data quality as an explanation for group differences. Interestingly, neural responses at standard offset showed a duration-dependent amplitude modulation in both groups, suggesting a comparable standard decoding. Overall, these results highlight a causal role of the cerebellum in shaping cortical dynamics of explicit timing. Specifically, the cerebellum is crucial for consistently adjusting anticipatory activity during the proactive use of a precise temporal anchor.

Disclosures: C. Zanonato: None. **R. Ivry:** None. **A. Breska:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

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Program #/Poster #: PSTR157.10/LL2

Topic: I.10. Human Learning and Cognition

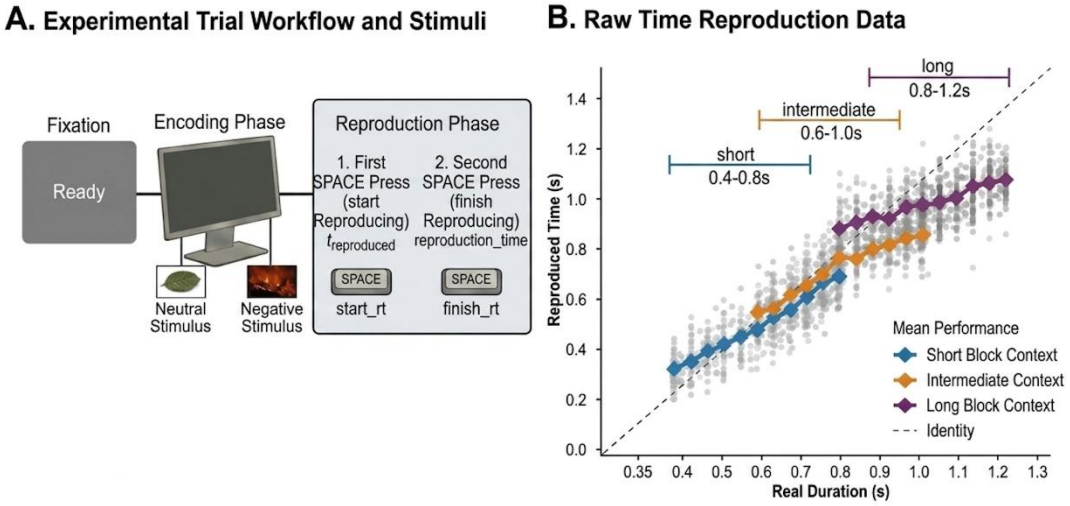
Title: Affective Modulation of Interval Timing Across Temporal Contexts

Authors: *R. YAGCI[1,2], I. TASDEMIR[3], M. AGARGUN[4];
[1]Dept. of Genet., Harvard Med. Sch., Boston, MA; [2]Intl. Sch. of Med. & Sch. of Engin. and Natural Sci., Istanbul Medipol Univ., Istanbul, Turkey; [3]Dept. of Psychiatry, Istanbul Medipol Univ., istanbul, Turkey; [4]Dept. of Psychiatry, Istanbul Medipol Univ., Istanbul, Turkey

Abstract: Human temporal perception is an active constructive process integrating sensory inputs with internal priors to estimate duration. While Bayesian models account for subsecond timing, how emotional valence and affective state influence temporal processing remains unclear. This study examines this relationship in a small dimensional sample (N=16) including healthy controls and individuals with anxiety and/or depressive symptoms, approved by the institutional ethics committee. Participants completed standardized affective scales (BAI, BDI, STAI-S/T) to assess symptom severity along a dimensional spectrum. Stimuli were drawn from the Open Affective Standardized Image Set (OASIS), matched for arousal across neutral and negative conditions. A time reproduction paradigm was used with three partially overlapping

temporal blocks (short: 0.4-0.8 s, intermediate: 0.6-1.0 s, long: 0.8-1.2 s), each presented 16 times and balanced across conditions. Participants reproduced perceived intervals via button press (see Figure 1). Preliminary results indicate contextual effects on temporal reproduction. A one-way model revealed a small but significant effect of block on reproduction bias (R^2=0.009, p=0.031), primarily driven by reduced bias in the short interval condition (Tukey HSD, p=0.039). Mixed-effects modelling confirmed this effect (short vs. reference: β=−0.081, p=0.024), whereas long intervals did not significantly differ from intermediate ones. Affective symptomatology did not show robust main effects; however, exploratory analyses suggested a trend-level modulation by depressive symptoms in longer intervals (BDI×long: p≈0.045). Overall, these findings suggest that temporal reproduction is primarily shaped by contextual structure,while affective influences require further investigation in larger samples. These findings should be interpreted cautiously given the small sample size and are intended as preliminary evidence motivating larger scale studies.

Figure 1. Time Reproduction Across Overlapping Contexts and Emotional Valence



Disclosures: R. Yagci: None. **I. Tasdemir:** None. **M. Agargun:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

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Program #/Poster #: PSTR157.11/LL3

Topic: I.03. Decision Making

Support: National Natural Science Foundation of China 32400914

Title: Age-related reorganization of conflict processing and neural choice predictability during intertemporal decision-making

Authors: *L. LIU[1], L. DAI[2];
[1]Dept. of Psychology, Univ. of Macau, Macau, Macao; [2]Dept. of Psychology, Univ. of macau, Macau, Macao

Abstract: Intertemporal decision-making requires individuals to balance immediate gratification against the value of delayed rewards, yet how the behavioral and neural mechanisms underlying it change across adulthood remains unclear. Using task-based fMRI data from 169 healthy adults aged 18-82 years, this study examined age-related differences in delay discounting, decision conflict, task-evoked neural activation, and multivariate prediction of smaller-sooner versus larger-later choices. Participants completed a monetary delay discounting task during fMRI. Behavioral models assessed age-group differences in choice preference and reaction time, while whole-brain models identified neural responses associated with choice type and low-, middle-, and high-conflict decisions. Age-related neural effects were examined while controlling for sex and education. LASSO-regularized principal component regression was used to test whether distributed neural activity predicted intertemporal choices across age groups. Behaviorally, middle-aged and older adults showed higher odds of choosing smaller-sooner rewards than young adults, and older adults showed slower responses and altered conflict-related modulation of reaction time. Neuroimaging analyses revealed overlapping but dissociable neural systems for delayed and immediate reward choices, involving visual, sensorimotor, prefrontal, insular, thalamic, and cingulate regions. High-conflict decisions preferentially recruited supplementary motor, cingulate, inferior frontal, and insular regions, consistent with increased cognitive control, salience processing, and response competition, whereas low-conflict decisions showed stronger activation in the occipital, fusiform, and sensorimotor regions. Age-related effects were most evident in the posterior parietal, occipital, precuneus, cingulate, and sensorimotor regions, suggesting lifespan differences in neural systems supporting reward valuation, conflict resolution, and action selection. Notably, multivariate prediction of smaller-sooner versus larger-later choices was significant only in young adults, with mean cross-validated accuracy of 56.76% and AUC of 0.599, indicating that choice-related neural representations may be more consistent or more linearly decodable earlier in adulthood. Together, these findings extend previous delay-discounting research by showing that adult differences in intertemporal decision-making are reflected not only in behavioral preference and regional neural recruitment but also in conflict-sensitivity neural dynamics and age-specific neural decodability.

Disclosures: L. Liu: None. **L. Dai:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.12/LL4

Topic: I.10. Human Learning and Cognition

Title: Modulating Spatial Representations in Motor Skill Learning Using Transcranial Ultrasound Stimulation of the Hippocampus

Authors: *M. P. MONTENEGRO, Y.-H. WANG, Y. LEI;
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Abstract: The hippocampus is implicated in procedural memory processes and in the formation of spatial representations underlying motor skill learning. In motor sequence learning, allocentric representations encode a sequence according to external spatial relationships, whereas egocentric representations encode the sequence relative to the body and specific motor movements used to execute the task. Although the hippocampus may contribute to the formation and consolidation of these representations, studies directly modulating hippocampal activity and evaluating the effects on motor sequence representations remain limited. This study investigated the effects of hippocampal neuromodulation, mediated by transcranial ultrasound stimulation (TUS), on the formation of allocentric and egocentric motor sequence representations. A micro-consolidation typing task adapted from Bönstrup et al. (2019) was used to assess sequence learning and transfer. Participants were assigned to one of three groups: a hippocampal stimulation group, a sham stimulation group, or a random-sequence control group practicing non-repeating sequences. Behavioral performance (keypress speed and accuracy) was evaluated during baseline, sequence training, and subsequent testing on either allocentric or egocentric sequence transformations. Participants returned one week later to complete the alternate testing condition. Results revealed that both the stimulation and sham groups exhibited faster keypress speeds during allocentric testing compared to egocentric testing, whereas the random-sequence control group performed similarly across both testing conditions. Between groups, the hippocampal stimulation group achieved the fastest overall keypress speeds across testing blocks, while the sham group recorded the slowest. Furthermore, the random-sequence control group demonstrated superior transfer performance relative to the sham group, suggesting that variable training promotes greater cognitive flexibility and generalization. Keypress accuracy remained consistent across all groups. Notably, participants in both sequence-learning groups demonstrated superior allocentric transfer, indicating that this training paradigm may preferentially foster external spatial representations of learned sequences. These findings highlight the complex role of the hippocampus in motor skill representation and warrant further investigation into the underlying neural mechanisms.

Disclosures: M.P. Montenegro: None. **Y. Wang:** None. **Y. Lei:** None.

Poster

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Program #/Poster #: PSTR157.13/LL5

Topic: I.10. Human Learning and Cognition

Support: NIH intramural fund

Title: Neural replay events during skill learning emerge during transient reduction of brain oscillatory activity

Authors: *W. HAYWARD[1], F. IWANE[2], E. R. BUCH[4], L. G. COHEN[3];
[1]NIH, Natl. Inst. of Neurolog. Disorders & Stroke (NINDS), Bethesda, MD; [2]Human Cortical Physiol. and Neurorehabilitation Section, [3]HCPS, NINDS, NIH, Human Cortical Physiol. & Neurorehabilitation Section, NINDS, Bethesda, MD, Bethesda, MD; [4]Human Cortical Physiol. & Neurorehabilitation Section, NINDS, NIH, Bethesda, MD

Abstract: Background: Neural replay, temporally compressed reactivations of task-related activity during rest (Eichenlaub et al., 2020) has emerged as a candidate mechanism for stabilizing newly acquired skills (Buch et al., 2021; Chen et al., 2025; Sjøgård et al., 2025). In non-human primates, replay occurs preferentially during periods of decreased bursting in 13-30Hz range (Griffin et al., 2025). However, the brain oscillatory dynamics governing neural replay emergence in humans are unknown. Here, we addressed this question by examining transient changes in the oscillatory rhythms surrounding neural replay events in the context of human motor skill learning. Given evidence that suppression of 8-30 Hz oscillatory activity facilitates motor learning (Pollok et al., 2014) and motor control (Lundqvist et al., 2024), we tested the hypothesis that transient reductions in power within this frequency range create a neural state permissive for replay eventsMethods: We analyzed magnetoencephalography (MEG) data from 31 participants performing a well-characterized motor sequence learning task in which 10-second bouts of sequence typing alternated with 10-second rest periods (Bönstrup et al., 2019). We implemented a previously described neural replay detection pipeline (Buch et al., 2021; Dash et al., 2025). Source-level MEG data were bandpass filtered into canonical frequency bands (theta: 4-7Hz, alpha: 8-12Hz, beta: 13-30Hz, gamma: 31-50Hz), Hilbert transformed, and epoched during each neural replay event. Each power band during replay was compared to frequency-band activity during the entire non-replay rest period using a paired t-tests.Results: Oscillatory power during neural replay events was reduced in theta (4-7Hz, t=-2.68, p=.013), alpha (8-12Hz, t=-3.73, p=.001) and beta (13-30Hz, t=-3.58, p=.002) oscillatory ranges compared to rest. Gamma (31-50Hz) power was comparable during replay and rest (t=0.15, ns). The largest effects were observed in the 8-12Hz, (Cohen's d=-0.73) and 13-30Hz (Cohen’s d = -0.70) ranges.Conclusion: We conclude that neural replay during human motor skill learning occurs in the context of transient reductions in 3-30Hz brain oscillatory power activity. Future directions include evaluation of causality links between oscillatory dynamics and neural replay as a step towards the design of brain stimulation interventions aimed at enhancing motor learning in rehabilitation settings.

Disclosures: W. Hayward: None. **F. Iwane:** None. **E.R. Buch:** None. **L.G. Cohen:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.14/LL6

Topic: I.10. Human Learning and Cognition

Support: NIH Intramural Grant

Title: Skill Learning Dynamics Shift from Online to Offline Expression as Task Context Changes

Authors: *F. IWANE[1], E. R. BUCH[3], L. G. COHEN[2];
[2]HCPS, NINDS, NIH, [1]Human Cortical Physiol. & Neurorehabilitation Section, NINDS, Bethesda, MD, Bethesda, MD; [3]Human Cortical Physiol. & Neurorehabilitation Section, NINDS, NIH, Bethesda, MD

Abstract: Skill learning is shaped by the context within which practice unfolds. Features such as task difficulty, or whether skill actions are intrinsically generated or dictated by extrinsic stimuli (reactive) may influence how effectively practice translates into skill gains. Critically, a key unresolved question is how context shapes skill learning and the relative contributions of practice and rest to that learning, namely, micro-online gains during practice and micro-offline gains during rest.
Because performance changes are not a direct readout of learning and may also reflect non-learning factors such as fatigue, we quantified trial-to-trial skill gains from one trial onset to the next, after an intervening rest break dissipated potential practice-induced fatigue effects. We then estimated session-wide micro-online and micro-offline gains for trials where performance gains were present and tested whether these microscale learning dynamics were preserved or differed across task contexts. In a large cohort (N=1291), we systematically manipulated three skill features: sequence difficulty (hard, medium, easy), task structure (reactive [REACT] vs. generative [GEN]), and learning state (fixed sequence-specific vs. difficulty-matched, random practice) resulting in12 distinct skill learning contexts.
Performance improvements during random keypress practice were comparable across contexts ($F=0.04$, $p=0.84$). By contrast, sequence-specific training produced larger overall learning ($F=445.54$, $p<0.001$), with this advantage being more prominent in the GEN than in the REACT task structure ($F=19.2$, $p < 0.001$). Learning evolved more rapidly in the GEN task structure for the medium and hard sequences. In GEN, 95% of the total skill gain was achieved by trials 9 and 10 for the medium and hard sequences, respectively, while in REACT, the same criterion was reached only by trials 21 and 20. Micro-offline gains were more prominent than micro-online gains across both medium and hard GEN (medium=66.5±1.5%; hard=70.6±1.6%) and REACT (medium=74.4±1.5%; hard=73.3±1.6%) tasks. In contrast, skill gains for the easy sequence were distributed roughly equally across both online practice and offline rest breaks (GEN: 51.5±1.4% online vs. 48.5±1.4% offline; REACT: 50.8±1.3% vs. 49.2±1.3%).
In conclusion, task context critically shapes the microscale dynamics of skill learning, influencing both the rate of learning and the relative contributions of online and offline processes to skill acquisition.

Disclosures: F. Iwane: None. **E.R. Buch:** None. **L.G. Cohen:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.15/LL7

Topic: I.10. Human Learning and Cognition

Support: NSF Award #2318685

Title: Learning to Code Reorganizes the Functional Connectome: Evidence from a Longitudinal fMRI Study of Programming Acquisition

Authors: *Q. J. COVINGTON[1], M. BEDNY[2], Y.-F. LIU[3];
[1]Psychological & Brain Sci., Johns Hopkins Univ., BALTIMORE, MD; [2]Psychological & Brain Sci., [3]Psychological and Brain Sci., Johns Hopkins Univ., Baltimore, MD

Abstract: Learning often involves the coordinated use of multiple cognitive processes supported by large-scale coordination between brain networks. Programming is one such complex behavior. As people develop their coding skills, they are able to more fluently understand and produce code, but how the development of this skill reorganizes the brain's functional connectivity is unknown. This study analyzes how this change in programming fluency is represented in the cerebral connectome. Twenty-two programming-naïve participants perform algorithm (plain-English "pseudocode") comprehension tasks during fMRI scans before and after taking a three-month long introductory Python course. From these scans, partial correlation-based functional connectivity was used to estimate two functional connectomes from each scan: one for pseudocode task and one for content-matched memory control task, resulting in four connectomes total for each participant (two in the Pre condition and two in the Post condition). Every participant displays functional fingerprints that are maintained across the three months; within condition, participant connectomes are more correlated with themselves Pre vs. Post than they are with others (100% identification accuracy; mean self-correlation $r=0.202$ vs. others $r=0.128$). Despite stable individual fingerprints, condition-specific reorganization correlates with learning. Comparisons revealed that across the entire 400-parcel network, change in similarity to the group average functional connectivity profile also correlates positively with change in task performance ($r=0.549$, $p=0.008$), but not with change in control performance ($r=-0.035$, $p=0.88$). We also found parcels in the medial default-mode network (DMN, specifically precuneus/PCC) that changed their functional connectivity profile across Pre and Post scans more for pseudocode than for the memory control condition (FDR $q<0.05$). The univariate degree of this functional reorganization also predicts change in overall performance on both pseudocode reading and memory control tasks ($r=0.519$, $p=0.012$ and $r=0.570$, $p=0.005$, respectively). This may reflect a general learning-related reorganization of connectivity profile which supports performance gains across trial types. Together, these findings suggest that successful programming learning is associated with reconfiguration of functional connectivity at multiple scales: local changes in medial DMN connectivity that track general task adaptation, and global alignment toward a shared connectivity profile that specifically predicts gains in algorithm comprehension.

Disclosures: Q.J. Covington: None. **M. Bedny:** None. **Y. Liu:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.16/LL8

Topic: I.10. Human Learning and Cognition

Title: Investigating the Test Retest Reliability of Cognitive-Motor Interactions Using Mobile Brain Body Imaging

Authors: *E. R. LANG, P. R. NICKLAS, D. P. RICHARDSON, E. G. FREEDMAN, J. J. FOXE;
Neurosci., Univ. of Rochester Med. Ctr., Rochester, NY

Abstract: Cognitive-motor (C-M) interactions are studied by comparing performance under 'single-task' and 'dual-task' conditions, to understand how the brain adjusts to simultaneous demands. Previous research has shown that a subset of young adults (YAs) significantly improve at task performance on a response inhibition (RI) paradigm (Patelaki et al. 2023) when walking, and no significant improvement or worsening of task performance at a cued task switching (CTS) paradigm (Richardson et al. 2023). A study by Malcolm et al. 2020 looked at the long-term test-retest reliability of C-M interactions in an RI task, having participants complete an identical experiment approximately 2 years later. This study showed no change in task performance between timepoints and showed stable neurophysiology in a cohort of 12 YAs. Notably, this study is limited to a small sample size and an inconsistent time between experiments (1.1-to-2.9-year range). The current study aims to investigate whether C-M interactions are stable across cognitive domain and time using Mobile Brain Body Imaging (MoBI). MoBI allows for simultaneous recording of behavioral, neurophysiological (electroencephalography, EEG), and kinematic data. 52 neurotypical YAs (24M/28F, age: 24.88 (3.79)) completed two identical MoBI sessions 3-5weeks apart. Each session consisted of a set of surveys aimed at examining sleep, fatigue, and physical activity, followed by 11 blocks (5 walking, 5 sitting, 1 walking only control) of the RI paradigm, and the same of the CTS paradigm. Paradigm order was counterbalanced for participants, but consistent within subject. Additionally, motion state was pseudorandomized. Data analysis is currently ongoing but preliminary results show no group level differences in event related potentials (ERPs), behavioral performance, or gait kinematic data between visits in the RI task. However, a small subset of individuals showed significant improvement or worsening in behavioral performance in the RI paradigm between visits which warrants further investigation. Gait kinematics reliably show less variability in dual-task blocks as compared to single-task walking blocks across task and time. Further analysis aims to include covariates from survey data to see if there is any impact of individual factors on performance, gait variability, or EEG measures.

Disclosures: E.R. Lang: None. **P.R. Nicklas:** None. **D.P. Richardson:** None. **E.G. Freedman:** None. **J.J. Foxe:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.17/LL9

Topic: I.10. Human Learning and Cognition

Support: NSF Award No. 2319108

Title: Specific motor expertise shapes sensorimotor function of the hand: expertise-dependent differences in proprioception and movement

Authors: *M. WANG[1], K. L. FOLCO[1], S. SIDDIQUI[2], H. J. BLOCK[1];
[1]Dept. of Kinesiology, [2]Dept. of Biol., Indiana Univ., Bloomington, IN

Abstract: Sensorimotor experience shapes perception and movement, acting as a foundation from which new skills are learned. The effects of long-term motor experience on motor learning and proprioceptive acuity have been widely studied in isolation with specific expert populations. Athletes and musicians have greater motion range and proprioceptive acuity than non-experts. Here, we tested whether individual differences in upper-limb motor expertise were associated with sensorimotor function (motor dexterity and proprioception) of dominant and non-dominant hands. Participants were musicians, athletes (e.g. baseball players, not runners), and/or gamers who completed five tasks with both hands: a Purdue Pegboard test (manual dexterity), a two-point discrimination test (tactile sensitivity), a tablet-based proprioceptive assessment (proprioceptive bias and sensitivity), a reaction time (RT) task using Hick's Law (motor control), and a touchscreen task (visuo-proprioceptive sensory weight). Preliminary data found the expected increased motor dexterity in the dominant vs. non-dominant hand. Additionally, gamers were faster than athletes on the RT-task only in the most challenging conditions, indicating that gamers' fine motor control outperformed athletes, possibly because athletes' expertise involves gross motor control instead. These results suggested that differences in expertise only emerge in sufficiently challenging tasks. Interestingly, athletes showed greater proprioceptive bias in the non-dominant hand, indicating a greater disparity between perceived and actual hand position. This effect was reversed for the gamers, where the disparity for the non-dominant hand was smaller than that for the dominant hand. These results could suggest that athletes re-allocate non-dominant hand sensorimotor resources to the dominant hand, whereas gamers who often need fine motor control in both hands must simultaneously improve dominant and non-dominant hands. Although not statistically significant, our data showed great disparities between measures of proprioception. For instance, the proprioceptive sensitivity measure showed the reverse effect from that of proprioceptive bias. These results suggest the importance in clinical assessment for multiple proprioceptive measurements. Overall, these data confirm that specific motor experiences shape proprioceptive representation of the hand, and suggest that motor skill expertise does not universally affect sensorimotor behavior. Our results emphasize the importance of considering prior sensorimotor experiences when evaluating learning and bias.

Disclosures: M. Wang: None. **K.L. Folco:** None. **S. Siddiqui:** None. **H.J. Block:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.18/LL10

Topic: I.10. Human Learning and Cognition

Title: Causal cortical dynamics of motor skill development

Authors: *R. PANDA, Q. NGUYEN, J. SELLERS, J. A. BRISSENDEN, T. G. LEE; Psychology, Univ. of Michigan, Ann Arbor, MI

Abstract: Motor skill acquisition is accompanied by a reorganization of cortical and subcortical brain activity supporting performance. This reorganization involves an increase in distinctiveness between patterns of neural activity underlying learned skills in many task-relevant brain areas. Neuroimaging studies suggest that dorsolateral prefrontal cortex (DLPFC) supports early, goal-directed stages of learning, whereas primary motor cortex (M1) becomes increasingly important as skills are automatized. However, the dynamics of how of goal-directed control evolves during the transition from novice to expert are currently unclear: Does the scaffolding provided by prefrontal networks completely yield to the automated execution enabled by a core motor network, or do both networks continue to run in parallel to support performance? While many neuroimaging studies have found a decrease in brain activity of DLPFC and M1 over the course of learning, it is unclear if this decrease reflects reduced importance or increased metabolic efficiency. Here, we combine transcranial magnetic stimulation (TMS) with fMRI to determine the causal role of DLPFC and M1 in supporting behavioral performance and skill-specific neural representations over the course of six weeks of training on a discrete sequence production task. Our design allowed us to concurrently assess motor skills at three different levels of expertise (extensively, moderately, and minimally trained sequences) during a single session. Representational similarity analysis (RSA) was used to quantify the distinctiveness of sequence-specific neural representations both within and across levels of expertise. Although extensively practiced sequences exhibited greater representational distinctiveness than minimally practiced sequences in cortical motor areas, minimally practiced sequences exhibited greater representational distinctiveness in prefrontal regions implicated in cognitive control. Stimulation of both M1 and DLPFC disrupts the representational distinctiveness of these codes both locally and across a broader network of brain regions. These results provide causal evidence for the dissociable roles of DLPFC and M1 in supporting the development of motor skill expertise.

Disclosures: R. Panda: None. **Q. Nguyen:** None. **J. Sellers:** None. **J.A. Brissenden:** None. **T.G. Lee:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.19/LL11

Topic: I.10. Human Learning and Cognition

Support: JSPS KAKENHI Grant No. JP25K03159
JSPS KAKENHI Grant No. JP26H02483

Title: Anthropomorphic Control Mapping Modulates Brain Activity During Robot Teleoperation: An fMRI Study

Authors: *J. PARK[1,2], E. OZTOP[2,4], E. NAITO[1,3];
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Abstract: Teleoperation requires the brain to map the operator's movements onto the actions of an external effector, whose morphology may or may not correspond to that of the operator's own body. How the anthropomorphicity of this control mapping influences neural processing, independently of the movements performed, remains poorly understood. We used functional magnetic resonance imaging (fMRI) to examine brain activity in 14 participants (mean age 23.6 years; 8 male, 6 female) while they operated (execution conditions) or passively observed robot figures depicted on a screen. The control of the robot is achieved by thumb-index pinch movements. The same movements controlled either a two-finger gripper with a hand-like mapping (anthropomorphic condition -AC) or a two-link arm with a non-corresponding mapping (non-anthropomorphic condition -NAC). In the observation condition, the participants watched a replay of robot movements without controlling them. Reaching the target was faster during AC than NAC control (4.08 vs. 5.24 s, paired t-test, $p < 0.05$). Group-level inference used two-tailed, non-parametric cluster-size FWE correction ($p < 0.05$; cluster-forming $p < 0.001$). The direct comparison between control conditions showed four clusters. Three left-hemisphere clusters showed NAC > AC control: inferior frontal gyrus ([-51, 18, 30]; $t = 7.9$), middle frontal gyrus ([-45, 30, 24]; $t = 6.5$), and lateral occipital cortex ([-36, -72, 33]; $t = 6.3$), where the activity (parameter estimate) for AC was below baseline and NAC control near baseline. The right superior parietal lobule showed the reverse, NAC < AC control ([27, -57, 60]; $t = 7.2$), with activity above baseline in both conditions but more so during intuitive control. The control-by-observation interaction [(NAC control − NAC observation) > (AC control − AC observation)] showed no significant clusters. Increased right superior parietal activity may reflect enhanced visuospatial representations for a body-compatible effector, whereas the occipital differences are more likely attributable to visual differences between the robotic figures. Together, these findings suggest that the anthropomorphicity of the operator-effector mapping influences neural processing during teleoperation and may inform the design of remote-control and assistive robotic systems.

Disclosures: J. Park: None. **E. Oztop:** None. **E. Naito:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.20/LL12

Topic: I.10. Human Learning and Cognition

Title: Sequence-Specific Motor Learning and 24-Hour Retention in Preschool Children: A Preliminary Tablet-Based SRTT Study

Authors: *I. ŠERBETAR, M. KUNJEŠIC SUŠILOVIC;
Fac. of Teacher Educ. Univ. of Zagreb, Zagreb, Croatia

Abstract: Introduction: The serial reaction time task (SRTT) enables assessment of sequence-specific procedural learning by comparing performance in blocks with a repeating hidden sequence and random blocks. **Aim:** This preliminary study examined whether preschool children show sequence-specific motor learning and 24-hour retention in a tablet-based SRTT. **Methods:** Forty-seven children (aged 3-4 years) completed Day 1_PRE, Day 1_POST and Day 2. Reaction time (RT) for correct responses was analyzed using linear mixed-effects models with Timepoint, Block type (sequence/random) and their interaction as fixed effects, and participant as a random intercept. **Results:** Children performed faster across time, especially in sequence blocks (M = 1338 ms at Day 1_PRE, 1203 ms at Day 1_POST and 1140 ms at Day 2). Random-block RTs showed a less consistent decrease (1367, 1325 and 1309 ms, respectively). The overall Timepoint × Block type interaction was not statistically significant, $\chi^2(2) = 4.08$, $p = .130$; however, the random-sequence learning score increased from 29 ms at Day 1_PRE to 122 ms at Day 1_POST and 169 ms at Day 2. The D2 interaction contrast was significant ($b = 140$ ms, $p = .046$), and the learning score was higher at Day 2 than at Day 1_PRE, $t(46) = 2.28$, $p = .028$. Stability and high accuracy were maintained, with no significant Timepoint × Block type interaction, $\chi^2(2) = 2.16$, $p = .340$. Exploratory Day 3-Day 5 follow-up data were available for a smaller subsample and suggested that later retention estimates were variable. **Conclusion**: Findings provide preliminary evidence that preschool children can extract and retain a hidden motor sequence over 24 hours, beyond general task familiarization. Because the primary interaction test was not significant and later follow-up data were incomplete, conclusions should remain cautious. A larger sample and models including sleep/napping status would be necessary to verify consolidation mechanisms more directly.

Disclosures: I. Šerbetar: None. **M. Kunješic Sušilovic:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.21/LL13

Topic: I.10. Human Learning and Cognition

Title: Differentiating Learners and Non-Learners During a Modified Serial Reaction Time Task: Preliminary Evidence Toward Personalized Neurorehabilitation

Authors: *O. SINHA[1], L. A. WHEATON[1], M. R. BORICH[2];
[1]Georgia Inst. Of Technol., Atlanta, GA; [2]Emory Univ., Atlanta, GA

Abstract: Individuals differ widely in their capacity to learn new motor skills, yet neurorehabilitation typically applies uniform treatment strategies. Identifying neurophysiological markers that distinguish learners from non-learners early in training could enable more individualized therapy and improve functional outcomes. Motor-cortical beta-band activity is a promising candidate, as it reflects movement preparation, sensorimotor integration, and early stages of motor learning.To determine whether cortical, behavioral, and oculomotor signatures differ between individuals who acquire an implicit sequence versus those who do not, using a modified Serial Reaction Time Task (mSRTT).Thirty-five healthy adults performed a mSRTT in which a 7-element sequence of block movements was repeated for 525 trials. Behavioral response times, EEG (64-channel), and eye movements were recorded. At the end of the task, participants completed an explicit recall test of the 7-element sequence. For this preliminary analysis, we categorized participants who correctly recalled all 7 elements as “explicit learners” (EXP; n=3) and those who recalled none as “non-learners” (NOEXP; n=3). Spectral analysis focused on beta-band (13-30 Hz) power during movement initiation was conducted.Preliminary results show clear behavioral and neurophysiological separation between EXP and NOEXP groups. EXP participants exhibited faster response times across sequence blocks, suggesting early sequence acquisition. Eye-tracking revealed higher probability of fixation (EXP: $M=0.84\pm0.04$; NOEXP: $M=0.2\pm0.06$) towards the expected sequence in EXP participants, indicating more efficient visuomotor sampling. Critically, beta-band power over motor cortex in EXP participants showed significantly ($p<0.05$) more suppression compared to NOEXP participants. These beta signatures emerged in the earliest phases, indicating learning (i.e, before the emergence of faster response times), suggesting that cortical markers of learning appear prior to behavioral evidence of learning. Motor-cortical beta activity may serve as an early biomarker of motor learning capacity, distinguishing learners from non-learners even before behavioral or explicit recall differences fully emerge. Ongoing work will evaluate participants with partial recall to determine whether beta power scales continuously with learning. These findings support the potential of EEG-based markers and eye tracking to guide personalized neurorehabilitation by tailoring therapy to an individual’s learning profile.

Disclosures: O. Sinha: None. **L.A. Wheaton:** None. **M.R. Borich:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.22/LL14

Topic: I.10. Human Learning and Cognition

Support: University of New Hampshire Summer Teaching Assistant Fellowship (STAF)

Title: Sensing the Stress - Evaluating Perceptive Task Performance Under Increasing Extraneous Load

Authors: *S. M. WALSH, S. HAARALA, K. L. CHRISTISON-LAGAY;
Biol. Sci., Univ. of New Hampshire, Durham, NH

Abstract: Our ability to cognitively process incoming information and demands at a given time is finite. Perceptual bottlenecks and limitations on processing speed and working memory constrain our capacity to perceive, cognitively manipulate information, and engage appropriate decision making and planning. As cognitive load increases, performance begins to suffer across domains. Importantly, cognitive load is determined by not just incoming information or task demands, but also by internal factors, such as stress and arousal. These internal states seem to consume cognitive resources that could otherwise be allocated to task demands. For example, fatigue is widely acknowledged to impair performance, and stress is associated with mental blocks during interviews or exams. However, while the effect of stress on memory and recall has been extensively studied, less is known about how stress may differentially affect performance and processing in multimodal environments that better reflect the complexity of real-world experiences. Given the increasing prevalence of self-reported stress among adults, understanding whether stress exerts uniform or domain-specific effects on cognitive processing represents an important unresolved question. Here we present a novel behavioral paradigm designed to evaluate participants' ability to maneuver through a dynamic maze which progressively increases in difficulty through added layers of visual, auditory, motor, and executive demands. Manipulations include changes in navigation rules, shifting visual features, and auditory target-detection criteria, requiring participants to continuously allocate attention across multiple modalities while maintaining goal-directed behavior. Pupillometry is used as a physiological measure of cognitive effort and arousal while performance is quantified by reaction time and accuracy in responses across task components. At the beginning of the study, participants' complete a self-report questionnaire to assess their current level of stress. Following completion of the initial session, participants are invited to return at a later date when their self-assessed stress is in a different state, thus allowing both within and across participant comparisons across naturally varying stress states.

Disclosures: S.M. Walsh: None. **S. Haarala:** None. **K.L. Christison-Lagay:** None.

Poster

PSTR157: Neural and Behavioral Mechanisms of Choice in Humans

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR157.23/LL15

Topic: H.02. Reward and Appetitive Learning and Memory

Support: MOST 110-2410-H-002-126
NSTC 113-2423-H-002-011
NSTC 113-2410-H-002-269
NSTC 113-2321-B-006-014

Title: Eudaimonic and Hedonic Rewards Differentially Modulate Neurobehavioral Processing of Cognitive Task Under Stress

Authors: *Y. FU, J. GOH;
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Abstract: Studies suggest that prospective rewards can buffer task-related mental stress and thereby enhance psychological resilience. However, the neural mechanisms underlying how distinct types of rewards modulate stress responses during online cognitive processing remain unclear, limiting applications for mental health. To address this gap, this study investigated how hedonic (self-oriented) versus eudaimonic (prosocial) rewards influence brain activity during the stressful math solving task (SMST). In this functional magnetic resonance imaging (fMRI) experiment, 36 participants (19 females, mean (SD) age = 22.18 ± 1.55 (yrs)) solved arithmetic problems under (a) no time constraints, (b) time pressure with score ranking (non-incentivized), (c) time pressure with performances linked to charity donations (eudaimonic reward), and (d) time pressure with remunerated performances (hedonic reward). With eudaimonic rewards, arithmetic calculation accuracies were higher and self-reported stress levels were lower, compared to the case with non-incentivized pressured performance. Critically, neural responses increased in the anterior cingulate cortex and declined in the default mode network (DMN) during incentivized relative to non-incentivized task performance. In addition, neural responses in the putamen were highest during non-incentivized pressured processing, followed by performance with hedonic reward, then performance with eudaimonic reward, and were lowest under the non-constrained case. These findings suggest that eudaimonic rewards are effective motivators for circumventing stress-related effects induced by task demands. Moreover, the provision of different task reward types modulates activity in corticostriatal and DMN regions implicated in value-based and self-related processing, respectively. Having non-self-centric motivations might afford more resilient neurocomputational strategies in these brain areas that bypass stressful reactions when facing challenging problems in life.

Disclosures: Y. Fu: None. **J. Goh:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

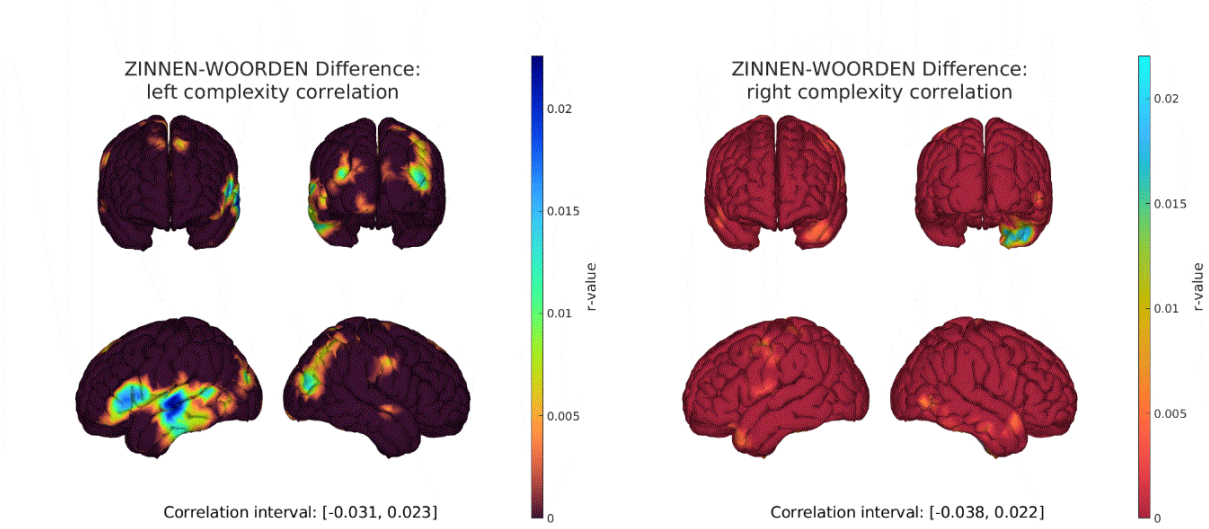
Program #/Poster #: PSTR158.01/LL16

Topic: I.11. Language

Title: Neural Bases of Syntax: Evidence from Magnetoencephalography

Authors: *J. YU[1], M. RIESENHUBER[2], P. CHO[3];
[1]Georgetown Univ., Washington D.C., DC; [2]Dept Neurosci, Georgetown Univ. Med. Ctr., Great Falls, VA; [3]Duke Univ., Durham, NC

Abstract: Numerous neuroimaging studies have been published to tackle the question of syntax processing in the brain, the majority of them being based on functional magnetic resonance imaging (fMRI) data. However, with fMRI's poor temporal resolution, it is not possible to capture the dynamics of how the brain performs syntactic processing of a sentence, given that sentences are processes at time scales much faster than the hemodynamic response. We performed a re-analysis of magnetoencephalography (MEG) data of N=55 adults processing spoken Dutch sentences (MOUS dataset, Schoffelen et al., 2019), allowing for temporally precise comparisons between reconstructed neural activity and dynamically—varying metrics of syntactic complexity, which were determined by calculating the number of simultaneously open syntactic dependencies, as performed in the fMRI study performed on the same dataset (Uddén et al., 2022). Since Dutch naturally contains both left-branching and right-branching structures, separate measures of complexity were determined for each. Whole-brain searchlight analyses of sentence conditions (ZINNEN) minus matched randomized wordlists (WOORDEN) revealed that instantaneous left-branching syntactic complexity correlated most strongly with activation in the left middle MTG and STG, as seen in Figure 1. Although right-branching complexity correlations returned weaker r-values overall, they nonetheless demonstrated syntactic localization in the left ATL. These results provide the first temporally precise evidence of word-level syntactic unification regions and establish a framework for future studies analyzing the temporal dynamics and information flow of syntactic processing in the human brain.



Disclosures: J. Yu: None. **M. Riesenhuber:** None. **P. Cho:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

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Program #/Poster #: PSTR158.02/LL17

Topic: I.11. Language

Support: National Science and Technology Major Project of China (2025ZD0217000)
National Natural Science Foundation of China (32371154)
Lin Gang Laboratory (LG-GG-202402-06)

Title: Multiband intracranial neural dynamics reveal convergence from visual script processing to articulation in logographic and alphabetic reading

Authors: *P. YANG[1], Z. WANG[1], J. LU[2], Y. LI[1];
[1]Sch. of Biomed. Engin., ShanghaiTech Univ., Shanghai, China; [2]Huashan Hosp., Shanghai, China

Abstract: Overt reading requires visually distinct written forms to be transformed into spoken output. Chinese characters and Pinyin provide a within-language contrast between a logographic script and an alphabetic phonetic system, allowing us to examine how distinct visual inputs converge onto matched spoken words. We recorded high-density intracranial electrocorticography (ECoG) from nine participants reading Pinyin and matched Chinese characters aloud to examine how multi-band cortical activity differentiates visually distinct scripts and converges toward shared articulation. Character and Pinyin reading recruited a broadly overlapping reading-production network, but showed frequency- and region-specific differences during early visual processing. Character reading preferentially involved theta-band activity in temporal cortex, whereas Pinyin reading more strongly involved beta-band activity in dorsal frontal and precentral regions. Electrodes responding to both scripts emerged in two main convergence responses after visual input and near articulation onset. Continuous tracking revealed frequency-dependent convergence dynamics: alpha- and beta1-band activity showed greater continuity between the early and late shared responses, whereas the late high-gamma response was largely formed by electrodes that were not shared after visual input. Cross-script temporal generalization further showed that these commonly engaged neural populations carried script-general representations rather than merely reflecting visual or task-evoked responses. These representations were closely related to phonological and semantic features, indicating that convergence was organized around shared linguistic features. Representational similarity analysis further showed that feature-significant shared electrodes had limited electrode-level continuity between the early and late convergence responses. This reorganization was clearest in high gamma, where early shared electrodes preferentially supported orthographic information and later shared electrodes preferentially supported phonological information; these two feature-significant electrode sets were largely distinct, although they occupied partially overlapping cortical regions. Together, these results indicate that logographic and alphabetic reading processes converge onto spoken output through dynamic band-specific reorganization within an overlapping reading-production network.

Disclosures: P. Yang: None. **Z. Wang:** None. **J. Lu:** None. **Y. Li:** None.

Poster

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Topic: I.11. Language

Support: NIH Grant R01DC012379
Susan and Bill Oberndorf Foundation
William K. Bowes, Jr. Foundation
Feldman Foundation

Title: Phonological representations underlying reading in the human superior temporal gyrus

Authors: *M. K. LEONARD[1,2], T. L. SCOTT[1,2], E. F. CHANG[1,2];
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Abstract: When we read, we are mapping visual input onto a language that is initially learned through speech. While there is evidence that we can access phonological representations during reading, the neural mechanisms of this process remain a mystery. Here, we used direct high-density cortical recordings to compare neural responses during naturalistic sentence reading and listening. We found that neural populations in the middle superior temporal gyrus (mSTG) have strong evoked responses to both written and spoken words, distinct from neural populations that are modality-specific. Within this shared population, reading activity is longer latency and lower amplitude compared to modality-specific populations. During reading, activity in mSTG shared populations encodes of phonological features that reflect an explicit mapping between sound and letter combinations. Compared to reading-only populations, shared populations have more specific and tightly-tuned representations, suggesting a unique role in mapping phonology and orthography. Furthermore, a subset of the shared neural population has the same phonological representations during reading and listening (e.g., tuning to acoustic-phonetic features like fricatives or high-front vowels), demonstrating a specific component of reading that is grounded in phonological decoding. Finally, we use a model of phonology-orthography mapping statistics in English to show that shared and reading-only neural populations perform phonological decoding during reading, while reading-only populations also track orthographic decoding features (i.e., spelling). Together, these results demonstrate that proficient reading in orthographically opaque languages like English relies on explicit mapping to sound-based representations, providing direct evidence for the importance of phonics-based curricula in reading education.

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Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.04/LL19

Topic: I.11. Language

Support: NIH Grant T32 NS047987
RF1NS125026

Title: Functional Network Signatures Identify Cortical Sites Critical for Speech and Language

Authors: *B. BAC[1], R. D. FLINT, III[2], T. PARRISH[1], M. C. TATE[1], N. E. CRONE[3], R. BETZEL[4], M. W. SLUTZKY[2];
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Abstract: Speech and language are complex processes involving multiple brain networks. Direct electrocortical stimulation (ECS) identifies cortical sites "critical" for these functions to guide resection and reduce post-operative deficits. Yet the network properties that distinguish cortical sites critical for speech and language from non-critical ones remain elusive. Our recent work using electrocorticography (ECoG) suggests that critical sites occupy distinct roles within functional networks. However, ECoG arrays capture only regional cortical coverage unlike functional magnetic resonance imaging (fMRI), which enables network analysis across the entire brain. We therefore hypothesized that critical sites exhibit distinct fMRI-derived functional network signatures. Eighteen participants with epilepsy or brain tumors performed five language tasks during fMRI: antonym, reading comprehension, rhyming, silent word generation and picture naming. Network nodes comprised electrode sites within each participant's ECoG grid and parcels from the 1000-node Schaefer atlas; edges were correlations of fMRI activity between node pairs. Critical electrode sites were defined as language error (LE) or speech arrest (SA) sites. We compared six network metrics between critical and non-critical sites: local efficiency (*Eloc*), clustering coefficient (*CC*), strength, eigenvector centrality (*EC*), participation coefficient (*PC)* and gateway coefficient (*GC*). Next, we examined the metrics' anatomical distribution averaged across participants. Finally, we used all six metrics to train support vector machines and balanced random forests to predict criticality. Critical sites exhibited significantly lower local (*CC*, *Eloc*) and global connectivity (*EC*, strength) than non-critical sites. LE sites also had significantly higher inter-subnetwork connectivity (*PC, GC*) than SA and non-critical sites. Further, connector sites (high *PC*) were concentrated primarily in temporal cortices. Finally, these metrics predicted critical sites significantly above chance. Rather than serving as local or global hubs, critical sites are less connected overall than non-critical sites. Sites critical to higher language function also act as connectors across functional subnetworks. The concentration of connector sites in temporal regions highlights the temporal lobe's role in linking speech and language subnetworks. By characterizing network signatures of critical sites and regions across the whole brain, we provide a framework for predicting cortical sites critical for speech and language function and greater understanding of the effects of ECS on the language network.

Disclosures: B. Bac: None. **R.D. Flint:** None. **T. Parrish:** None. **M.C. Tate:** None. **N.E. Crone:** None. **R. Betzel:** None. **M.W. Slutzky:** None.

Poster

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Program #/Poster #: PSTR158.05/LL20

Topic: I.11. Language

Support: NIH R21 MH135314

Title: Robust electrophysiological measures of the effects of prior knowledge on the perception of degraded speech

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Abstract: Perception is the process by which sensory input is organized and interpreted in a behaviorally relevant manner, shaped by memory, experience, and contextual information. Within a Bayesian inference perspective, perception is understood as a probabilistic process in which uncertain sensory evidence is combined with prior knowledge to generate the brain's best estimate of the causes of sensory input. Degraded speech paradigms such as noise-vocoded speech provide a useful framework for studying this process because the perceived clarity of ambiguous acoustic signals can be systematically influenced by preceding contextual information. Neurophysiological studies of this phenomenon have primarily focused on how it affects neural indices of low-level sensory encoding. These indices tend to show small-and often inconsistent-effects that do not mirror the dramatic behavioral enhancement that comes with prior information. We recorded EEG from 27 healthy adult participants where in each trial, they first viewed a written sentence that either matched or mismatched the subsequent vocoded speech sentence, then provided a subjective intelligibility rating of the vocoded speech sentence. The matching text priors led to a large "pop-out" effect when listening to degraded speech. Separate analyses of the resulting EEG revealed: 1) significant - but relatively weak - effects of prior information on the sensory and linguistic encoding of the speech; and 2) a robust centroparietal positivity (CPP) - like signal at channel Pz, with significantly greater mean amplitude for match trials than mismatch trials. This CPP-like amplitude also scaled with subjective intelligibility: higher perceived clarity was associated with larger Pz amplitudes. These signals likely relate to separate components of a Bayesian inferential process during the predictive perception of degraded speech. Although the task was not optimized to isolate a traditional response-locked CPP, the observed pattern is consistent with prior-facilitated accumulation of sensory evidence during vocoded speech comprehension. Broadly, these findings also have implications for understanding predictive perception in general and provide a foundation for future work on individual differences in prior-guided perceptual inference in clinical populations.

Disclosures: W. Li: None. **S. Synigal:** None. **J. Thompson:** None. **E.C. Lalor:** None.

Poster

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Topic: I.11. Language

Support: NIH RF1NS125026

Title: Cortical sites critical to speech and language function have distinctive static and dynamic network properties

Authors: *R. D. FLINT[1], J. K. HSIEH[1], P. R. PRAKASH[1], N. E. CRONE[3], J. W. TEMPLER[1], T. PARRISH[1], M. C. TATE[1], R. BETZEL[4], J. D. GREENLEE[5], M. W. SLUTZKY[2]; [2]Neurol., [1]Northwestern Univ., Chicago, IL; [3]Neurol., The Johns Hopkins Univ., Baltimore, MD; [4]Dept. of Psychological and Brain Sci., Univ. of Minnesota, Minneapolis, MN; [5]Dept Neurosurg, Univ. of Iowa, Iowa City, IA

Abstract: Electrocortical stimulation (ECS) mapping identifies focal brain areas that are "critical" for speech and/or language prior to clinical resection procedures. ECS has been standard-of-care for decades, yet it is imperfect, and the mechanism of its effects remains in question. The behavioral impacts of ECS could be mediated by either local disruption of cortex or network-based changes in speech and language circuits. We investigated functional cortical networks' role in a speech task (word reading) by recording electrocorticography (ECoG) in frontal, temporal, and parietal areas of human participants. We extracted high-gamma (70-200 Hz) as a proxy for local synaptic potential activity, and described functional networks by computing pairwise correlations between all electrodes. We employed graph theory methods to quantify the network modulations that accompany speech/language behaviors. In particular, we investigated differing timescales, including static (several minutes) and dynamic (<1s sliding windows) patterns of network connectivity.

Static network properties, measured during entire speech behavior sessions, enabled accurate differentiation of speech arrest and language error sites on cortex from non-critical sites. Overall connectivity (global and local) was lower in critical sites, and language error sites in particular showed an increased role as connectors between subnetworks.

Dynamic network changes occurred on the timescale of the behavior itself, and often deviated substantially from static network profiles. Transitions from rest to task engagement, or the onset of speech, modulated network connectivity within and between local subnetworks.

These results suggest that the pattern of connectivity between a given location in the language network helps determine its importance to language function. Further, these network patterns change dynamically and asymmetrically during behavior. This highlights the importance of examining brain activity during active behavior, at the resolution of the behavior itself, in addition to resting state analysis.

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Poster

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Topic: I.11. Language

Support: Undergraduate Research Grant- Psi Chi: The International Honor Society in Psychology
Undergraduate Research Fellowship- Texas State University

Title: Differences in electrocortical activity during inner vs. spoken speech production.

Authors: *E. ZATORSKI[1], R. GRAHAM[2], M. MILBY[1], E. SCHULZ[1];
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Abstract: Understanding how inner speech is manifested electro-cortically is important for the development of brain-computer interfaces for communication, as well as gaining insight into disorders where inner speech is disrupted/misattributed. This study examined similarities and differences between event-related potentials (ERPs) during inner vs spoken speech preparation and production. Thirty-five Texas State University students (28 females; mean age: 19) first viewed a response preparation cue (inner vs. spoken), followed by a word that they either spoke inwardly or aloud, depending on the cue. Current analyses focused on ERP amplitudes obtained during speech production. ERPs were quantified in 50-millisecond (ms) windows from 150-350 ms over frontal, central, and posterior sites as a function of laterality (left, middle, right). Analyses indicated that changes in response began in the initial 150-200 ms epoch, exemplified by larger positive amplitudes associated with inner speech in the posterior medial regions. Differences then plateaued in the 200-250 ms epoch, followed by larger positive amplitudes in the central medial regions during inner speech in the 250-300 ms epoch. Conversely, larger positive amplitudes in the left frontal regions during overt speech were also measured in this epoch, consistent with the location of Broca's area. Significantly larger positive amplitudes during overt speech conclude in the final epoch, 300-350 ms, in the central right regions and posterior medial and right areas. Interestingly, negativity for overt speech was simultaneously measured, beginning in the left posterior regions during the 250-300 ms epoch, and expanding to the left central regions in the 300-350 ms epoch. Finally, larger negative amplitudes associated with inner speech were measured in the posterior medial region during the 300-350 ms epoch. In summary, there seems to be a continuous transition to extreme polarity during overt speech production compared to inner speech production, somewhat consistent with previous findings. Although tentative, results provide evidence of dissociable electrocortical signatures of brain

activity for inner and spoken speech production. Exploring these interactions within their clusters will enrich preliminary findings.

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Poster

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Program #/Poster #: PSTR158.08/LL23

Topic: I.11. Language

Support: KAKENHI JP 23K21851

Title: Semantic Priming Reconstructs Conceptual Similarity Networks in the Human Brain

Authors: *Y. UESUGI[1,2], S. IWAKI[1,3];
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Abstract: Semantic associations define relationships between real-world concepts (e.g., “yellow-lemon,” “researcher-science”), forming structured representations in the brain. While prior studies have characterized these large-scale representations, it remains unclear how they are dynamically updated during ongoing semantic processing. One well-established phenomenon reflecting such dynamic processing is semantic priming, in which responses to a target stimulus are facilitated when it is preceded by a semantically related stimulus (prime). In this study, we used semantic priming to examine structural changes in the organization of brain-represented semantic association. Forty-three right-handed Japanese participated in the fMRI scanning. In each trial, a word or nonword (control) was presented as a prime, followed by a scene image containing multiple objects. Each prime word was semantically related to one of the objects in the subsequent image. For analysis, object-specific brain activity was estimated for each of the 41 objects. Regions of interest (ROIs) included the left posterior middle temporal gyrus (pMTG), inferior frontal gyrus (IFG), and presupplementary motor area (preSMA), associated with semantic control, as well as the left anterior temporal lobe (ATL) and angular gyrus (AG), related to semantic representation (Jefferies et al., 2020; Gao et al., 2023). Semantic similarities between objects were evaluated by computing the cross-validated mahalanobis distance between brain activity patterns to construct a conceptual similarity network, where higher similarity defined stronger links. We characterized the resulting networks calculating graph-theoretical metrics, including clustering coefficient, path length, and modularity, and compared them between priming and control conditions. Preliminary results showed that semantic priming came to decreased clustering in pMTG, decreased clustering and increased path length in ATL, and decreased modularity in AG and preSMA. These findings suggest that priming tends to fragment the semantic similarity network, not only in regions responsible for context-dependent semantic

control but across the whole semantic system. However, substantial individual differences were observed, with participants showing either increases or decreases in graph-theoretical metrics. Thus, while priming reconstructs semantic associations, the nature of these changes varies across individuals. E. Jefferies et al., Philos. Trans. R. Soc. B Biol. Sci., 375(1791), 2020. Z. Gao et al., Cereb. Cortex, 33(1), 152-166, 2023.

Disclosures: Y. Uesugi: None. **S. Iwaki:** None.

Poster

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Topic: I.11. Language

Support: NIDCD R01DC020483A

Title: Spatiotemporal dynamics and age-related changes in language production revealed by magnetoencephalography

Authors: *Y. WEI[1], P. LOGANATHAN[2], L. SLEVC[3], Y. FAROQI-SHAH[1], C. BRODBECK[4]; [1]Dept. of Hearing and Speech Sci., [2]Dept. of Electrical and Computer Engin., [3]Dept. of Psychology, Univ. of Maryland, Col. Park, College Park, MD; [4]Dept. of Computing and Software, McMaster Univ., Hamilton, ON, Canada

Abstract: Fluent sentence production relies on the precise and timely coordination of lexical retrieval, morphosyntactic planning, and motor execution. A left-dominant fronto-parieto-temporal network has been identified for these subcomponents of sentence production, but less is known about the temporal dynamics of their engagement (e.g., whether the engagement of neural regions is simultaneous or sequential). While age-related changes in language production and speech rate have been documented, the neural mechanisms underlying these changes are understudied. The aim of the present study was to 1) delineate spatiotemporal patterns of subcomponents activation during sentence production, namely lexical retrieval, inflection, and constituent assembly, 2) identify age-related variation across these processes.
Concurrent magnetoencephalographic (MEG) and electromyography (EMG) responses were measured using a novel picture-icon paradigm. In this task, overt verbal responses were elicited using object or action pictures, followed by an icon indicating the required subcomponent sentence processes: lexical access, inflection (plurals for nouns, tense for verbs), and constituent assembly (adjective + object or pronoun + action). MEG data from twenty native English-speaking right-handed neurotypical younger adults and two older adults (data collection is ongoing) were analyzed using both stimulus-locked and response-locked time windows. Analysis focused on left hemisphere speech-language regions of interest (ROI): precentral gyrus (M1), inferior frontal gyrus (IFG), anterior temporal lobe (ATL), posterior temporal lobe (PTL), and inferior parietal lobe (IPL).

Results from younger adults showed: 1) early and largely simultaneous engagement of ROIs for lexical access and certain morphosyntactic processes; 2) greater activation for noun morphosyntactic planning across multiple ROIs compared to noun lexical access, with more heterogeneous activity pattern observed between morphosyntactic planning of verbs and verb lexical access. 3) coactivation of M1 with other ROIs, suggesting simultaneity of language and motor planning. Preliminary observations from a limited sample of older adults suggest that the present approach may be sensitive to age-related variation in activation patterns. However, additional data are required to evaluate these effects. Together, these findings support a partially parallel model of sentence production and suggest that aging may be associated with differences in the coordination of these subprocesses.

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Poster

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Topic: I.11. Language

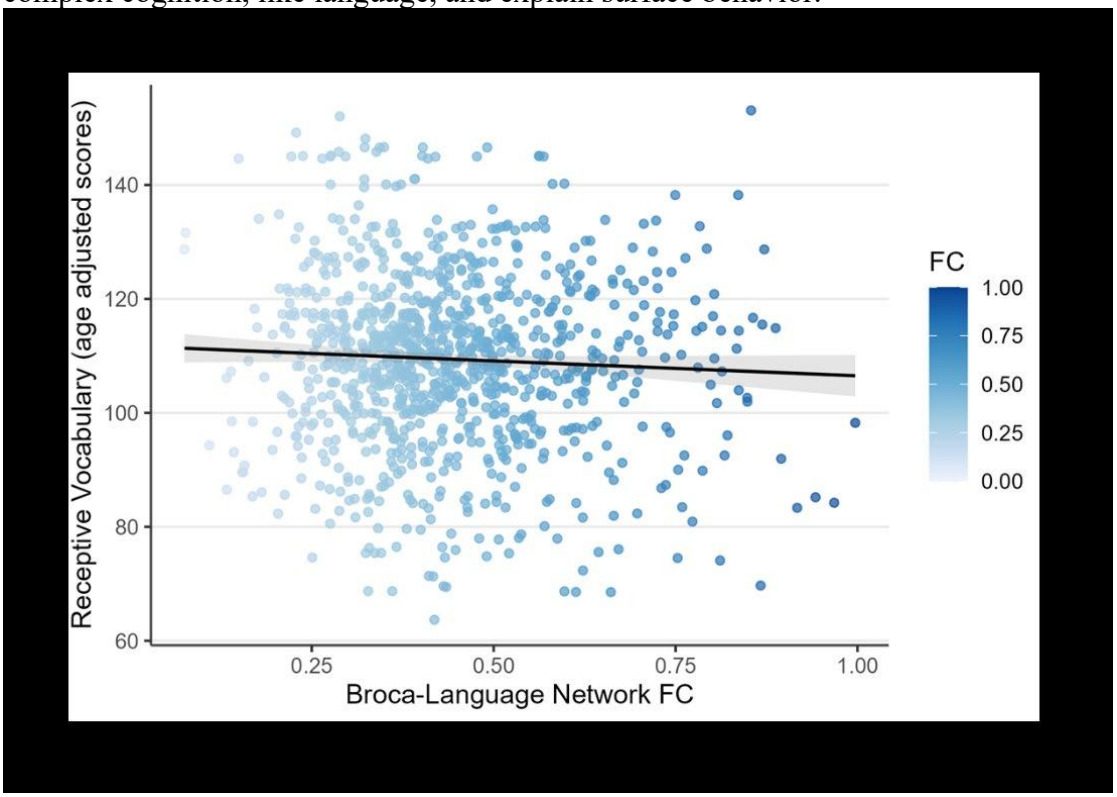
Support: NIDCD T32DC017703
NIMH R01MH112687
University of Missouri Startup Funds

Title: Lateralization is not a fundamental characteristic of language network connectivity

Authors: *C. LARSON[1], J. CRUTCHER[2], **J. BAILEY**[1], H. THOMAS[3], I.-M. EIGSTI[4], M. STEVENS[5];
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Abstract: Background. Lateralization of brain function is viewed as a fundamental characteristic of the brain, yet there is mounting evidence suggesting that theories of lateralization are too simplistic. There is a critical gap in the literature on the degree to which task-elicited functional connectivity (FC) is lateralized and how lateralization in general is associated with behavior. The current study addressed this gap by analyzing lateralized FC in the context of language, drawing on data from the Human Connectome Project. **Methods.** We tested seed-based and within-network FC elicited by the Human Connectome story recall language task. Seed regions were Broca and Wernicke and language network regions were frontal, temporal, and global semantic regions (Baker et al., 2018; Briggs et al., 2018). Generalized linear models tested whether FC was significantly lateralized, and significantly associated with out-of-scanner language behavior, over and above nonlinguistic behavior. All models were tested using a discovery (n = 507) and

replication *(n* = 508*)* approach in a sample of healthy non-language-impaired adults ages 22-36 years old. **Results.** Results indicated inconsistent patterns of lateralized FC and few associations with behavior. FC within the language network was stronger in the *right hemisphere*, and FC between Wernicke and the language network was significantly lateralized to the left hemisphere. Additionally, relatively weaker(non-lateralized) FC between Broca and the language network was associated with *better* language behavior (receptive vocabulary; Figure 1). **Conclusions.** This study demonstrated that lateralization does not appear to be a fundamental characteristic of *brain networks* in the manner hypothesized based on brain structure and brain activation. In fact, our findings highlight the critical nature of examining distributed brain networks to understand complex cognition, like language, and explain surface behavior.



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Poster

PSTR158: Language: Neural Circuits and Mechanisms II

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Support: NIH R01 DC014960
NIH R01 DC016902

Title: The development of the language network functional connectivity across age

Authors: *N. VLADYKO[1], P. E. TURKELTAUB[2,3], W. GAILLARD[4], E. L. NEWPORT[1,3]; [2]Neurol., [1]Georgetown Univ. Med. Ctr., Washington, DC; [3]MedStar Natl. Rehabil. Hosp., Washington, DC; [4]Children's Natl. Hosp., Washington, DC

Abstract: In the adult brain, language processing relies on a left-lateralized network. When the left hemisphere (LH) language network (LN) is disrupted early in life, for example, after a perinatal stroke, the right hemisphere (RH) can support language without deficits (Newport et al.,2022). In contrast, adult strokes show only partial recovery and persistent aphasia. How does LN organization differ between developmental periods when RH language development is possible versus constrained? We hypothesized that robust LH language connectivity has not yet consolidated in early life and that the trajectory of its maturation over age should correspond to the developmental window in which post-stroke RH reorganization remains possible.We examined LN functional connectivity (FC) in four developmental cohorts: infants (n=54, 0-6 months), toddlers (n=61, 2-3years), children (n=111, 9-11 years), and adults (n=154, 18-22 years). Data for infants and toddlers came from the Baby Connectome Project, data for children and adults came from the Human Connectome Project Development. Data were acquired during rest or movie watching. After preprocessing, we calculated FC between 246 regions of the Brainnetome atlas (Fan et al.,2016). To define LN, we used the Neurosynth meta-analysis map of studies with a key phrase 'language comprehension.' The LH parcels overlapping the map and their RH homotopes were included in the LN. We then tested the hemispheric asymmetries using edgewise t-tests within the LN (91 total). All results were corrected for multiple comparisons.Within the adult LN, we observed a clear LH bias: among 91 LN edges, 41 were stronger in the LH and 5 in the RH ($\chi^2(1)= 28.17, p<.001$). Similarly, children showed 24 LH-biased and 9 RH-biased edges ($\chi^2(1)=6.82, p=.009$). Crucially, this pattern of LH-dominant FC was not present in early life. In infants, the proportion of strong connections did not differ between the hemispheres (4LH and 9RH, $\chi^2(1)=1.9, p=.17$). Toddlers showed a significant RH-bias in FC (3LH and 17RH, $\chi^2(1)=9.80, p=.002$). In addition, the adult and child brain showed strong frontotemporal FC in both hemispheres, whereas in infants and toddlers such FC was weak.Our findings suggest a developmental shift in the number of strong LH LN connections. In early life, LN FC has not yet reached an adult-like state. With maturation, FC within the LH LN strengthens, driven by the strengthening of frontotemporal FC, thus forming a more specialized and efficient language-processing network. We believe that this developmental change may affect the RH's capacity to take on language after stroke, a hypothesis we are investigating in ongoing work on early and later childhood stroke.

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Poster

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Topic: I.11. Language

Support: NIH R01 NS129703

Title: Multimodal Sensory-Motor Transformations for Speech

Authors: *A. MAJUMDAR[1], A. EARLE-RICHARDSON[2], G. A. GRANT[3], S. C. HARWARD[1], B. FRAUSCHER[3], D. G. SOUTHWELL[4], G. B. COGAN[5];
[2]Neurosurg., [1]Duke Univ., Durham, NC; [3]Duke Univ., Duke University, NC; [4]Neurosurg. and Neurobio., [5]Dept. of Neurosurg., Duke Univ., Durham, NC

Abstract: Auditory and motor systems are tightly coupled in speech perception and production through sensory-motor transformations. In language production, auditory feedback supports monitoring and error correction, while the motor system is thought to contribute to perception by engaging articulatory representations of heard sounds. Since the primary modality for language is auditory speech, these sensory-motor transformations may be mediated by a specialized auditory circuit rather than a general system for all input modalities. However, language input from other visual modalities such as images or written words can also access internal representations and elicit spoken responses, suggesting that visual input may access overlapping or parallel pathways to support speech production. Therefore, it is possible that speech-related sensory-motor circuits may be multimodal, but the nature of this overlap remains unclear. We hypothesized that sensory-motor speech circuits differ by modality, with auditory to motor pathways serving as the primary route. To test this, we recorded intracranial electroencephalography (iEEG) from 32 subjects (mean age = 34, 14 female) during epilepsy monitoring for surgical intervention as they performed a delayed multimodal repetition task. A set of 4 words was presented as spoken words, images, or written text. Electrodes with significant increases in high-gamma activity (HG - 70-150 Hz) relative to baseline were identified and classified as sensory, motor, or sensory-motor, and as either modality common (responsive to auditory and visual input) or modality specific (responsive to auditory or visual input). Within the sensory-motor network, we identified distinct auditory-specific, visual-specific, and modality-common electrodes. Consistent with a privileged auditory pathway, auditory-specific sensory-motor electrodes were more numerous and exhibited earlier, stronger responses than visual-specific electrodes. Modality-common electrodes displayed intermediate response profiles. Decoding analyses revealed stimulus-specific representations within sensory-motor networks. Auditory and image stimuli were decoded from both modality-specific and modality-common networks, whereas written-word stimuli were decodable only within the modality-common network. Complementary representational similarity analyses support the presence of both modality-specific and -general processes within sensory-motor networks. Together these findings suggest that speech-related sensory-motor transformations are mediated by both distinct modality-dependent pathways and shared modality-general mechanisms.

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Poster

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Program #/Poster #: PSTR158.13/LL28

Topic: I.11. Language

Title: Non-invasive EEG decoding of word-level imagined speech

Authors: *H. WANG[1], P. H. LUCKETT[2], E. C. LEUTHARDT[3], B. T. ACLAND[4]; [1]Washington Univ. in st. Louis, St. Louis, MO; [2]Dept. of Neurolog. Surgery, Washington Univ. Sch. of Med., Saint Louis, MO; [3]Neurosurg., Title (Optional), St. Louis, MO; [4]Washington Univ. in St.Louis, Saint Louis, MO

Abstract: Internally generated speech engages neural systems for speech planning and language, but word-level imagined speech remains difficult to study non-invasively because EEG signals are noisy. We tested whether the identity of an imagined word could be decoded from scalp EEG during a cued covert speech task. Participants performed imagined production of eight words (kick, open, throw, stop, clap, jump, yes, no) and a matched no-speech control condition while 28-channel EEG was recorded. Event-aligned EEG trials were preprocessed and used to train neural-network decoders to identify which word — or the control condition — had been imagined on each trial. Decoding accuracy approached 80% for the nine-way word/control classification, well above the 11.1% chance level. Channel- and time-resolved analysis indicated that the most informative recording sites and time windows differed across imagined words, suggesting partially distinct neural evidence for different speech targets. Together, these findings indicate that imagined speech generates reproducible, word-specific neural structure that can be captured non-invasively and decoded at the word level. The representational basis of this structure is the focus of ongoing analyses.

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Program #/Poster #: PSTR158.14/LL29

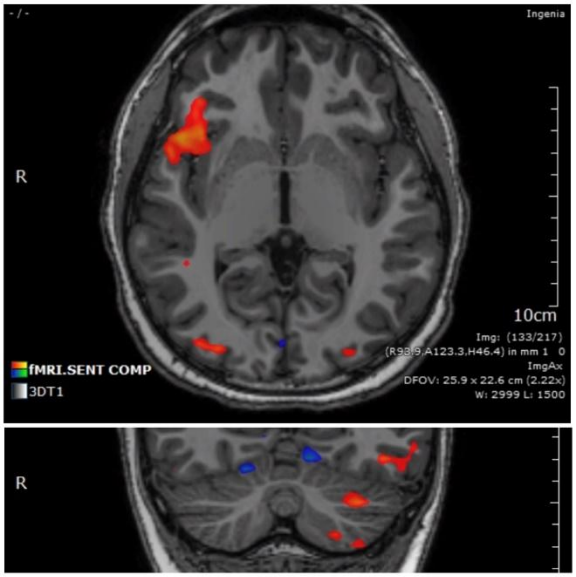
Topic: I.11. Language

Title: Mapping Cerebellar Language Networks with Functional MRI: Insights from Healthy Controls and Brain Tumor Patients

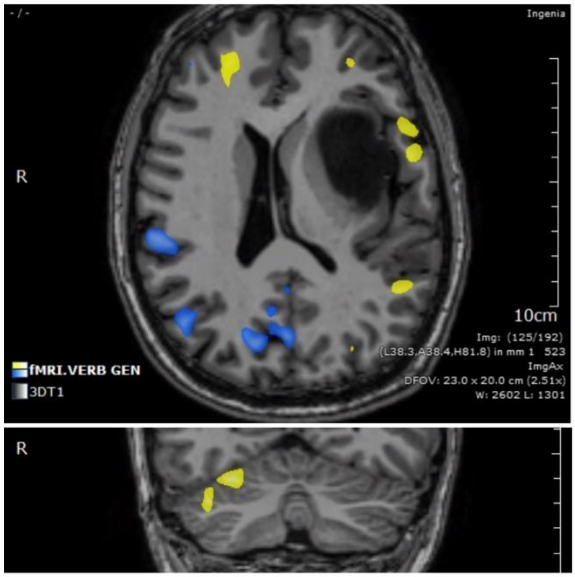
Authors: *C. R. LEDBETTER;
Neurosurg., Louisiana State Univ. Hlth. Sci. Ctr. Shreveport, Shreveport, LA

Abstract: Although language is traditionally associated with left-hemisphere cortical regions, the cerebellum is increasingly recognized as a component of distributed language networks. Because cerebro-cerebellar pathways are predominantly crossed, cerebellar language activation is typically observed contralateral to dominant cortical language regions. Brain tumors involving language cortex provide a unique model for investigating the stability and reorganization of these networks in the presence of cortical displacement and language dysfunction.Controls (n=12) and patients with frontal, temporal, or parietal lobe tumors (n=40) underwent task-based functional MRI (fMRI) language mapping that included word generation, verb generation, and sentence completion paradigms. Data were analyzed with DynaSuite Neuro, SPM, and AFNI. A multiple case series design examined cerebellar language organization across patients with aphasia, atypical language lateralization, and cortical displacement.Controls demonstrated robust cerebellar activation within Crus I and II and in Lobule VIIb contralateral to dominant language cortex. Tumor patients without language impairment exhibited similar activation patterns despite substantial anatomical distortion. Patients with aphasia frequently demonstrated expanded cortical activation, including bilateral recruitment of language regions, accompanied by bilateral activation within cerebellar Crus I. Among left-handed patients, individuals with right-hemisphere language dominance demonstrated left cerebellar activation (1A). Notably, cerebellar activation remained relatively stable even in cases with marked cortical displacement (1B).These findings suggest that cerebellar language networks maintain contralateral organization while participating in adaptive language reorganization. Preservation of cerebellar activation despite substantial cortical displacement suggests cerebellar mapping may provide a stable marker of language organization when cortical localization is altered by tumor mass effect.

Figure 1. Representative examples of cerebellar language organization.



A. R-hemisphere lang dominance associated with contralateral (left) cerebellar activation, demonstrating preservation of crossed cerebro-cerebellar lang organization in an atypically lateralized patient.



B. Preserved cerebellar language activation despite marked displacement of cortical language regions by tumor mass effect.

Disclosures: C.R. Ledbetter: None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.15/LL30

Topic: I.11. Language

Title: A Hierarchical Speech Gradient in Premotor Cortex Mirrors Temporal Auditory Cortex

Authors: *S. GUO, A. G. HUTH;
Neurosci., Univ. of California, Berkeley, Berkeley, CA

Abstract: Classic neurobiological models of human speech and language have emphasized the dominant role of temporal lobe in speech perception, while premotor regions including the ventral premotor cortex (PMv) are situated at the level of articulatory processing. However, accumulating evidence from neuroimaging, clinical, and computational studies suggests that premotor cortex may contribute to speech processing beyond articulation. The precise extent and functional organization of these speech-related representations, however, remain unclear. In this study, we combined naturalistic speech perception with computational encoding models to characterize the organization of speech representations within PMv. We functionally localized a

cortical region that encompasses previously described premotor speech areas, which we term the premotor language area (PML). Using acoustic, phonemic, semantic, and deep neural speech representations, we found that PML contains representations spanning the full speech-processing hierarchy, from low-level acoustic features to high-level semantic information. Within PML, these representations are arranged along a smooth posterior-anterior gradient, with increasingly abstract speech representations emerging toward the anterior cortex. Moreover, this organizational gradient mirrors the canonical speech processing hierarchy in the temporal auditory regions. These findings challenge the traditional view of premotor cortex as primarily an acoustic-articulatory unit, and instead identify PML as a hierarchically organized speech-processing region that parallels the temporal auditory cortex. This provides a new framework for understanding the role of premotor cortex in speech perception.

Disclosures: S. Guo: None. **A.G. Huth:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.16/LL31

Topic: I.11. Language

Support: E. H. Solomon Center for Neurodevelopmental Research

Title: Auditory Training in Infancy Is Associated With Developmental Changes in Task-Evoked and Spontaneous Cortical Activity

Authors: *B. MAHMOOD[1], T. REALPE-BONILLA[2], A. A. BENASICH[3];
[2]Neurosci., [1]Rutgers Univ., Newark, NJ; [3]Neurosci., Rutgers University-Newark, New York, NY

Abstract: Both spontaneous and task-evoked cortical activity contribute to the formation of stable and efficient neural networks during early development via activity-dependent mechanisms. Prior work suggests that spontaneous and task-evoked activity coevolve across infancy, indicating that these forms of neural activity are not independent but interact during periods of heightened plasticity. As a result, early changes in one form of activity may impact the other thus shaping broader patterns of network maturation. In the current study, dense-array EEG was collected at 6, 9, and 18 months of age to examine how a six-week auditory training experience, provided between 6.5 and 8 months, may influence both task-evoked auditory processing as well as spontaneous cortical activity across development. Task-evoked EEG/ERP responses were used to assess neural activity underlying the recognition and discrimination of rapidly presented auditory cues, skills important for spoken language processing. ERP analyses revealed maturational changes across development, including faster neural responses to auditory stimuli with age. Group differences were also observed following training, with infants in the active training group showing improved performance on the rapid auditory processing task post-training. In addition, frontal spectral power was examined from spontaneous EEG (sEEG)

activity at each age. Spectral maturation trajectories in sEEG measures differed between groups in the gamma frequency band, suggesting that early auditory training may be associated with changes in the developmental progression of resting-state cortical activity. Further, the analyses show that frontal spectral power, including raw and aperiodic-adjusted measures, covaries with task-evoked responses. This approach allows us to assess how changes in high-frequency power (i.e., gamma-range activity) may shape auditory ERP responses and how this relationship evolves across development. Together, these analyses provide insight into how the early auditory environment contributes to the refinement of acoustic processing and the development of neural systems that support emerging cognitive and language abilities.

Disclosures: B. Mahmood: None. **T. Realpe-Bonilla:** None. **A.A. Benasich:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.17/LL32

Topic: I.11. Language

Support: University of Toronto Mississauga Postdoctoral Fellowship Award
Grammy Museum Foundation

Title: EEG hyperscanning and eyetracking in the classroom: does music benefit foreign language learning?

Authors: *A. M. CZEPIEL[1,2], L. K. FINK[2], C. M. DER NEDERLANDEN[1];
[1]Univ. of Toronto Mississauga, Mississauga, ON, Canada; [2]McMaster Univ., Hamilton, ON, Canada

Abstract: Learning a new language is challenging. Music is often described as an excellent tool to support such learning. The mechanisms through which music may benefit language learning are manifold: rhythmic regularity, enhanced arousal/engagement, or social bonding. The current study attempts to tease apart these mechanism(s), by assessing whether foreign language learning is improved by sung relative to spoken instruction in a live interactive classroom setting. In an introductory language German class (~90-minute session), a professional teacher sang or spoke target words in carrier sentences across four topics to groups of undergraduates (Experiment 1: N = 24; Experiment 2: N = 47). Participants reported their engagement, enjoyment, mood, and social bonding throughout the session. Target word learning was assessed before instruction, immediately after instruction, and at one-week delay. We recorded continuous EEG (SMARTING PRO) and eye-tracking (Pupil Labs NEON and SocialEyes) data from participants and the teacher during the class. Topic presentation modality (sung/spoken) was counter-balanced across groups. We predicted that compared to the spoken condition, the sung condition would yield higher engagement, increased learning, more eye fixations on the teacher, and stronger neural tracking of auditory information. Preliminary results from Experiment 1 show

that compared to baseline, the lesson promoted learning for both spoken and sung target words ($p = .007$), social bonding ($p = .049$), and engagement ($p = .025$), regardless of condition. Preliminary EEG data from Experiment 1 also showed that auditory information was neurally tracked more in sung than spoken topics, especially in the beta band (15-30 Hz, $p < .001$). Our results shed light on neural processing of language learning and can inform how educators can use music to support student learning by fostering engagement and classroom social dynamics.

Disclosures: A.M. Czepiel: None. **L.K. Fink:** None. **C.M. der Nederlanden:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.18/LL33

Topic: I.11. Language

Support: Chan Zuckerberg Biohub
Weill Neurohub

Title: Single-neurons across a cortical network encode semantic relations for word retrieval

Authors: *D. XU[1], Y. ZHANG[1], P. PARRAMON-ARCOS[1], T. CHEN[2], Q. R. GREICIUS[1], J. DUNKEL WILKER[1], S. HU[1], X. GONG[1], C. WANG[1], J. E. CHUNG[1], Y. KIM[1], X. YANG[1], A. SARKAR[1], E. F. CHANG[1];
[1]Neurolog. Surgery, [2]Univ. of California, San Francisco, San Francisco, CA

Abstract: Language allows us to communicate ideas by exchanging words with specific meanings. Meanings of words do not exist in isolation but are connected by various semantic relations such as antonym (opposite), hyponym (member of a category), agent-action, and whole-part. Different relations have been hypothesized as distinct operators in a semantic vector space to map meanings to their related targets. However, the neural substrate of semantic relations has been elusive and it is unknown how neurons compute relational operations in the semantic coding space. Here, by combining functional magnetic resonance imaging (fMRI) and electrocorticography (ECoG), we localized the brain regions involved in representing semantic relations to SMG, STS/MTG, aSTG, IFG, and MFG, largely matching the previously described semantic control network. Using Neuropixels recording, we found that semantic relations are encoded by single-neurons in these localized regions as well as in SFG, with a gradient of sparsity in tuning. Neurons that are selective to distinct relations are often found in the same recording sites. At the neuronal population level, semantic relations can be decoded from SMG, STS, IFG, aSTG, and SFG. However, not all relation-encoding regions represent different relations equally. The encoding subspace can change across listening, thinking, and speaking phases. However, the geometries of relational vectors often remain consistent, suggesting separate semantic and executive control. Preliminary results suggest that deviations in neural responses are correlated with incorrect use of semantic relations. To understand the

computational principles of relational operations, we extracted relational representations from artificial language neural network models when performing the same semantic search task. By mapping the relation code between biological and artificial neurons, we test the hypothesis that the unequal representations of different relations in different regions reflect an increasing degree of abstraction across a cortical network of semantic relational processing.

Disclosures: D. Xu: None. **Y. Zhang:** None. **P. Parramon-Arcos:** None. **T. Chen:** None. **Q.R. Greicius:** None. **J. Dunkel Wilker:** None. **S. Hu:** None. **X. Gong:** None. **C. Wang:** None. **J.E. Chung:** None. **Y. Kim:** None. **X. Yang:** None. **A. Sarkar:** None. **E.F. Chang:** A. Employment/Salary (full or part-time):; E.F.C. is a co-founder of Echo Neurotechnologies Corporation..

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.19/LL34

Topic: I.11. Language

Support: NIH Grant DC021140

Title: Attention or prediction? Characterizing the top-down influence of predictive context on speech encoding

Authors: *E. C. LALOR, W.-C. LIN;
Univ. of Rochester, Rochester, NY

Abstract: Theories of predictive coding propose that perception is the process of inferring the causes of our sensory input by combining that input with predictions derived from our learned and evolved model of the world. Such predictive processes are thought to play a central role in language comprehension, however, robust neurophysiological evidence for such processes, particularly during natural speech perception, remains limited. Previous work has suggested that the early acoustic-phonetic encoding of words in natural speech is influenced by their semantic relationship to the preceding linguistic context. However, it remains unclear whether this effect is driven by prediction per se or attentional fluctuations based on contextual uncertainty. To distinguish between these alternatives, we recorded electroencephalography (EEG) from 17 healthy adults while they listened to naturalistic audiobook stimuli. Critically, unsurprising content words were replaced with more surprising words while controlling the contextual uncertainty provided by the preceding context. This allows us to distinguish between prediction error (as indexed by lexical surprisal) and contextual-uncertainty-modulated attention (as indexed by cohort entropy) as the driving influence on the lower-level sensory encoding. We quantified early acoustic-phonetic encoding using a word-level measure of speech-envelope reconstruction accuracy (RA) and examined its relationship to lexical surprisal and cohort entropy. We found that words with higher lexical surprisal showed enhanced early auditory

encoding despite matched contextual constraint. Moreover, the temporal profile of this enhancement depended on the point at which the incoming speech signal diverged from the predicted phonological sequence, consistent with the emergence of prediction-error responses. Linear mixed-effects modeling further revealed that lexical surprisal had a substantially stronger influence on early acoustic-phonetic encoding than cohort entropy. Together, these findings indicate that early acoustic-phonetic encoding during natural speech perception is more strongly influenced by prediction-error computations than by uncertainty-driven attentional gain. While attentional processes may still contribute to language comprehension, the present results demonstrate the importance of distinguishing between top-down prediction and top-down attention when interpreting context-dependent modulations of speech processing.

Disclosures: E.C. Lalor: None. **W. Lin:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.20/LL35

Topic: I.11. Language

Support: NIH

Title: Neural Dynamics Underlying Switching Attention in Speech

Authors: *A. FIROOZI[1], S. DINDAR[2], V. CHOUDHARI[3], N. MESGARANI[2];
[1]Electrical Engin., Columbia Univ., NYC, NY; [2]Columbia Univ., New York, NY; [3]Electrical Engin., Columbia Univ., New York City, NY

Abstract: Neural representation of the auditory cortex has been well shown to represent the attended conversation more strongly than the unattended one in a cocktail party situation. In other words, a high level cognitive process in humans is picking out the attended talker out of the complex scene to give the person the ability of focusing and therefore better understanding of the conversation within the noisy environment. What remains unclear is the cognitive process driving the change of the neural representation in the auditory cortex. Leveraging intracranial EEG (iEEG) brain recording while changing attention throughout the trials makes it possible to have a better understanding of the cognitive network behind this process, and timing properties of the attention switches.To identify brain regions engaged in this process, we applied statistical analyses to the activity of the recorded regions during the attention build up of the new source. To further characterize timing dynamics of the attention switch, a projection of brain activity to a latent space was used allowing us to track different processing states over time. For this study, 5 human subjects having drug-resistant epilepsy were implanted with subdural ECoG grids and sEEG electrodes. An auditory scene of two simultaneous conversations were presented to the subjects by two speakers positioned at the front right and front left. An arrow on the screen indicates which conversation the subject should attend to. Observations show multiple stages the

brain goes through to redirect attention over a time scale of a few seconds.This study provides evidence of large scale cortical networks contributing to attention switching in auditory scenes. It highlights the temporal dynamics of this process. Findings of this study helps how attention shifts are coordinated in the human brain in auditory scenes.

Disclosures: A. Firoozi: None. **S. Dindar:** None. **V. Choudhari:** None. **N. Mesgarani:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.21/LL36

Topic: I.11. Language

Title: A Dorsal Language Area Encoding Hierarchical Representations for Speech

Authors: *J. LI[1], N. TANDON[2];
[1]Rice University/UT Hlth. Houston, Houston, TX; [2]Neurolog. Surgery, McGovern Med. Sch. at UT Hlth., Houston, TX

Abstract: The dorsal language area (DLA), spanning the posterior middle frontal gyrus (pMFG) and mid-precentral gyrus, has been implicated in prosodic and laryngeal control and in articulatory planning and sequencing, and is engaged during both speech perception and naturalistic comprehension. Its major compartment, HCP area 55b, has become a primary target for communication brain-computer interfaces (BCIs). Whether it responds homogeneously across speech and language, and at what spatiotemporal scale it encodes linguistic features, remains unknown. We analyzed intracranial high-gamma activity from the dominant hemisphere of 30 participants performing an auditory naming-to-definition task and 17 participants listening to naturalistic stories.Using non-negative matrix factorization (NMF) on single-trial responses aligned to acoustic onset and offset, we identified three temporally distinct prototypes: an acoustic-onset response locked to the stimulus, a semantic-integration response ramping toward offset, and a lexical-semantic retrieval response emerging after offset and absent at onset. Across 10,712 channel-trials, latency-sorted activity confirmed peak timing followed this onset, offset, post-offset sequence, and a t-SNE embedding separated the three responses once offset-aligned activity was included.These response types were not uniformly distributed across dorsal frontal parcels. Area 55b and the frontal eye field were dominated by the acoustic-onset response (48% and 52% of channels), whereas the anterior area 8C was dominated by lexical-semantic retrieval (67%); area 8Av showed a balanced mixture. Projected onto a cortical surface, these proportions traced a posterior-to-anterior shift from speech-acoustic toward semantic processing.To test sensitivity to hierarchical linguistic features, we fit ridge-regression encoding models to BGA responses during story listening across six feature families (phonoacoustics, prosody, lexical, constituency syntax, GloVe embedding, discourse). Surface-based maps showed the DLA encoded not only prosodic information input but also higher-order lexical, syntactic, semantic, and discourse structure.Together, these results indicate the DLA integrates temporally organized

linguistic structure from acoustics through discourse. The posterior-to-anterior gradient points to functional specialization the DLA, and the encoding results suggest compositional representations beyond surface acoustic statistics. These maps offer anatomical guidance for BCIs that reconcile higher-order linguistic and articulatory representations for decoding.

Disclosures: J. Li: None. **N. Tandon:** None.

Poster

PSTR158: Language: Neural Circuits and Mechanisms II

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR158.22/LL37

Topic: A.07. Development of Neural Systems

Support: NIH Grant R01DC018734

Title: Characterizing the Maturation of Syllable-Evoked Neural Responses in Early Infancy

Authors: *L. PETLEY[1], C. BLANKENSHIP[2], M. BARNES-DAVIS[2], D. MOORE[2], J. VANNEST[2], L. HUNTER[2];
[1]Clarkson Univ., Potsdam, NY; [2]Cincinnati Children's Hosp. Med. Ctr., Cincinnati, OH

Abstract: The early postnatal period represents an optimal window for detecting and mitigating risk for adverse outcomes later in life. While universal neonatal hearing screening illustrates the dramatic benefits of early screening, referrals to speech-language therapy remain delayed until the preschool years or later. Populations at risk for poor language outcomes, such as those who are born preterm, might benefit most from early screening for speech perception deficits. Language development in early infancy involves learning phonemes, prosody, and linguistic stress patterns, thus we studied the event-related potentials (ERPs) evoked by natural consonant-vowel syllables /ba/ and /da/ in very preterm (<32 weeks gestational age) and full-term infants between one and four months of age (corrected age when preterm). Hearing and language outcomes were also assessed at 2 and 3 years of age for the preterm group. Given the paucity of information regarding the development of such responses in early infancy, our current analysis focuses on the full-term group, as well as a sample of young adults to illustrate the mature response. Forty-one full-term infants between 1.3 and 4.7 months of age (M = 3.0 months, 20 F) and 20 healthy young adults (M = 20.3 years of age, 12 F) were used to investigate this developmental process. Measurements in our adult group indicate that, on average, the mature response typically involves a P1-N1-P2 sequence of ERP components, but for infants, similar waveforms were uncommon until 3-4 months of age. These maturational changes are poorly captured by existing systems for classifying infant auditory ERPs. Instead, they are best described as a transition from a broad, frontocentral P2 response to a sequence of positive and negative deflections. Significant individual differences were observed in the structure of this sequence, which involved either frontocentral N1-P2 responses or a bilateral P1 response followed by an intermediate N1 phase and a frontocentral P2. In some cases, these were followed

by N2. Our results call for flexible definitions in characterizing the maturity of syllable-evoked ERPs at the individual level and provide a normative profile against which to compare the responses observed in infants who are born preterm.

Disclosures: L. Petley: None. **C. Blankenship:** None. **M. Barnes-Davis:** None. **D. Moore:** None. **J. Vannest:** None. **L. Hunter:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.01/LL38

Topic: J.04. Physiological Methods

Support: DFG / SFB TRR225 Biofabrication: 326998133

Title: Purposedaptable 3D models of the brain and spinal cord for health and disease conditions

Authors: M. S. ANDRADE[1], N. MURENU[1], E. TÜRKER[1], A.-L. WIESSLER[1], J. FABER[3], J. WEIGELT[2], Z. LAMBERGER[2], I. LIASHENKO[4], L. GREGOR[2], S. BUDDAY[3], C. VILLMANN[1], **N. SCHAEFER**[1];
[1]Inst. for Clin. Neurobio., [2]Dept. of Functional Materials in Med. and Dent., Univ. Hosp. Würzburg, Würzburg, Germany; [3]Dept. of Mechanical Engineering, Inst. of Continuum Mechanics and Biomechanics, Friedrich-Alexander-Universität Erlangen-Nürnberg, Fürth, Germany; [4]Phil and Penny Knight Campus for Accelerating Scientific Impact, Univ. of Oregon, Eugene, OR

Abstract: Three-dimensional (3D) in vitro models have emerged as essential tools to recapitulate the structural and functional complexity of the central nervous system (CNS). However, the intrinsic ultra-soft mechanical properties and highly specialized extracellular matrix (ECM) composition of neural tissue pose significant challenges for the development of stable and physiologically relevant models. Here, we present a versatile and purpose-adaptable 3D platform composed of hyaluronic acid-based hydrogels with melt electrowritten (MEW) microfiber scaffolds, enabling the controlled reconstruction of spinal and brain cortical microenvironments. The ECM is engineered using commercially available and custom-synthesized components e.g. laminins, collagen, and fibronectin. In turn, the 3D composites support neuronal maturation, network formation, and cell-cell interactions. Mechanical reinforcement via MEW scaffolds ensures structural integrity while preserving the ultra-soft properties required for neuronal functionality. The 3D platform has been used to produce multiple CNS models, generating engineered synaptic systems, cortical brain networks and spinal cord networks. Functional validation is achieved through calcium imaging, protein expression profiling, and mechanical characterization. The platform enables the investigation of neuron-glia interactions and synaptic dynamics under both physiological and pathological conditions. Importantly, this system allows the study of diverse disease mechanisms. Including

glioblastoma multiforme and breast cancer brain metastasis, where tumor-neuron interactions and microenvironmental signaling drive proliferation. Furthermore, neurodegenerative and autoimmune disorders such as amyotrophic lateral sclerosis, spinal muscular atrophy, and Stiff Person Syndrome, where patient-derived factors induce functional neuronal impairment can be elucidated. Ultimately, the system provides a scalable foundation for future multicellular models for an ample variety of neurological disorders. In this manner, offering a powerful tool for uncovering disease pathomechanisms. Bridging the gap between simplified in vitro and in vivo models, this approach advances the study of CNS diseases supporting the development of targeted clinically-relevant models.

Disclosures: M.S. Andrade: None. **N. Murenu:** None. **E. Türker:** None. **A. Wiessler:** None. **J. Faber:** None. **J. Weigelt:** None. **Z. Lamberger:** None. **I. Liashenko:** None. **L. Gregor:** None. **S. Budday:** None. **C. Villmann:** None. **N. Schaefer:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.02/LL39

Topic: J.04. Physiological Methods

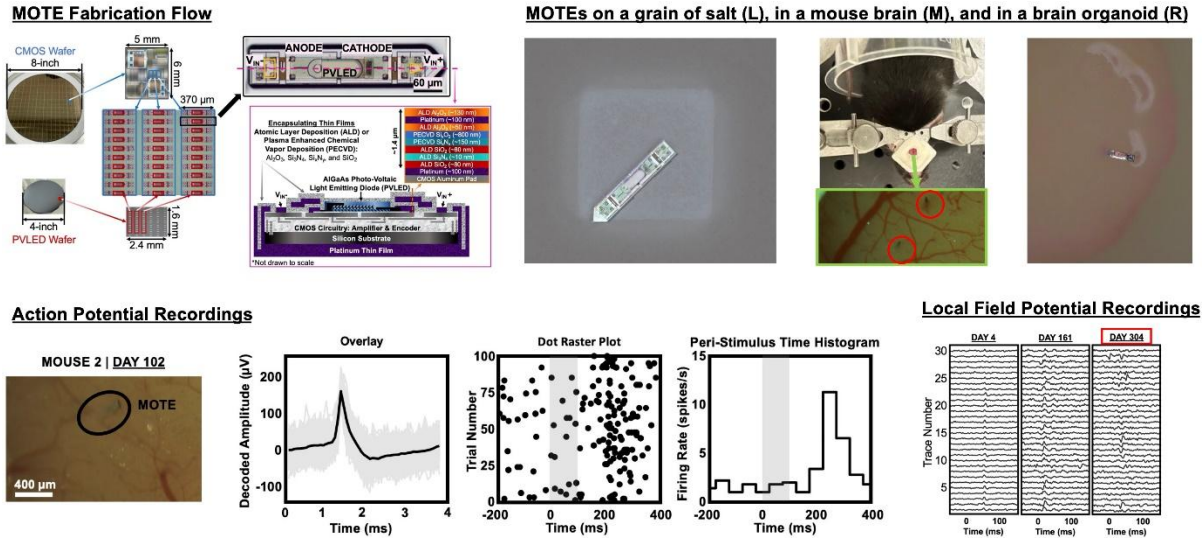
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Cornell NanoScale Facility, a member of the National Nanotechnology Coordinated Infrastructure (NNCI), which is supported by the National Science Foundation (grant NNCI-2025233)
Nanyang NanoFabrication Centre, NTU, Singapore

Title: Subnanolitre microscale optoelectroic tetherless electrode (MOTEs) for chronic neural recording in awake mice

Authors: *S. LEE[1], W. GU[2], T. A. CLELAND[3], M. R. WARDEN[6], J. H. GOLDBERG[4], C. XU[5], J. J. CHUA[7];
[1]Nanyang Technological Univ., Singapore, Singapore; [2]Nbb, [3]Psychology, [4]Neurobio. and

Behavior, [5]Applied and Engin. Physics, Cornell Univ., Ithaca, NY; [6]Translational Neurosciences, The Univ. of Arizona, Tucson, AZ; [7]Dept. of Physiol., Natl. Univ. of Singapore, Singapore, Singapore

Abstract: Implantable neural interfaces can play a critical role in understanding complex behaviors and neurological disorders. However, existing neural implants are often tethered and substantially larger than individual neurons, leading to insertion damage, foreign body responses, and recording instability arising from relative motion between the implant and biological tissue. Here, we present a subnanoliter (~70 µm × 20 µm × 330 µm) microsystem, **microscale optoelectronic tetherless electrode (MOTE)**, that enables chronic electrophysiological recording from cardiomyocytes, brain organoids, and awake mice for up to one year. A MOTE, small enough to be placed on a grain of salt, heterogeneously integrates a low-power CMOS (TSMC 180 nm) analog front-end with an AlGaAs photovoltaic light-emitting diode (PVLED), enabling battery-free optical power transfer and wireless data telemetry. CMOS post-processing and assembly methods enable parallel fabrication of hundreds of devices with high yield (~80%), while dedicated manipulation and injection protocols facilitate implantation into the mouse brain and brain organoids. *In vivo* studies demonstrate chronic recordings of local field potentials and action potentials from the barrel cortex of awake mice, with neural activity correlated with whisker stimulation. Recordings from brain organoids further demonstrate the versatility of the platform across biological subjects. Histological analysis revealed minimal tissue disruption, consistent with the exceptionally small device footprint. Unlike optical imaging approaches, MOTEs rely on optical power transfer rather than image formation, allowing scattered photons to be utilized for device operation and enabling recordings beyond the optical scattering limit. Furthermore, the underlying CMOS circuitry and electrode interfaces can be adapted for multimodal sensing, including chemical biomarker detection. These results establish a foundation for distributed networks of microscale implants capable of long-term recording across the brain and other biological systems.



Disclosures: S. Lee: None. **W. Gu:** None. **T.A. Cleland:** None. **M.R. Warden:** None. **J.H. Goldberg:** None. **C. Xu:** None. **J.J. Chua:** None.

Poster

PSTR159: Electrophysiology Techniques I

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.03/LL40

Topic: J.04. Physiological Methods

Support: UIC AHS EXITO pilot funding
UIC CCTS pilot funding
UIC CURA

Title: Design and test novel EEG electrodes attachment for type IV hairstyles

Authors: *K. OGUNNIYI[1], M. BROOR[2], L. WILLIAMSON[2], C. LIU[1];
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Abstract: Conventional EEG caps frequently fail on Type IV (Afro-textured) hair, as the current electrode design fails to penetrate thick hair and make reliable contact with the scalp; which contributed to underrepresentation of Black participants in EEG research (Brown et al., 2023; Bradford et al., 2024). This gap is consequential because Black individuals face disproportionately higher risk of neurological conditions, including stroke (Howard et al., 2011; Barnes, 2022). This study focuses on the development of 3D-printed electrode attachments designed improve signal quality by allowing direct electrode contact with the scalp, targeting natural and braided hair configurations. We developed three resin-printed electrode attachments for dense coily, cornrowed or braided, and less dense coily hairstyles (Figure 1). To evaluate our design, we compared the novel direct-placement electrode attachments to a conventional actiCAP EEG cap. Participants completed resting and walking recordings while impedance, percentage of electrodes disconnected, electrode to scalp distance, signal quality measured via peak alpha power, and comfort were measured Impedance measurements ranged from 0-114Kohm with the conventional cap, with 20% electrodes disconnected (distance to scalp: ~0.5-3.8cm), while the novel attachment ranged from 0-37Kohm with 0% electrodes disconnected (distance to scalp: ~0.3-2.1cm). At rest, mean alpha SNR across all electrodes was 10.00 dB (novel) versus 7.95 dB (cap; n=9, one participant with box braids excluded), with novel higher in 7/9 participants (range: 2.35-13.56 dB vs. −1.39-12.89 dB). Comfort ratings favored novel attachments after placement, rest, and walking (mean 9.0-9.1 versus 8.6-8.9; n=7). These findings suggest the novel electrode attachment design improves scalp contact and enhances signal quality across channels, supporting more inclusive data collection for individuals with Type IV hair. Ongoing recruitment (n=15) will further evaluate performance across hairstyle conditions.



Figure 1: Three 3D-printed electrode attachment designs for Type IV hairstyles.
Design 1 (Type 1) uses lateral stabilizing wings for dense coily hair; Design 2 (Type 2) uses a lateral peg for cornrowed or braided hair whose length can be manipulated; Design 3 (Type 3) uses an expanded version of Type 1's wings for less dense coily hair

Disclosures: K. Ogunniyi: None. **M. Broor:** None. **L. Williamson:** None. **C. Liu:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.04/LL41

Topic: J.04. Physiological Methods

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National Natural Science Foundation of China (62336007)
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Title: A wirelessly powered home-cage system for autonomous mouse behavior learning and 24/7 wireless neural recording

Authors: *B. YU[1], J. HAN[2], H. XU[1], P. LI[2], Z. WANG[2], Y. HAO[3];
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Abstract: A central goal of cognitive neuroscience is to understand how neural circuits support learning as animals acquire and update behavior. Combining behavioral training and electrophysiology offers a powerful approach to probe these circuits, but conventional workflows rely on human-guided training and tethered recordings that constrain freely moving animals. Autonomous home-cage training provides one partial solution. Our previously developed Home-cage Assisted Behavioral Innovation and Testing System (HABITS, Yu et al., eLife, 2025) has enabled 24/7 automated training across more than 300 mice and 20 cognitive paradigms, demonstrating that complex behaviors can be shaped with minimal human handling. Wireless electrophysiology has advanced rapidly; however, many systems remain session-based or battery-limited, hindering their integration with continuous autonomous training. To move toward an automated behavior-to-neural-recording workflow, we developed the eHABITS system (HABITS-ephys), a wirelessly powered home-cage system for long-term neural, behavioral and movement recording in freely behaving mice. The eHABITS integrates a 16-channel head-mounted recorder (13 x 14.5 mm), wired to an implanted wireless power receiver (12 x 15 x 2 mm), which was wirelessly powered by an inductive charging array (20 x 30 cm) surrounding the home-cage. The device transmits 16-channel AP/LFP, envelope spike activity, spike rasters, 6-axis IMU, power state, and behavioral events over a 2.4GHz link. Power consumption ranges from 17 to 82 mW, while wireless charging can deliver up to 198 mW. The head-mounted device, including a 50 mAh battery, weighs 2.7 g and remains compatible with long-term free movement. As an initial validation, eHABITS achieved continuous around-the-clock recording of prefrontal neural signals and fully autonomous learning process for more than 30 days during a complex rule-switching two-alternative-choice task. The resulting dataset captured neural activity, task performance, movement states (inferred from video tracking and IMU signals), and power-state telemetry across uninterrupted day-night cycles. This allows learning trajectories to be analyzed together with rest/sleep-like epochs, circadian context, and task engagement, providing a route to test how sleep-wake history and long-timescale neural state changes relate to cognitive performance. By minimizing handling and experimenter-dependent variability, eHABITS offers a continuous neural dataset of an unprecedented kind during learning in freely moving animals, potentially advancing our understanding of the neural mechanisms that underlie learning.

Disclosures: B. Yu: None. **J. Han:** None. **H. xu:** None. **P. li:** None. **Z. Wang:** None. **Y. Hao:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

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Topic: J.04. Physiological Methods

Support: NFRFE-2024-01253
NSERC Discovery-2024-O66O7
DMCBH Innovation Fund Kickstart Award awarded to L.A. Raymond

Title: A scalable textile-based architecture of iontronic microfiber electrodes for in-vivo neural recording

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Abstract: Neuroscience research requires neural interfaces that combine mechanical compliance, electrochemical stability, and facile assembly into scalable electrode configurations. Here, we engineered iontronic microfiber electrodes through wetspinning of a composite polymer solution into one-dimensional fibers. The incorporation of liquid-based iontronic conductors within the polymer matrix provides ionic and electronic conduction pathways at the sensing interface. This enables an efficient coupling for detecting extracellular neural signals while maintaining the intrinsic softness of the polymer network for mechanical compliance. Post-treatment of microfibers through parylene-c insulation and tip exposure results in suitable electrodes with recording sites for sensing extracellular neural signals. The individual microfiber electrodes are then assembled in a hierarchical textile architecture on a custom-built assembly jig to create a customisable network of electrode arrays which can be bundled into single or multi-filament electrode configurations for probing different brain regions and depths based on the study requirements. Static electrochemical data for 12 mm long microfiber electrodes demonstrated a low phase angle change ($\Delta\theta$) of 8.03° across a wide frequency band of 1-100k Hz. A dynamic electrochemical test was performed to study the sensing capability under cyclic micro-compressions with an amplitude range of 100 μm at 20 Hz. The microfiber electrodes demonstrated a high degree of repeatability for impedance sensing under those conditions with a Coefficient of Variation (CV) of 4.51 % across 100-6000 Hz, which covers the frequency band relevant for filtering single-unit activity (SUA) and multi-unit activity (MUA) data. These findings suggest the electrode interface with a low phase lag can potentially maintain a stable coupling and reduce micromotion related distortions in the recorded data during acquisition. In-vitro biocompatibility test performed with cortical neuronal cells using an MTT assay, demonstrated no significant difference between the negative control and microfiber treated groups with a cell viability of 82.2% for 800 μg/ml of the microfiber. The microfiber electrodes successfully detected SUA and MUA in the cortex and striatum in single and multi-electrode configurations during in-vivo recordings in anesthetized and awake mice. These results demonstrate that the microfiber electrodes can potentially be a cost-effective and scalable platform for in-vivo neural interfacing and be assembled into multimodal architectures integrating recording, stimulation, drug delivery and optical fiber interfacing.

Disclosures: N. Suvindran: None. **M.D. Sepers:** None. **S. Soltanian:** None. **D. Ramandi:** None. **L.A. Raymond:** None. **P. Servati:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.06/LL43

Topic: J.04. Physiological Methods

Support: HHMI Hanna H. Gray Fellows Program
Burroughs Wellcome Fund

Title: Chronic implantation of polymer-based microelectrode arrays for simultaneous electrophysiology and two-photon imaging

Authors: *G. M. ADAMS, D. WOODS, D. L. GONZALES;
Biomed. Engin., Vanderbilt Univ., Nashville, TN

Abstract: Electrophysiology is the gold-standard for studying neuronal dynamics, enabling in vivo recordings with single-spike resolution, but these recordings sample only a small fraction of neurons within a local population. Two-photon (2P) calcium imaging is a powerful alternative for monitoring neural circuit activity with cell-type specificity and a high spatial resolution. Combining these approaches would provide unprecedented spatiotemporal access to neural populations. Yet, traditional microelectrode arrays are made from opaque materials that block optical access to the area of interest. To address this, we developed a polymer-based microelectrode array compatible with 2P imaging to achieve months-long single-unit recordings paired with cell-specific imaging of neurons surrounding the implant. We used photolithographic techniques and thin-film microfabrication to develop 32-channel microelectrode arrays fabricated from surface-modified platinum and Parylene C. Prior to probe implantation, transgenic Thy1-GCaMP6s-expressing mice were fitted with a customized headpost. Flexible probes were stiffened against a tungsten microwire with polyethylene glycol (PEG) and perpendicularly lowered 1.5 mm into tissue through a 3 mm-diameter craniotomy over the primary visual cortex (V1). Once implanted, PEG was dissolved in saline and the microwire was retracted, leaving the flexible array in the brain. A 3 mm coverslip was secured over the craniotomy, fixing the probe in place. The flexibility of the array allowed for securing the breakout board to the back of the skull and away from the cranial window. In a second cohort of animals, we performed this surgical procedure in C57BL/6 animals and injected CaMKII-targeted GCaMP6s prior to probe insertion. After full recovery, we presented drifting gratings to awake, head-fixed animals while simultaneously performing electrophysiological recordings spanning the cortical depth and 2P calcium imaging in layer 2/3 surrounding the implanted probe. We achieved 5-25 single units per recording and imaged between 50-200 active cells in the field of view surrounding the probe. Single units and imaged neurons were tracked for up to 100 days post implantation. As expected, 40-50% of cells were responsive to visual stimuli, and 10-35% were tuned to a preferred grating direction. Furthermore, an oddball paradigm was implemented to identify neurons responsive to deviant stimuli. Combined use of transparent electrodes and 2P imaging introduces significant technological advances for investigating fundamental circuit mechanisms of sensorimotor behavior.

Disclosures: G.M. Adams: None. **D. Woods:** None. **D.L. Gonzales:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.07/LL44

Topic: J.04. Physiological Methods

Support: The Marcus Foundation

Title: Mechanized Manipulation and Placement of Ultrasmall Carbon Fibers for Assembling Minimally Invasive Wireless Motes

Authors: *J. G. LETNER[1], D. F. LEMMERHIRT[2], D. RUBENSTEIN[1], A. KAMBOJ[3], M. AALIZADEH[1], N. GREGORY[4], M. G. COPENHAVER[1], I. B. TOWNE[1], J. D. WEILAND[1], M. Z. MISKIN[3], D. BLAAUW[2], C. A. CHESTEK[1];
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Abstract: Arrays of individualized and minuscule wireless chips for neural interfacing, often called “neural dust” (Seo, 2016), could improve brain machine interfaces (BMIs) by removing the need for transcutaneous wires and by reducing the size of each implant. To safely and effectively sample the neural activity required for precision BMIs, these chips require biocompatible electrodes capable of reaching neurons deep in cortex from their positions on the brain’s surface. Ultrasmall carbon fiber (CF) electrodes (<10 μm diameter) could fulfill this role, as chronically implanting 16-fiber arrays in rats shows a minimal foreign body response (FBR) with high signal yield (Patel 2016; Welle 2020). Additionally, implanting 10x10 CF arrays into sheep is facile and induces minimal bleeding (Lam, SfN 2025). Previously, we successfully demonstrated the feasibility of surgically delivering wireless CF motes by implanting non-functional proxies into rat cortex (Letner 2026) with initial successes in sheep (Lam SfN 2025). However, the CFs in these mote proxies were attached entirely by hand, which is labor-intensive. In order for CF electrodes and CF motes to become clinically viable, their assembly must become manufacturable to increase both their consistency and the throughput of their production (Lucio Boschen, 2021; Hejazi 2021). Here, we present efforts in mechanizing the assembly of CF motes. Our group has acquired a custom semiautomated robotic system that can manipulate pre-cut and pre-individualized CFs such that the robot can thread them into the micromachined holes of mote chips. Operation consists of a sequence of programmed movements initiated by the operator and joystick-driven actions, such as procuring a CF and finely aligning it with the target hole. While evaluating an initial prototype, we threaded CFs into 74 mote proxies with 22 μm diameter through-holes and secured the CFs via silver epoxy manually pre-populated at target locations. We also extracted the time expended for each step during robotic assembly from videos capturing CF population for N=8 motes and measured that the total time per mote was less than four minutes. As only 11±2% ($\bar{X}$±S) of the time measured was expended by our initial attempts at automation, we anticipate that this time will decrease as more programmed movements are incorporated into the process. Overall, these preliminary results demonstrate the feasibility of manufacturing CF motes for neural dust intended for clinical BMIs and highlight

ways to increase the throughput of CF mote production through further automation in future work.

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Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.08/LL45

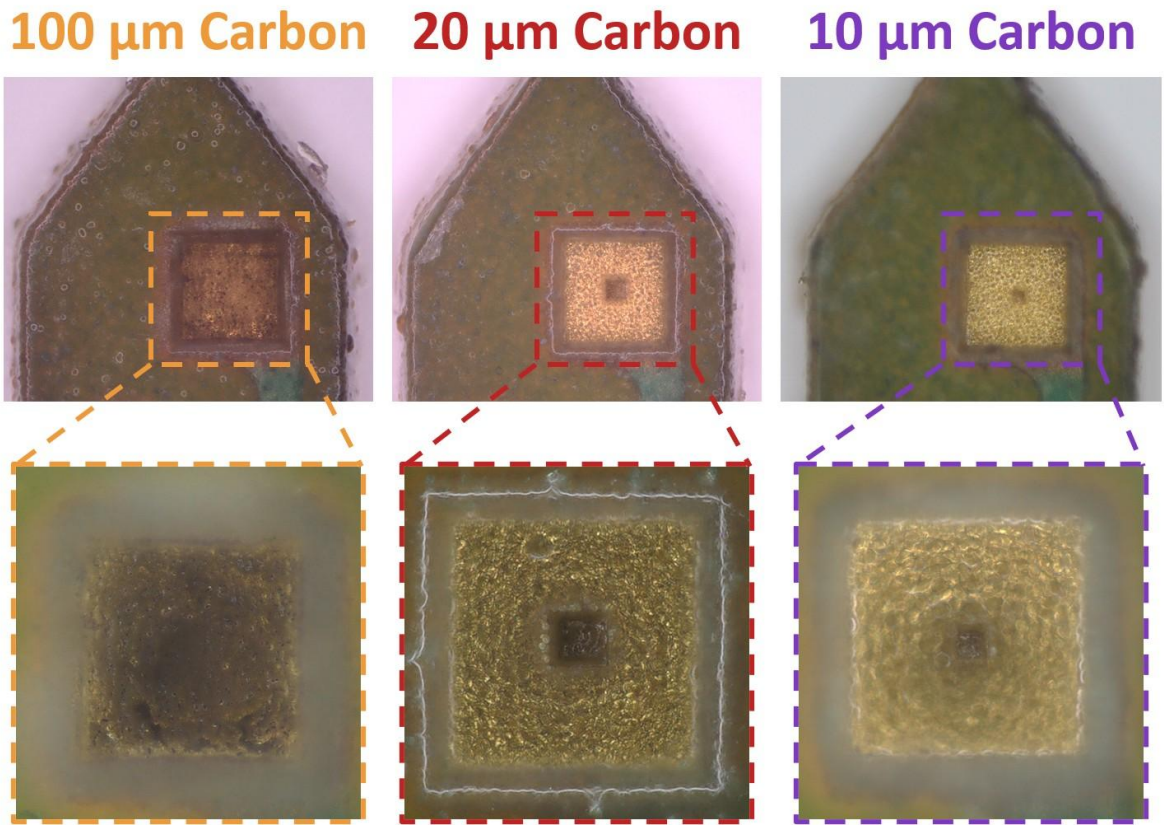
Topic: J.04. Physiological Methods

Support: JSPS KAKENHI JP25K24569
JSPS KAKENHI JP26K21626

Title: Laser-Carbonized Parylene-C Microelectrodes for In Vivo Action Potential Detection

Authors: *V. G. CASTILLO[1], Y. OHTA[2], Y. SUNAGA[2], K. TSO[2], J. OHTA[2];
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Abstract: Integrating electrodes for electrophysiological recording into optical imaging devices for multimodal neural activity detection presents significant fabrication and material challenges. This integration is particularly difficult for implantable on-chip imaging devices, where conventional lithographic processes, harsh chemicals, and high-temperature fabrication steps may be incompatible with the imaging chip and its optical or electronic components. Here, we report an optimized laser carbonization process for the direct fabrication of high-performance carbon microelectrodes compatible with on-chip imaging platforms. We investigated the effects of laser power and repetition rate on the carbonization of parylene-C to maximize graphitization while avoiding ablation. Raman spectroscopy confirmed the formation of graphitic carbon, with laser irradiation at 303.86 μW producing the most ordered graphitic structure. However, this laser condition resulted in excessive material loss from ablation. The optimal balance between carbon quality and material retention was achieved at 212.69 μW and 30 Hz. Using these optimized parameters, we fabricated implantable carbon electrodes of different sizes (100 × 100, 20 × 20, and 10 × 10 μm²) on flexible polyimide substrates. The impedances of these electrodes were 12.10 ± 0.22 kΩ, 596.38 ± 84.86 kΩ, and 8.969 ± 0.991 MΩ for 100 × 100, 20 × 20, and 10 × 10 μm² laser carbonized electrodes, respectively. Although larger electrodes had lower impedances, spontaneous single-unit action potentials were only detectable using the 20 × 20 μm² electrodes. These results establish a maskless fabrication process for high-quality, flexible carbon microelectrodes and demonstrate their suitability for electrophysiological recording.



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Poster

PSTR159: Electrophysiology Techniques I

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.09/LL46

Topic: J.04. Physiological Methods

Support: ARL Grant G10002772

Title: Flexible, Lens-Integrated Electrode Array for Chronic Multimodal Hippocampal Recording in Behaving Rodents

Authors: *K. G. VOKT[1], N. RIVEIRA[4], P. ZOLOTAVIN[2], C. KEMERE[3];
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Abstract: Head-mounted calcium fluorescence imaging captures large neuronal populations with high spatial resolution across extended timescales, providing valuable insight into neural circuit dynamics during natural behavior. However, achieving high temporal resolution remains challenging due to limitations in imaging frame rate and fluorescent indicator kinetics. Electrophysiology complements imaging by resolving fast oscillatory events such as sharp-wave ripples with millisecond precision, but existing approaches to combine both modalities either obstruct the optical field of view, require head-fixation, or fail to position recording sites at the imaging focal plane.
To address this, we fabricated a customizable, flexible polyimide thin-film electrode array designed to wrap conformally around an implantable GRIN lens or imaging cannula, with probe shanks extending precisely to the focal plane of the CA1 hippocampal cell layer. Devices are produced via wafer-scale photolithography, bonded to a custom PCB backend with up to 32 electrode channels, and wrapped around the chosen imaging lens. We characterize electrode arrangements spanning contact sizes of 30-100 μm and shanks of various lengths and geometries are designed to reach the imaging plane. We verify that shank dimensions empirically withstand insertion forces sufficient for direct implantation into brain tissue without requiring an additional stiffener. Gold electroplating reduces electrode impedance below 500 kΩ, stably maintained in saline over one week and verified with accelerated aging testing. Copper shielding and notch filtering mitigate noise during simultaneous microscope operation, and benchtop imaging confirmed an unobstructed field of view through the electrode-wrapped lens.

Disclosures: K.G. Vokt: None. **N. Riveira:** None. **P. Zolotavin:** None. **C. Kemere:** None.

Poster

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Topic: J.04. Physiological Methods

Support: NIH Brain Initiative UG3NS123723-01
NIH Brain Initiative R01NS123655-01
NIH NBIB DP2-EB029757

Title: Wireless platform for high channel count electrocorticography and stereoelectroencephalography

Authors: *S. FISHER[1], S. DAYEH[4], J. LEE[2], K. LEE[5], F. KHOURY[1], T. PORTER[6], K. FORSETH[3];
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Abstract: The development of new neural probe technologies has the potential for a transformative impact across a wide range of clinical applications including pre-surgical evaluation, intraoperative brain mapping, and brain computer interfaces. Our recent work has resulted in the development of high channel count thin-film electrodes providing major steps forward in both the channel count and brain conformality compared to the current clinically available state-of-the-art. The advent of increasingly high channel count neural probes necessitates the development of hardware systems capable of acquiring large amounts of neural data in a compact form factor. Our high channel count wireless neural recording and stimulation platform supports both electrocorticography surface grids and stereoelectroencephalography depth probes in a compact wireless form factor allowing for minimally restricted movement post-implantation. Our electrocorticography system supports 4096 recording channels and 256 stimulation channels in a hermetically sealed chronically implantable device. Our stereoelectroencephalography system supports up to 16 independently implantable probes with a total 2048 recording channels and 256 stimulation channels. Our platform has been validated both on benchtop and with pig implantation. Following successful validation of system functionality we aim to translate our technology into a clinical setting, allowing our technological advances to have a meaningful impact on human health.

Disclosures: S. Fisher: None. **S. Dayeh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cortical Science. **J. Lee:** A. Employment/Salary (full or part-time):; Cortical Science. **K. Lee:** A. Employment/Salary (full or part-time):; Cortical Science. **F. Khoury:** None. **T. Porter:** None. **K. Forseth:** None.

Poster

PSTR159: Electrophysiology Techniques I

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Program #/Poster #: PSTR159.11/LL48

Topic: J.04. Physiological Methods

Support: KIST Grant 26E0131
NRF Grant RS-2023-00262880
NRF Grant RS-2024-00444714
KEIT & MOTIR Grant RS-2024-00432143
NGS Grant RS-2026-25545224

Title: A Simplified, Low-cost Post-CMOS Process for Manufacturable, Chronically Validated Multimodal Neural Probes

Authors: *J. MUN[1,2], M. KIM[1,3], C. LEE[1,4];
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Abstract: Multimodal neural probes combining high-density electrophysiology with cell-type-specific calcium imaging across distributed brain regions require active CMOS integration to overcome the wiring limits of passive devices. Yet turning a fabricated CMOS chiplet into an implantable, chronically viable probe remains a bottleneck: SOI-based active probes constrain foundry access, while post-processing bulk-CMOS chiplets introduces fabrication barriers and unverified biocompatibility. Manufacturability and chronic readiness—not circuit design—thus limit adoption of large-scale multimodal probes. To address these challenges, we developed a 13-shank bulk CMOS multimodal neural probe with 416 electrodes and 832 photodiodes enabling simultaneous high-density electrophysiology and fluorescence imaging across distributed brain regions; readout performance is reported separately. The probe was fabricated through a simplified post-CMOS process requiring only two photolithography and three etching steps. A key fabrication challenge-edge beading formation across the millimeter-scale chiplet-was addressed by a 3D-printed edge-beading suppression frame (EBSF), reducing non-uniformity 3.2-fold across all 13 shanks. Mechanical robustness and biological compatibility were systematically validated. Histological trajectory assessment confirmed successful targeting of intended cortical regions across all shanks, enabled by the rigid multi-shank architecture with CMOS multilayer metal stack. Insertion force measurements on dura-intact mouse brain confirmed sufficient penetration without structural failure (17.1mN/shank, N=3). Iba1 immunohistochemistry at acute and chronic timepoints in C57BL/6 male mice (N=2; 10 weeks) showed no significant microglial activation versus non-implanted controls ($p>0.05$; one-way ANOVA with Dunnett's post hoc). Open field testing after 1-week implantation confirmed intact motor function with no significant differences in distance or speed ($p>0.05$; unpaired two-tailed t-test). Pre- and post-implantation device inspections further confirmed structural integrity throughout the implantation period, supporting feasibility of extended chronic recording. This work establishes a simplified, MPW-compatible post-CMOS fabrication and validation framework that makes high-shank-count active multimodal probes manufacturable and chronically implantable with standard research-facility processes. By decoupling sensor definition from the CMOS front-end, the two-mask, three-etch flow generalizes to other sensor geometries, lowering the barrier to large-scale multimodal interfaces.

Disclosures: J. Mun: None. **M. Kim:** None. **C. Lee:** None.

Poster

PSTR159: Electrophysiology Techniques I

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NRF Grant RS-2024-00444714
KEIT & MOTIR Grant RS-2024-00432143
NGS Grant RS-2026-25545224

Title: A Dual-Modality CMOS Readout for Simultaneous High-Density Electrophysiology and Cell-Type-Resolvable Optical Recording in a Single Neural Probe

Authors: ***M. KIM**[1,2], J. MUN[1,3], C. LEE[1,4];
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Abstract: Relating identified cell types to the spiking and local field activity of the surrounding network requires reading electrical and cell-type-specific optical signals from the same tissue, site, and time. Extracellular electrodes report population dynamics but cannot resolve which cell types contribute, while optical reporters resolve cell identity but are usually acquired on a separate instrument. No implantable device integrates complete on-chip readout for both modalities at electrode and photodetector densities approaching single-neuron resolution. We therefore built a 13-shank CMOS neural probe with dual-modality on-chip readout, interleaving electrode and photodetector sites along each shank.The optical channel uses a 3-transistor N-well photodiode pixel with correlated double sampling, chosen over a single-photon avalanche diode to keep pixel area and power compatible with dense per-shank integration; 64 pixels/shank feed a 12-bit single-slope ADC. The electrophysiology channel uses a chopper-stabilized operational transconductance amplifier (OTA) integrator with capacitive feedback and a 4-bit, 250×-oversampled successive approximation register (SAR) ADC giving 12-bit resolution at 8 kS/s, with capacitor-ratio gain for process and temperature independence. Channels are software-configurable for shank-level multiplexing.This is a confirmatory device-validation study. Across 16 electrodes (n=4 shanks), bandwidth was 3.75 kHz at 23 dB gain, with root mean square (RMS) noise of 5.83±2.1 μV in the local field potential (LFP) band (1-300 Hz) and 10.8±0.7 μV in the spike band (300-3750 Hz). Optical signal-to-noise ratio (SNR) was 62 at 1 nW/mm² (520 nm), linear (R^2=0.9998) over 1-25 nW/mm² at 400 fps. Replaying pre-recorded CA1-MEC signals and an ex vivo GCaMP6 projection, we recovered LFP, spike, and optical waveforms simultaneously on one probe. In anesthetized C57BL/6 mice (n=1), electrical and optical signals were acquired concurrently across multiple cortical sites.To our knowledge this is the first electrical and cell-type-resolvable optical neural recording acquired simultaneously within a single implantable multi-shank CMOS probe. Providing both signals from the same tissue at once supplies data for questions single-modality tools cannot reach: which cell types accompany a given field rhythm, how identified populations time spiking to ongoing oscillations, and how these shift across brain states. The readout extends to other optical reporters and sensing modalities, toward circuit-level studies linking neuronal identity to network dynamics.

Disclosures: M. Kim: None. **J. Mun:** None. **C. Lee:** None.

Poster

PSTR159: Electrophysiology Techniques I

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Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.13/LL50

Topic: J.04. Physiological Methods

Support: HHMI GT16792
Burroughs Wellcome Fund G-1021695.01
NIH R01 EY017077
NIH R01 EY036089

Title: Flexible microelectrodes for stable recordings in nonhuman primates

Authors: *D. P. WOODS, G. ADAMS, C. CONSTANTINIDIS, D. L. GONZALES;
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Abstract: Neurophysiological recordings in nonhuman primates (NHPs) typically rely on rigid microelectrode arrays that exhibit mechanical mismatch with surrounding cortical tissue, leading to signal instability and neuronal drift. Flexible penetrating electrodes may mitigate these limitations, however their adoption in NHPs has been hindered by challenges of implantation through intact dura mater and the absence of direct comparisons with traditional recording arrays. Here, we developed a reliable approach for repeated implantation of flexible microelectrode arrays in awake NHPs and directly benchmarked them against commercial rigid probes, evaluating recording yield and neuronal drift between probe types. We fabricated 32-channel Parylene-C microelectrode arrays and developed a telescopic insertion approach that enables penetration of free-floating flexible probes through chronic recording chambers without dura removal. We performed acute recordings in dorsolateral prefrontal cortex and posterior parietal cortex of two awake rhesus macaques performing an oculomotor-delayed response task. Across 29 implantation attempts, 24 penetrations were successful, and 21 recordings yielded stable single-unit activity. Recordings obtained from 18 behavioral sessions produced 232 putative single units. Of these, 197 displayed task-related activity. To compare with commercial electrodes, flexible arrays were directly compared with rigid Plexon, Diagnostic Biochips, and Neuropixel probes. We found that flexible arrays substantially reduced single-unit drift, with mean maximum displacement of 39.5 μm compared with 256 μm, 178 μm, and 246 μm for rigid probes, respectively. Furthermore, with geometric changes, we optimized the single-unit yield of the flexible array to 0.49±0.04 units/channel, similar to the standard yield of commercial electrodes. We then fabricated a 128-channel version of the array and produced recordings of population-level activity comparable to the commercial state-of-the-art. These results demonstrate that flexible microelectrodes can be reliably implanted in behaving NHPs with a similar scale and yield to traditional microelectrode arrays, but with significantly reduced recording drift. Overall, our work establishes flexible microelectrodes as a high-performing approach for scalable and stable neurophysiological recordings in nonhuman primates.

Disclosures: D.P. Woods: None. **G. Adams:** None. **C. Constantinidis:** None. **D.L. Gonzales:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.14/LL51

Topic: J.04. Physiological Methods

Title: Reproducible by default: a portfolio of open neuroscience instrumentation

Authors: *F. LOESCHE, K. SAKAKI, C. MORROW;
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Abstract: Much of modern systems neuroscience depends on highly integrated custom hardware and software. Prominent examples include head-fixed or tethered animals placed in controlled visual-stimulus settings with tightly synchronized data-acquisition chains, such as fly-on-ball setups, rodents on treadmills, and fish in closed-loop virtual-reality arenas. Building such rigs ad hoc, or outsourcing them to machine shops, carries recurring costs: build knowledge stays siloed in individual labs, effort is duplicated across groups solving the same problem, and engineering choices drift from current best practices in optics, mechanics, and software engineering. Here we describe an alternative approach: a centralized small and agile team of scientists with engineering backgrounds embedded in a research campus.

We present the operating model through a portfolio of deployed projects. For Drosophila, these include contributions to a high-speed Modular LED Display (visual-stimulus refresh rates above 1 kHz), and a family of parametric, resin-3D-printed fly holders generated from open CAD models that adapt to each microscope and specimen, produced at roughly $0.20 per unit and up to 30 in parallel. For microfluidics, we use SLA-printed molds and PDMS casting in place of cleanroom photolithography - dramatically reducing cost and turnaround time for rapid device prototyping. We also contribute to multi-component virtual-reality systems for closed-loop sensorimotor experiments spanning rodent, fish, and insect models, and we maintain a connectome cell-type navigator, a web tool released freely to the community.

Our role varies by project: from consultation and knowledge transfer across machine shops, scientific computing groups, labs, and model organisms, to delivering working hardware, integrating complex systems, and providing versioned, openly available documentation that builds institutional knowledge across generations of researchers.

In the past year, this model served projects in more than 10 laboratories; at least five projects reused designs across labs and two across species, showing that centrally developed, openly released tools propagate rather than being rebuilt from scratch. We argue that a well-documented engineering model is itself a transferable methodological contribution, one that other institutes can adopt to make custom neuroscience instrumentation accessible and reproducible by default, helping to innovate the research practices and technologies that solve biology's deepest mysteries.

Disclosures: F. Loesche: None. **K. Sakaki:** None. **C. Morrow:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.15/LL52

Topic: J.04. Physiological Methods

Support: Grossman Charitable Trust R01NS135240

Title: The GT4 Drive and Targeting System: a custom drive and targeting workflow for high-density, multi-probe Neuropixels recordings in nonhuman primates

Authors: *M. T. CORNACCHIA[1], R. A. GULLI[5], S. VYAS[6], E. TRAUTMANN[7], C. D. SALZMAN[2], T. TABACHNIK[3], M. M. CHURCHLAND[4];
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Abstract: The next generation of systems neuroscience will require simultaneous, high-density recordings from neuronal populations distributed across multiple brain regions. The Neuropixels 1.0-NHP Long probe enables dense sampling in primate brains by providing 4,416 selectable recording sites along a 45-mm shank, with 384 channels recorded simultaneously. However, deployment of multiple probes in nonhuman primates remains technically demanding. Each probe must be aligned to a planned trajectory, stabilized during insertion, advanced to depth, and coordinated with neighboring probes within cranial chamber constraints. Here, we present the GT4 Neuropixels Drive and Targeting Workflow, designed to support repeatable, high-density multi-probe recordings in nonhuman primates. The platform includes a custom cranial chamber adaptor, independently motorized probe and guide-tube positioning arms, and a planning-to-recording workflow for maintaining spacing, targeting trajectories, and controlling insertion depth. We evaluated the system across 13 macaque recording sessions with 50 Neuropixels 1.0-NHP Long probe insertions targeting areas 8, 45, 46, PMd, and M1 at depths up to 9 mm. Sessions used a mean of 3.84 probe insertions per session and yielded 19,387 well-isolated units after spike sorting, with session-level yields ranging from 1,008 to 2,194 units and a mean yield of 1,491 units per session. Together, these demonstrations show that the GT4 Drive and Targeting Workflow can support repeatable insertion trajectories, controlled depth placement, coordinated multi-probe spacing, and stable neural access across sessions. Importantly, these results were obtained with earlier versions of the system; lessons from these recordings have since been incorporated into updated drives with improved alignment, targeting, and insertion control. Near-term configurations are designed to expand practical probe counts and support two- to four-fold more simultaneous insertions. By combining drive hardware, trajectory planning, guide-tube stabilization, and standardized insertion methods into a single workflow, GT4 lowers the technical barrier to high-density Neuropixels recordings and provides a scalable platform for multi-region electrophysiology in nonhuman primates.

Disclosures: M.T. Cornacchia: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Columbia University. **R.A. Gulli:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Columbia University. **S. Vyas:** None. **E. Trautmann:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Columbia University. **C.D. Salzman:** E. Ownership Interest (stock, stock options, royalty,

receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Columbia University. **T. Tabachnik:** None. **M.M. Churchland:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Columbia University, E.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.16/LL53

Topic: J.04. Physiological Methods

Support: NIH BRAIN Initiative Phase I and Phase II SBIR (NS105500)
NIH NIAAA Phase I SBIR (AA030512)
NIH NIA Phase I SBIR (AG084801)
DARPA HR0011-16-C-0094

Title: Lower-force Insertion of microelectrode arrays, Neuropixels Probes, optics, and chemogenetic delivery needles with the NeuralGlider Insertion System.

Authors: *R. BAGWELL[1], J. GREASER[1], K. A. SNOOK[1], S.-H. LEE[2], V. C. CUZON CARLSON[3], A. DELELLIS[1], R.-U. HAQUE[4], T. D. KOZAI[5], T. THAI[5], N. SHELCHKOVA[6], C. M. GREENSPON[7], Y. ALKHALID[6], A. VAN DRIESCHE[6], N. ADHIKARI[8], Y. LI[9], S. GAUTAM[8], R. THAPA[10], M. L. MULVIHILL[1];
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Abstract: Development of neuroscience tools such as microelectrode arrays (MEA), Neuropixels Probes (Neuropixels), optics, and chemogenetic delivery needles have propelled neuroscience research forward. Despite efforts to minimize tissue damage from these devices through design optimization, the resultant biological response continues to limit research. Use of micron-scale ultrasonic vibration (NeuralGlider® Inserter, NeuralGlider, Actuated Medical, Inc.) has lowered the insertion force and reduced cortical dimpling of various tools during placement. Prior work has demonstrated how minimizing mechanical forces during tool insertion can improve physiological and experimental outcomes, such as chronic neural activity and reactive gliosis. In vivo, acute recordings following NeuralGlider-implanted MEAs into porcine cortex saw higher single unit yield compared to controls. Herein, we currently investigate NeuralGlider-aided placement of Neuropixels, gradient-index (GRIN) lenses, and infusion cannulas/needles on bench, ex vivo, and in vivo models. NeuralGlider lowered the force required for Neuropixels probes to penetrate an agarose model, reducing both probe buckling and dimpling. Specifically, insertion force decreased by 77% for Neuropixels 1.0 single-shank probe (PRB_1_4_0480_1_C)

and by 73% for Neuropixels 2.0 probe (NP2014). In vivo, NeuralGlider-assisted cortical insertions reduced tissue buckling and enabled insertion depths of up to 10 mm with Neuropixels 1.0 NHP single-shank probe (NP1032). Additionally, Neuropixels 2.0 multi-shank (NP2014) and single-shank (NP2004) probes were successfully inserted without buckling into the cortex of large and small preclinical models, respectively. NeuralGlider insertions of 0.5 mm GRIN lenses and 1.0 mm optical lenses into ex vivo porcine brain tissue reduced pial puncture force by >50% and resultant tissue compression compared to control ($p<0.01$, Student's T-test). In vivo NeuralGlider GRIN lens insertions into the mouse medial prefrontal cortex were completed utilizing controlled insertion speed, omitting tissue aspiration, and demonstrating improved implantation success, offering a reliable GRIN lens implantation procedure for deep-brain calcium imaging. Ex vivo testing demonstrated that infusion needle vibration reduced puncture force by >75% at speeds up to 500 μm/s compared to Control and enabled puncture of porcine dura with 33G needles. In vivo testing showed that these smaller gauge infusion needles reduced aliquot backflow along needle tracks. Entrance and infusion sites also showed higher cellular density (less damage) with vibrated insertion after 6 weeks.

Disclosures: R. Bagwell: A. Employment/Salary (full or part-time):; Actuated Medical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical. **J. Greaser:** A. Employment/Salary (full or part-time):; Actuated Medical. **K.A. Snook:** A. Employment/Salary (full or part-time):; Actuated Medical. **S. Lee:** None. **V.C. Cuzon Carlson:** None. **A. DeLellis:** A. Employment/Salary (full or part-time):; Actuated Medical. **R. Haque:** None. **T.D. Kozai:** None. **T. Thai:** None. **N. Shelchkova:** None. **C.M. Greenspon:** None. **Y. Alkhalid:** None. **A. Van Driesche:** None. **N. Adhikari:** None. **Y. Li:** None. **S. Gautam:** None. **R. Thapa:** None. **M.L. Mulvihill:** A. Employment/Salary (full or part-time):; Actuated Medical. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Actuated Medical.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.17/LL54

Topic: J.04. Physiological Methods

Support: 1R01NS142069-01

Title: End-to-end large-scale/high-resolution microLED-based optoelectrophysiology system for use in freely behaving mice

Authors: P. MCCOMMONS, W. CHEN, S. OH, *J. R. LOPEZ RUIZ, E. YOON;
EECS, Univ. of Michigan, Ann Arbor, MI

Abstract: To date, simultaneous large-scale electrophysiology recordings and high-resolution optogenetic stimulation in freely moving mice remains unachievable with available state-of-the-art tools. In this work we present an ultra-compact (17.5 x 15 mm) and lightweight (~1g) probe that integrates our existing high-density HectoSTAR optoelectrodes (128R and 64 blue-microLEDs) with a custom application specific integrated circuit (ASIC), enabling simultaneous electrophysiology readout and microLED control via a single 3m tether. To command the headstage we developed an FPGA based back-end interface compatible with the OpenEphys ecosystem, further expanding its usability. The system's update rate (20kS/s/channel) is equivalent across recording/stimulation; therefore, it can acquire 16-bit full-band neural signals (LFP and SB) and generate arbitrary stimulation patterns with 1uA step resolution. To validate and stress test the system, we chronically implanted the 4-shank version of the optoelectrode in the hippocampus of a Thy1-ChR2 transgenic mouse. We recorded spontaneous and optogenetically evoked single unit and field potential activity for over a 4-month period. We explored the capabilities of the system by delivering a variety of optogenetic pulses, waveforms and patterns. We were able to reliably identify direct optogenetic activation of pyramidal neurons when short (10ms) pulses were delivered. Furthermore, the neuron sized LEDs evoked confined responses without perturbing the neighboring neuron population. Interestingly we also observed characteristic local and long-range firing patterns in response to different waveforms when adjusted for total accumulated optical stimulation (i.e. square pulse vs sawtooth vs sine vs wavelet). To assess the platform's compatibility with the open-ephys ecosystem, we implemented an online location-based closed-loop stimulation. The system's latency for closed-loop triggering was measured at ~25ms, consistent with open-ephys ecosystem. Altogether these results demonstrate the platform's potential by enabling for the first time large-scale longitudinal optoelectrophysiology experiments in freely behaving mice.

Disclosures: P. McCommons: None. **W. Chen:** None. **S. Oh:** None. **J.R. Lopez Ruiz:** None. **E. Yoon:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neurolight Technologies.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.18/LL55

Topic: J.04. Physiological Methods

Title: Nanoscale topographies to minimize neuroinflammation and promote chronic integration of flexible neural interfaces

Authors: *C. KAEO[1], G. M. JEANPIERRE[2], S. SEIDLITS[1], S. R. SANTACRUZ[1,2,3]; [1]Biomed. Engin., [2]Electrical and Computer Engin., [3]Interdisciplinary Neurosci. Program, The Univ. of Texas at Austin, Austin, TX

Abstract: While highly biocompatible polymers like Parylene-C are widely utilized as substrates for flexible neural interfaces, their limited integration with brain tissue often triggers a persistent foreign body response. Over time, activated glial cells gather at the interface, causing signal degradation and eventual chronic device failure. Although it is known that surface features at the nanometer scale can modulate cellular adhesion and inflammatory pathways, the relationship between specific nanogeometries, feature spacing, and cell-type-specific responses remains poorly understood. To establish systematic, evidence-based design guidelines for neural probe modifications, we have systematically fabricated and evaluated distinct nanotopographies. To investigate how neural interface surface properties mediate tissue integration, we examined nanopillars, nanopits, and nanogrooves on Parylene-C substrates. Continuous, anisotropic features like grooves are selected for their potential to reduce astrocytic inflammatory markers, while isotropic, interrupted features like pillars and pits are implemented because they support mature neuronal network growth. We characterized intrinsic surface properties by measuring surface wettability using water contact angle (WCA) goniometry and assessing the temporal composition of adsorbed protein coronas via liquid chromatography-mass spectrometry (LC-MS). In addition, we tested the response of cultured mouse iPSC-derived and adult neurons, microglia, and astrocytes directly onto the nanopatterns. Microglia and astrocytes were comprehensively evaluated for viability, proliferation, inflammatory cytokine profiles, gene expression changes via targeted RNA sequencing, and hallmarks of glial scarring. Concurrently, neurons were monitored for neurite alignment, branching complexity, network connectivity, cell-intrinsic stress, and calcium signaling dynamics. We found that smaller nanofeature spacing promoted microglial and astrocytic quiescence, lower pro-inflammatory activation markers, and encouraged healthier, more interconnected native-like neuronal networks. Conversely, larger feature spacing accelerated active inflammatory morphologies and increased cell stress. This multi-modal assay will inform the first integrated predictive framework and evidence-based design rules for engineering surface architectures that minimize the foreign body response and maximize the lifetime performance of polymer-based neural interfaces.

Disclosures: C. Kaeo: None. **G.M. Jeanpierre:** None. **S. Seidlits:** None. **S.R. Santacruz:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.19/LL56

Topic: J.04. Physiological Methods

Title: Automated microwire and tetrode tip shaping for reduced insertional damage and chronic stability

Authors: C. ENDRES[1], *D. C. KLORIG[2];
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Abstract: Microwire and tetrode electrodes are widely used for chronic intracranial neural recordings, yet conventional cut, flat, or angled tips can disrupt microvasculature and neural tissue during insertion, contributing to gliosis and long-term signal degradation. Our hypothesis was that smoother, more rounded electrode geometries might cause less acute tissue damage and attenuate inflammatory responses; however, rounded tips are difficult to fabricate reproducibly and at scale using conventional methods. We developed and characterized an automated, high-throughput method for reproducible modification of pre-insulated microwire electrode and tetrode tips, enabling controlled fabrication of rounded and conical geometries suitable for chronic neural recording applications. An automated orbital diamond polishing system was used to modify Formvar-insulated 35 µm tungsten microwire, or 10 µm nichrome tetrodes. Microwires or tetrodes were threaded through a ceramic ferrule and secured in a compliant clamp mounted to a linear actuator. Tip modification occurs via abrasive removal of material at an angle resulting from elastic deformation of the wire as it contacts the orbiting polishing disk. Controlled vertical motion of the wire relative to the disk produces reproducible inelastic deformation at the tip. A programmed vertical "bobbing" motion generates rounded tips, while fixed-depth exposure yields conical tips with adjustable taper. Tip geometries were assessed using scanning electron microscopy (SEM). SEM imaging demonstrated that controlled actuator motion reliably processed conventional cut microwire tips into smooth, rounded geometries with clean uninterrupted transitions from insulation to the core conductive material. Tetrodes polish to a smooth round tip without wire separation. This simple and rapid orbital shaping approach enables reproducible fabrication of several useful microelectrode tip variations suitable for chronic in vivo applications. By providing a scalable alternative to cut electrodes, this method enables systematic investigation of how rounded and conical tip geometries influence gliosis, vascular disruption, and long-term recording stability in epilepsy-relevant neural implants. From an engineering perspective, this platform decouples electrode tip geometry from wire fabrication constraints, enabling rapid, low-cost optimization of neural implant designs for chronic performance.

Disclosures: C. Endres: None. **D.C. Klorig:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.20/LL57

Topic: J.04. Physiological Methods

Support: NIH UO1 7-U01-NS126052-03

Title: Longitudinal Electrochemical Impedance Spectroscopy as a Non-Destructive Monitor of Neural Electrode Degradation In Vivo

Authors: *Q. DONG[1], S. SHARMA[2], E. OLIVO[3], J. WONG[2], B. W. BINEY[5], P. MORALES VASQUEZ[3], J. F. HETKE[6], M. ORAZEM[5], S. COGAN[7], K. J. OTTO[4];

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Abstract: Chronic neural implants undergo progressive changes at the electrode-tissue interface that compromise recording and stimulation performance over time. Identifying reliable, non-destructive metrics that track these changes without requiring explantation remains an open challenge. Here we correlate longitudinal electrochemical impedance spectroscopy (EIS) modeling with post-explant scanning electron microscopy (SEM) and energy dispersive x-ray spectroscopy (EDX) to further characterize electrode degradation across the implant lifetime in a rodent model. Silicon shanks (3 shanks, 1 device) were implanted in the rat somatosensory cortex over 425 days and subjected to chronic electrical stimulation around 100 days. EIS measurements were acquired weekly throughout the stimulation period. Spectra were fitted using the Orazem-Watson weighted measurement model, which yields physically interpretable parameters, including solution resistance, SIROF interface components, and double-layer capacitance, while accounting for measurement error structure. Post-explantation shank surfaces are imaged by SEM, tissue residue is cleaned with enzymatic cleaner to assess electrode delamination, corrosion, and other device-based degradation at the microscale. By aligning the time-series of model-derived impedance parameters with SEM-identified surface features on each shank, we evaluate how EIS captures the onset and progression of degradation modes that are only directly observable post-explant. Data suggests that systematic shifts in fitted impedance parameters correspond to morphological changes visible in SEM, including insulation failure and electrode material loss. This study supports the use of impedance-based modeling as a longitudinal biosensor of electrode integrity, with implications for closed-loop neural devices that must maintain stable interfaces across months to years.

Disclosures: Q. Dong: None. **S. Sharma:** None. **E. Olivo:** None. **J. Wong:** None. **B.W. Biney:** None. **P. Morales Vasquez:** None. **J.F. Hetke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroNexus. **M. Orazem:** None. **S. Cogan:** None. **K.J. Otto:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.21/LL58

Topic: J.04. Physiological Methods

Support: 7-U01-NS126052-03

Title: Insertion Mechanics of Staggered Ultra-Microelectrode Arrays: Velocity Characterization and Ogden-CZM Finite Element Analysis of Pial Puncture

Authors: *A. CHEUNG[1], M. KHAJEHZADEH[2], J. HETKE[3], S. COGAN[4], K. OTTO[1];
[1]Purdue Univ., West Lafayette, IN; [2]Case Western Reserve Univ., Cleveland, OH; [3]NeuroNexus Technologies, Ann Arbor, MI; [4]Univ. of Texas at Dallas, Dallas, TX

Abstract: Intracortical microelectrode arrays enable high-resolution neural recording and stimulation but cause mechanical trauma that triggers a foreign body response (FBR), limiting chronic performance. Reducing probe cross-sectional area to create ultra-thin microelectrode arrays (UMEAs) can mitigate FBR. To prevent buckling while scaling channel count, we developed a custom four-shank UMEA with an ultra-thin layer stack (5 µm silicon, 1.5 µm α-SiC) utilizing depth-staggered shank lengths (1.457 to 1.757 mm, 100 µm offsets) and tapered widths towards an 11° tip angle to enforce sequential pial penetration, distributing insertion load sequentially to prevent buckling. Previously, groups have demonstrated that staggered shanks mitigate cumulative insertion forces and avoid a "bed-of-nails" effect. We fully characterized the insertion force profiles of this design and implemented an Ogden-cohesive zone model (CZM) finite element model (FEM) to resolve pial puncture mechanics. Critical buckling forces (F_{cr}) were evaluated empirically using an automated micro-inserter compressing individual shanks against a PDMS-coated silicon wafer and modeled via ABAQUS. In vitro insertions were conducted at fixed velocities (20, 50, 100, 200 µm/s) to 1500 µm depths in biomimetic 1.2% w/v agarose gel phantom (N=62 trials, 3 electrodes) to extract the maximum insertion force (F_{max}), force at rest post insertion (F_{rest}), and drag force post retraction (F_{drag}). Cortical dimpling was annotated via video recordings. Measured F_{cr} matched FEM predictions for shanks ≤1.657 mm but diverged significantly at 1.757 mm due to curvature. All empirical values never exceeded the modeled upper bound. In vitro insertion profile with one-way ANOVA revealed that only F_{max} scaled directly with velocity ($p<0.001$; 3.11±0.28 to 3.48±0.49 mN, mean±SD), F_{rest} showed no velocity dependence, and F_{drag} decreased significantly with velocity ($p<0.001$). Increasing speed significantly decreased dimpling duration (2.98±1.01 to 0.70±0.15 s, $p<0.001$) and increased the percentage of zero-dimple trials (7% to 50%). In vivo rodent cortical insertions (n=5 successful, n=3 failed) identified a successful pial penetration threshold at <6 mN, separating successful events (4.12±1.20 mN) from failures (6.67-14.72 mN). The Ogden-CZM framework demonstrated that trailing shanks exert higher peak forces due to wider proximal contact geometry, elastic strain energy dominates the insertion budget over cohesive fracture dissipation, and global pial deflection extends up to 2.5 mm beyond the array footprint. This model can serve as a geometry-aware tool to optimize next-generation UMEA design.

Disclosures: A. Cheung: None. **M. Khajehzadeh:** None. **J. Hetke:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); NeuroNexus Technologies. **S. Cogan:** None. **K. Otto:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.22/LL59

Topic: J.04. Physiological Methods

Support: NIH R01 NS121764-02
NIH RF1 NS132041-01

Title: A low-cost flexible probe platform for stable chronic cortical single-unit recordings across weeks in mice

Authors: *R. BAIN;
UC Irvine, Irvine, OR

Abstract: Chronic extracellular recordings in mice are limited by probe cost, implant weight, tissue response, and loss of single-unit identity across days. These constraints are especially problematic in cortical areas where acute probes can yield many units but stable chronic unit tracking is difficult. We developed a low-cost chronic electrophysiology platform built around ultra-flexible polyimide probes, compact Intan-based headstages, and lightweight resin-printed headcaps for long-duration recordings in freely moving and head-fixed mice.The recording interface consists of 64-channel flexible polyimide probes with gold traces and PEDOT-coated recording sites. Probes are fabricated using standard cleanroom processes and assembled onto compact PCBs with 64-channel SlimStack connectors. During implantation, each probe is inserted using a removable fine shuttle threaded through a distal loop, allowing placement without leaving a rigid insertion element or glue in the brain. After hydration, the probe forms a compact three-dimensional braid-like structure that provides local multichannel recording neighborhoods while minimizing residual implant volume. Custom 128-channel headstages containing Intan RHD2164 chips support two 64-channel probes per headstage, and two headstages can be used for 256-channel recordings with a total implant mass of approximately 4 g including headcap, probes, connectors, and electronics.We tested this platform in posterior parietal cortex across chronic recording sessions. At week 6 after implantation, high-quality single units remained detectable with stable waveforms across multi-day intervals. In one dataset, 71 putative single units were matched across a 48-hour gap from W6D2 to W6D4 without volume-conduction modeling or probe-drift correction. In a separate analysis combining recordings from W6D1 and W8D4, many units remained recognizable across a 17-day interval, indicating that the flexible interface can preserve single-unit identity over timescales that are challenging for many acute or semi-chronic approaches.Together, these results demonstrate a scalable chronic recording platform combining low probe cost, low implant mass, removable insertion hardware, and long-term unit stability. This platform enables repeated high-channel-count recordings from the same cortical circuits across days to weeks and provides a practical foundation for longitudinal studies of neural population stability, learning, sleep, and circuit dynamics.

Disclosures: R. Bain: None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.23/LL60

Topic: J.04. Physiological Methods

Title: High-density thin-film interfaces for integrated mapping of optic nerve and cortical visual responses in swine

Authors: ***J. YI**[1], K. SHUKLA[2], F. KHOURY[3], K. FORSETH[4], J. C. GARRETT[5], H. SHIN[6], S. DAYEH[7];
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Abstract: Directly resolving how visual signals propagate from the retina to the brain has been limited by the separation of conventional recording sites, which typically sample activity either within the eye or at the cortical endpoint, leaving the optic nerve itself largely inaccessible and sparsely characterized. Here, we present two flexible high-density thin-film interfaces designed for simultaneous interrogation of the porcine visual pathway: a circumferential optic nerve array for dense peripheral nerve recording and a microelectrocorticography array for concurrent measurements from early visual cortex. This integrated platform substantially increases spatial sampling across the optic nerve, enabling visually evoked activity to be decomposed into components with distinct propagation trajectories, latencies, and recruitment patterns. By varying stimulus wavelength, intensity, and temporal structure, we further identify stimulus-dependent differences in the timing and spatial spread of optic nerve responses. Focal retinal stimulation demonstrates that the interface retains information about retinal origin, producing spatially segregated activation patterns across the nerve. In addition, stimulation contacts integrated within the same device evoke propagating optic nerve and cortical responses that resemble activity elicited by controlled visual stimuli. Together, these findings establish a high-density interface platform for large-scale, simultaneous mapping of visual signal transmission from the optic nerve to the brain, providing a functional framework for assessing regenerated visual pathways and guiding the development of future visual prostheses and neurointerfaces.

Disclosures: J. Yi: None. **K. Shukla:** None. **F. Khoury:** None. **K. Forseth:** None. **J.C. Garrett:** None. **H. Shin:** None. **S. Dayeh:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Cortical Science Inc..

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.24/LL61

Topic: J.04. Physiological Methods

Support: NIH Grant UH3NS117944
NINDS Grant R01NS112497

Title: A Rapid-Prototyping Framework for In Vivo Real-Time Visualization, Continuous Monitoring, and Spectroscopy of Four-Point Tissue Impedance

Authors: *J. L. OKKABAZ[1,4], E. ARSLAN[1,4], H. HEYDARI[1,4], M. AMANAT[2], G. A. WORRELL[2], N. F. INCE[1,4,3];
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Abstract: Tracking the physical state of brain tissue yields valuable physiological data that electrophysiology alone cannot capture. However, conventional two-point impedance measurements are heavily confounded by electrode-tissue interface polarization, obscuring small but meaningful changes in the tissue microenvironment. To address this, a continuous four-point (Kelvin) impedance and broadband spectroscopy framework was developed to decouple tissue impedance from interface artifacts. Implemented on the Ripple Explorer Summit system using Macro2+Stim front ends, the framework generates quantized sine waves (0.5 Hz to 1 kHz) driven by a 30 kHz state clock. The sine wave is approximated using a 1 μA minimum current step size scaled to a 5 μA peak amplitude and delivered through the outer electrode contacts as phase-inverted current waveforms, with one contact driven positive while the other is driven negative. The resulting voltage response is measured differentially across the inner contacts. For accurate phase calculation, the identical stimulation command is simultaneously executed at an independent channel across a known reference resistor to ground, creating an ideal, purely resistive reference signal. Phase shifts are determined via cross-correlation between the measured inner-contact voltage and this reference signal to compute time delays. The approach was validated using custom resistive and capacitive circuit phantoms, alongside clinical stereoelectroencephalography (sEEG) electrodes submerged in normal (0.9%) and hypotonic (0.45%) saline. Continuous 1 kHz monitoring on a 100-ohm resistive phantom demonstrated ±0.5 ohms accuracy. Frequency sweeps across the 0.5 Hz to 1 kHz range with sEEG electrodes in saline confirmed a purely resistive, zero-phase profile with no effective frequency dispersion, yielding stable measurements of 13.6 and 28.5 ohms for normal and hypotonic saline, respectively. Tests on capacitive circuit elements showed strong phase and magnitude alignment with theoretical models. By eliminating interface artifacts, this platform enables both continuous monitoring and broadband spectroscopy. Continuous measurement allows real-time spatial mapping during electrode insertion and surveillance of physiological states like sleep. Furthermore, spectroscopy characterizes frequency-dependent tissue dispersion, providing insights into cellular and extracellular composition. Together, these capabilities support the development of versatile impedance-based biomarkers for diverse neurological applications, such as tracking peri-ictal seizure dynamics.

Disclosures: J.L. Okkabaz: None. **E. Arslan:** None. **H. Heydari:** None. **M. Amanat:** None. **G.A. Worrell:** None. **N.F. Ince:** None.

Poster

PSTR159: Electrophysiology Techniques I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR159.25/LL62

Topic: J.04. Physiological Methods

Support: NIH Grant R01NS123069
NIH Grant 1R01AG095248

Title: A 32-Channel Flexible Fiber-Based Neural Probe with PCB-Based Backend Connection for Electrophysiological Recording

Authors: *X. YANG[1,2], N. YOUSEFPOUR[1,2], H. HUANG[1,2], Y. LIU[1,2], Y. GUAN[1], R. WU[1,2], D. F. ENGLISH[1,3], J. WANG[1,2], X. JIA[1,2];
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Abstract: The in-vivo electrophysiological recording quality of implantable neural interfaces depends on how much information can be extracted from tissue without sacrificing signal fidelity or biocompatible form factor. Higher electrode density improves the odds of isolating nearby neurons, tracking activity across layers, and sampling distributed cortical fields with finer spatial granularity. For high-electrode-count thermally tapered fiber-based neural interfaces, the densely packed electrodes must be connected one by one, while the small probe cross-section limits the feasibility of the electrode connection. Here, we present a 32-electrode thermally drawn fiber device with a customized PCB. The PCB was designed to establish one-to-one electrical connections between the neural probe's electrodes and the external recording hardware. Electrical characterization of the probe demonstrated that PCB bonding yielded stable electrical interconnections across all channels. In vivo electrophysiological recordings were performed on awake, behaving mouse models to validate probe capabilities, where local field potentials and extracellular spiking activity were successfully detected. Such a probe holds potential for integrating high-density thermally drawn neural probes with PCB-based backend packaging and advancing flexible neural interfaces for chronic electrophysiological recording applications in the future.

Disclosures: X. Yang: None. **N. Yousefpour:** None. **H. Huang:** None. **Y. Liu:** None. **Y. Guan:** None. **R. Wu:** None. **D.F. English:** None. **J. Wang:** None. **X. Jia:** None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.01/LL63

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

Support: NSFC32471055
NSFC82171090
FudanX24AI046

Title: From Hodgkin-Huxley to Pretrained Neural Inference AI

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Abstract: High-density probes record from thousands of neurons simultaneously, yet resolving single-neuron identity remains an illposed inverse problem. While detailed simulations precisely characterize the biophysical forward process, their utility for interpreting brain signal remains unclear. We show that biophysical simulations of population neuronal electrical signals serve as an effective bridge between theory and experiment. By pre-training artificial neural networks exclusively on largescale synthetic data, we demonstrate robust zero-shot generalization across diverse brain regions, experimental paradigms and species, enabling the accurate inference of single-unit activities and cell-type properties without exposure to real data. Furthermore,uncovering a substantial population of functionally competent but weakly active neurons systematically obscured by conventional heuristics, our framework resolves a long-standing discrepancy regarding ocular dominance in mouse primary visual cortex. These findings establish biophysical simulations as a reference standard, bridging the gap between theoreticalunderstanding and experimental observation through data-driven inference.

Disclosures: Y. Gu: None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.02/LL64

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

Title: Multidimensional Edit Distance and its Applications in Abstract Concepts Recognition

Authors: *A. KATZ[1], M. TEICHER[2];
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Abstract: In a time when computational tools and technology are advancing quickly, the focus is mainly on AI and LLMs. These tools primarily provide access to supercomputing and knowledge; however, they require textual, or at least fixed-shape vector, input. Moreover, such models tend to underperform on complex tasks that involve reasoning and the exact calculation of multiple-step analytical problems. Thus, applying them to neuroimaging data may reach an upper bound when addressing a challenging problem domain. We introduce a well-defined metric for synchronized data, such as neural activity, and use it to measure the similarity between real brain recording trials as a test case. Applying this metric shows that it corresponds directly

to the abstract concept underlying the perception of the visual number/object, resulting in clustering of identical or similar concepts, specifically numbers. We defined new methodology and algorithms to characterize properties of brain activity related to different numbers (e.g., number 2 and number 3) and to distinguish brain activity during different visual stimuli of the same number (e.g., figure 3 or three circles). Guessing the one-digit number a person is thinking of was done via MEG recording. One hundred percent (100%) accuracy can be reached after 45 seconds (on average) of trials, and in many cases after 15 seconds. So far, we have proved this finding for distinguishing between numbers from 1 to 5. This is the most refined thought identification achieved so far. Moreover, the results show that there is an abstract concept of a number in the brain that is invariant under visual stimuli such as classical digits and white circles on a black background.

Disclosures: A. Katz: None. **M. Teicher:** None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.03/LL65

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

Title: Computational design of an implantable waveguide-integrated plasmonic photothermal interface for in vivo neural stimulation

Authors: K. ANAN[1,2], A. RAHMAN[3], ***Z. AHMED**[4];
[2]Electrical and Electronic Engin., [1]United Intl. Univ., Dhaka, Bangladesh; [4]Electrical and Electronic Engin., [3]Bangladesh Univ. of Engin. and Technol., Dhaka, Bangladesh

Abstract: Photothermal stimulation with plasmonic gold nanoparticles offers a way to excite neurons without genetic modification and without passing current through tissue. The gold absorbs resonant light and converts it to local heat, giving high spatial precision for millisecond-scale neural stimulation. Earlier implantable in vivo photothermal stimulators delivered this light through optical fibers, making each stimulation site constrained by the fiber cross-section and limiting dense multi-site access. Here, we evaluated a simulation-based implantable probe architecture in which multiple waveguides route light to plasmonic nanoparticle arrays placed at distal stimulation zones. We modeled the stimulation site consisting of ten ellipsoidal gold nanoparticles patterned at the end of a waveguides with sub-micron dimensions. A biocompatible aluminum nitride layer capped the array and spread the concentrated nanoparticle heat laterally before it reached tissue, shielding neurons from the peak particle temperature. Optical absorption was computed with full-field optical simulations, and the resulting per-particle power was passed into a Pennes bioheat model solved. The geometric parameters were co-optimized with Bayesian optimization for highly efficient operation of the plasmonic photothermal stimulator. The optimized array absorbed close to 90% of the guided power at 1550 nm. At an input of 1.45 mW, the model predicted a 1 K tissue temperature rise out to a

radius of roughly 14 μm, giving an effective stimulation volume near 11,200 μm³, while maintaining thermal damage threshold of tissue at the stimulator interface. A perturbation study spanning ±4% fabrication error showed that the broad plasmon band held absorbed power between 88% and 93%, so the thermal target survived realistic tolerances. These simulations suggest that co-designing the optical and thermal layers could yield compact waveguide-addressed photothermal stimulation sites for millisecond-scale in vivo neural excitation while satisfying stimulation-volume and safety constraints. The results support waveguide-integrated plasmonic arrays as a route toward implantable multi-site photothermal neural stimulator with compact device footprint.

Disclosures: Z. Ahmed: None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.04/LL66

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

Title: Orofacial tracking in freely moving animals captures behavioral phenotypes beyond standard 3D pose analyses

Authors: *A. SABATH[1], D. ZALLES[2], Y. SHI[1], J. WU[3], R.-Z. ZHAN[1], T. W. DUNN[3]; [1]Duke Univ., Durham, NC; [2]Duke Univ., Miami, FL; [3]Biomed. Engin., Duke Univ., Durham, NC

Abstract: Methods for computational ethology of lab animals have advanced to enable automated high-throughput behavior quantification with unprecedented spatial and temporal resolution. However, current studies either focus on the full body in freely moving animals, or movement of specific body part(s) of animals when animals are restricted to a single task (forepaw, tongue, face, etc.), essentially limiting the study to a single spatial scale. As a result, it remains unclear how behavioral representations derived from full-body movements vs those from specific body parts are related, especially for parts, such as the face, not typically tracked in freely moving animals. Here we investigated the degree to which facial movements, which have recently been shown to express a rich set of behaviors, are associated with full-body kinematics. We hypothesized that facial movements could provide phenotypic information in mouse models of neuropsychiatric disorders that was complementary to full-body behavioral motifs. To test this, we video-recorded C57BL/6 mice in an open-field test (OFT) with and without lippolysaccharide (LPS) administration as a model of anxiety-like behavior (4 hours post-injection) and depression-like behavior (24 hours post-injection) or control vehicle (saline). To enable simultaneous tracking of face and full-body in freely moving mice, we extended DANNCE to track 16 facial landmarks in addition to standard full-body 3D poses. This approach, facial-DANNCE (f-DANNCE) achieved ~1.7 mm mean keypoint position error, and close agreement with anatomical measurements of mouse head dimensions (<20% deviation in

segment lengths). Unsupervised segmentation of 3D body and facial keypoint dynamics revealed novel facial behavioral motifs distinct from full-body motifs (Normalized Mutual Information 0.28±0.02, Adjusted Rand Index 0.13±0.03). Analyzing importance of features in supervised machine learning models classifying video segments into depressed (for 24 hr post LPS sessions) vs control (24 hrs post saline) revealed higher importance of facial features (6.14% ±1.3 gain in accuracy, 0.22±0.03 gain in F1 score, 4/5 facial features in top 5 features used by all models). Together, these results illustrate the utility of freely moving facial tracking for phenotyping models of depression and provide a framework for future studies of the relationship between body and facial expression and their neural underpnnings.

Disclosures: A. Sabath: None. **D. Zalles:** None. **Y. Shi:** None. **J. Wu:** None. **R. Zhan:** None. **T.W. Dunn:** None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

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

Support: NSERC Grant PDF-599687-2025
NSERC Discovery Grant RGPIN-2022-04162
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Title: MEAP-vis: A tool mapping network activity to consciousness

Authors: *J. E. ST JEAN[1], É. P. SELLAR[1], N. ROULEAU[1,2];
[1]Hlth. Sci., Wilfrid Laurier Univ., Waterloo, ON, Canada; [2]The Allen Discovery Ctr., Tufts Univ., Medford, MA

Abstract: The neuronal networks underlying the complexity of the human brain are intimately connected through electrophysiological signals making the ability to measure these signals crucial in understanding network function. The implementation of high-density microelectrode arrays (HD-MEA) not only yield high resolution signals but also provide a method of input directly to cells. This has recently been used in the generation of sentience - the ability to alter the internal state of a system in response to sensory information - in neuronal cultures. However, this sentience has caused some to prematurely claim that these neurons are conscious. Although required for consciousness, sentience is not sufficient, necessitating further study. The field of consciousness research is hotly contested, with the emergence of artificial intelligences encouraging some researchers to examine substrate independent tools. Integrated information theory (IIT) defines consciousness as the total amount of integrated information in a network, demarked as φ. Considering that φ is defined based on networks rather than the brain, it is a substrate agnostic metric of consciousness (MoC) that could be potentially applied to neuronal cultures.

Currently the open-source Python package PyPhi can be used to calculate φ, however, being implemented through Python makes it inaccessible for many users. The presented work has two primary goals, first to simplify the pipeline between the generation of electrophysiological data obtained through HD-MEA and PyPhi and second to characterize φ in neuronal cultures under various parameters. The first goal was achieved through the production of Multielectrode Array - PyPhi Visualization Tool (MEAP-vis), a graphical user interface which reads .h5 or .csv data files produced by HD-MEAs and returns both the calculated φ and its required intermediary parameters. Measurements of φ will be calculated from a network of four nodes, with activity defined as the number of neuronal spikes measured at four temporal grains (100 ms to 5000 ms). Further, the spatial separation of recording signals will also be measured ranging from no space between recording electrodes to a distance of 5 electrodes between each recording electrode (87.5 μm). For each temporal and spatial value φ will be measured based on cortical neurons obtained through three-separate isolations. The generation of MEAP-vis and its associated data may support the use of φ while enabling similar processes for other MoCs and their application to other systems, dramatically simplifying the study of consciousness and allowing more researchers to participate in the field.

Disclosures: J.E. St Jean: None. **É.P. Sellar:** None. **N. Rouleau:** None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.06/LL68

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

Title: TRIM it! Multilevel Latency Estimation for EEG Data Analysis

Authors: S. BARAL[1], C. CARROLL[3], K. WINSLER[2], *S. J. LUCK[4];
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Abstract: Event Related Potential (ERP) research relies on averaging EEG recordings across multiple trials to obtain reliable estimates of brain activity. However, a major challenge is trial-to-trial latency variability in the underlying neural components. Trials within the same condition may share identical waveform morphology but differ in timing. Such temporal misalignment can distort averaged waveforms, attenuate and broaden peaks, and potentially generate spurious differences between experimental conditions (Luck, 2014). Consequently, observed ERP differences may not reflect genuine changes in neural amplitude or morphology, thereby complicating interpretation, causing loss of power or inflation of Type I errors.
ERP data are inherently multilevel, with trials nested within conditions and conditions nested within subjects. Latency variability can occur at each of these levels. For example, in an N170 experiment, one participant may consistently process faces more rapidly than another participant, while the face stimuli may elicit an earlier onset of the neural component than scrambled face

stimuli. Ignoring this hierarchical structure risks obscuring meaningful sources of temporal variation and limiting the interpretability of ERP findings.
To address these challenges, we propose a novel Time Registration method Integrating Multilevel analysis (TRIM). Our approach extends time registration approaches from functional data analysis, which estimate nonlinear temporal shifts among functions that share a common underlying shape (Ramsay & Silverman, 1997; Wrobel et al., 2018). While existing registration methods are generally restricted to a single level of variation, our framework accommodates an arbitrary number of hierarchical levels and is implemented here for the common three-level ERP structure of trials, conditions, and subjects. TRIM estimates level-specific nonlinear warping functions that can be used directly to study latency variability or to obtain latency-corrected data for conventional ERP analyses.
Using realistic EEG simulations, we demonstrate that latency variability can induce apparent condition differences even when underlying amplitudes are identical. Conversely, latency variability may artificially inflate or attenuate true amplitude differences. By correcting temporal misalignment, our method accurately recovers the true underlying waveform structure. These results highlight the importance of modeling latency variability in ERP research and demonstrate how multilevel registration can improve the validity and interpretability of neural measures.

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Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

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Program #/Poster #: PSTR160.07/LL69

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

Support: 1690
1286

Title: Optical structural biology via conventional microscopy

Authors: *S. CHANDA[1], D. KRAH[2], A. NTOLKERAS[4], S. RIZZOLI[3], A. SHAIB[2];
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Abstract: Optical structural biology via conventional microscopy Sushovan Chanda[1], Donatus Krah[1], Antonios Ntolkeras[1], Silvio O. Rizzoli[1], and Ali H. Shaib[11] Department of Neuro- and Sensory Physiology, University Medical Center Göttingen, Göttingen, Germany

Structural biology has revealed the architecture of proteins, but its main methods, as X-ray crystallography, NMR and cryo-EM, remain dependent on specialized instruments and infrastructure. Fluorescence microscopy is molecularly specific, widely available, and compatible with routine biological workflows, yet it has not generally been able to recover protein structures. The limitations include not only optical resolution, but also by labeling density, linkage error, probe size, noise, and user-dependent particle selection. Here we describe an optical route for extracting structural information from individual protein molecules using expansion microscopy, fluorescence fluctuation imaging, and automated computational reconstruction on data acquired with conventional confocal microscopy. Proteins are physically enlarged in a hydrogel, labeled after expansion, and imaged as single expanded particles. This converts molecular fluorescence from a localization readout into a structurally informative measurement, while reducing the relative impact of linkage error and improving access to molecular surfaces. Across purified protein datasets, the workflow enables automated particle recognition, selection, and three-dimensional reconstruction, improving recovery of molecular shape. The resulting reconstructions reach Fourier shell correlation-based resolution estimates around 11 Å, sufficient to distinguish major features of individual proteins. These results suggest that conventional optical microscopes can be pushed beyond mapping molecular position toward recovering molecular form, opening a practical route to accessible optical structural biology of single molecules.

Disclosures: S. Chanda: A. Employment/Salary (full or part-time):; University Medical Center Göttingen, Göttingen, Germany, Göttingen, Germany. **D. Krah:** A. Employment/Salary (full or part-time):; Department of Neuro- and Sensory Physiology, University Medical Center Göttingen, Göttingen, Germany. **A. Ntolkeras:** A. Employment/Salary (full or part-time):; Department of Neuro- and Sensory Physiology, University Medical Center Göttingen, Göttingen, Germany. **S. Rizzoli:** A. Employment/Salary (full or part-time):; Department of Neuro- and Sensory Physiology, University Medical Center Göttingen, Göttingen, Germany. **A. Shaib:** A. Employment/Salary (full or part-time):; Department of Neuro- and Sensory Physiology, University Medical Center Göttingen, Göttingen, Germany.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.08/Web Only

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

Support: NRF Grant 2021R1F1A1062265
DGIST R&D Program 26-NT-01

Title: pNMS: A Python package for biophysical modelling and parallel simulation of the neuromuscular system

Authors: *H. KIM;
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Abstract: Neuromuscular cells play a pivotal role in generating and controlling muscle force for our daily activities. The heterogeneity in their properties and organization across body parts and ages has challenged the development and utility of computational models and simulations across a wide range of research and application contexts related to the neuromuscular system. Applying an inverse approach, we developed an open-source Python package called pNMS that allows users to automatically construct and parallelly simulate populations of biophysical models for heterogeneous neuromuscular cells at multiple levels: motoneuron, muscle-tendon fiber, and motor unit. We demonstrate example simulations and their validity in comparison to experimental findings. The pNMS may serve as an accurate and efficient computational platform for basic research, educational settings, and motor rehabilitation.

Disclosures: H. Kim: None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.09/LL70

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

Title: Discovering Solvable Inverse Problems with the Brain Emulation Challenge

Authors: *R. A. KOENE;
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Abstract: Reverse-engineering neural systems requires reconstructing circuit architecture, identifying components, and estimating parameters across appropriate scales, yet for all but the smallest animal brains, available experimental data are insufficient relative to the number of latent variables, leaving predictions valid only within narrowly constrained tasks and short time windows. Progress depends on principled system decomposition: determining where black-box representations are acceptable given obtainable data, and where they are not.The Brain Emulation Challenge (BEC) addresses this by providing a suite of in-silico model systems paired with synthetic datasets generated by virtual instruments, creating a controlled bootstrapping environment for benchmarking methods of neural system identification. Here we demonstrate how this platform enables systematic exploration of inverse problems of increasing complexity: from single-neuron parameter estimation to feedforward and recurrent network architectures exhibiting balanced excitation and inhibition, rhythmic modulation of network states, and multiple forms of synaptic plasticity including spike-timing-dependent plasticity (STDP) and behavioral timescale synaptic plasticity (BTSP). By making ground-truth parameters accessible within each in-silico system, the BEC allows rigorous evaluation of where current methods succeed or fail, and what data would be required to resolve presently underdetermined problems.

Disclosures: R.A. Koene: None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

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Title: Assessing computational reaction-diffusion simulation tools for modeling astrocyte calcium signaling in realistic morphologies

Authors: S. SEPPÄLÄ, L. KETO, D. NDUBUAKU, A. MÄKI, T. MÄKI-MARTTUNEN, M.-L. LINNE, *T. MANNINEN;
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Abstract: Astrocytes are key regulators of synaptic plasticity and contribute significantly to complex brain processes, yet the detailed mechanisms through which they exert these effects are still not fully clarified. Our research focuses on constructing brain-region-specific computational models to study astrocyte characteristics that are important for synaptic plasticity, as well as learning and memory. When aiming to build highly detailed and morphologically realistic astrocyte models, it is essential to critically assess tools that have not traditionally been applied to glial research. These tools include a variety of simulation platforms that are available for modeling cellular dynamics, such as NEURON (Carnivale and Hines, 2006), STEPS (Hepburn et al., 2012), MCell (Stiles and Bartol, 2001), and NeuroRD (Oliveira et al., 2010). To investigate the applicability of these platforms, we implemented models of calcium diffusion and calcium-calmodulin reaction-diffusion dynamics using mouse and human astrocyte morphologies derived from high-resolution electron microscopy datasets (Nguyen et al., 2023; Shapson-Coe et al., 2024; Bae et al., 2025). These reconstructions were processed with the CellRemorph toolkit (Keto and Manninen, 2023), enabling detailed representation of fine astrocytic processes. Our findings show notable differences in implementation, usability, and computational demands across the tested tools. These observations indicate that, although many existing tools perform well for neuronal systems, they are not always ideally suited for capturing the intricate structure and signaling dynamics of astrocytes. In particular, there are clear trade-offs between modeling precision and flexibility, especially when representing thin astrocytic branchlets and complex intracellular signaling patterns. With the help of this tool analysis, our ongoing work involves extending our previous synapse model (Manninen et al., 2020) with realistic astrocyte morphologies, enabling us to systematically explore how astrocytic calcium dynamics and structural properties shape synaptic plasticity. Ultimately, this modeling strategy provides a

robust platform for studying astrocyte function in both healthy neural circuits and pathological conditions.

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Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

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

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Title: Self-supervised recovery of calcium dynamics from fluorescence measurements

Authors: *H. YU, Y. YOON;
KAIST, Daejeon, Korea, Republic of

Abstract: Fluorescent calcium imaging provides an accessible readout of neural activity, but the measured signal can differ substantially from the underlying biological dynamics. This mismatch complicates comparisons across recordings, indicators, and experimental conditions, particularly when transient activity patterns are of interest. We developed a self-supervised reconstruction framework that estimates latent calcium-related dynamics directly from fluorescence measurements without requiring paired ground-truth signals. The approach uses information contained within each recording to generate reconstructions that remain consistent with the observed data while reducing measurement-dependent distortions. In preliminary evaluations using simulated and experimental calcium-imaging data, the reconstructed signals exhibited sharper temporal structure, improved robustness to noise, and greater consistency across recording conditions than the original fluorescence measurements. The method was computationally efficient and did not require extensive manual tuning, suggesting that it could be incorporated into routine analysis workflows. These results support self-supervised

reconstruction as a practical strategy for extracting more interpretable activity dynamics from fluorescence-based neural recordings.

Disclosures: H. Yu: None. **Y. Yoon:** None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.12/LL73

Topic: G.02. Neuroendrocrine Processes and Behavior

Support: NIH/NIMH grant R01MH142540
NIH/NIDA grant R01DA058653
NSF/CAREER grant 2235858

Title: Informational Dimension Selection Based Spike Sorting Using Feature Core Clustering, and Neural-Network Quality Estimation

Authors: *L. D. DAVILA[1], D. W. BECK[2], C. N. HEATON[3], A. FRIEDMAN[4];
[1]Biol., The Univ. of Texas at El Paso, El Paso, TX; [2]Biol., The Univ. of Texas at El Paso, Gig Harbor, TX; [3]Biol., Univ. of Texas at El Paso, El Paso, TX; [4]Biological Science, UTEP, El Paso, TX

Abstract: Extracellular recording probes now range from single microwires to high-density arrays with hundreds of sensors, producing datasets whose dimensionality and structure vary substantially across experimental preparations. This variability creates challenges for spike sorting, as many algorithms produce method-dependent assignments and often require manual curation that does not scale to modern recording volumes. Here, we developed a feature-core clustering algorithm that identifies low-dimensional subsets of features that preserve separable cluster structure and performs spike assignment within these core spaces. Because ground-truth labels are unavailable in experimental recordings, we also trained neural-network ensembles to estimate cluster quality and identify split-unit detections, in which spikes from the same unit are assigned to multiple clusters. The method was benchmarked on 10 simulated extracellular datasets, with additive Gaussian noise standard deviations ranging from 1 to 10 μV and 600 ground-truth neuronal units per recording. Matching accuracy was defined as True Positive/(True Positive + False Positive + False Negative) × 100, where True Positive, False Positive, and False Negative were computed between each detected cluster and its matched ground-truth unit. Unit detection rate was defined as the fraction of ground-truth units detected with matching accuracy ≥ k. Mean unit detection rates were 22%, 40%, 53%, and 65% at k = 80%, 70%, 60%, and 50%, respectively. The split-unit ensemble achieved 88%-98% recall and 90%-97% precision across hyperparameter settings. The cluster-quality ensemble predicted matching accuracy without ground-truth labels with a median absolute error of 7.6 percentage points. These findings support

feature-core detection as a strategy for spike sorting and suggest that neural clustering algorithms may benefit from explicitly identifying the subspaces in which separability is expressed.

Disclosures: L.D. Davila: None. **D.W. Beck:** None. **C.N. Heaton:** None. **A. Friedman:** None.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.13/LL74

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

Support: AFOSR FA9550-23-1-0727

Title: Characterizing dynamics in spiking neural networks via a differentiable rate approximation

Authors: *N. GOVINDARAJAN[1,3], A. VERMANI[2], C. VERSTEEG[2], N. AU YONG[1], C. PANDARINATH[4];
[1]Emory Univ., Atlanta, GA; [2]Emory Univ., Decatur, GA; [3]Georgia Inst. of Technol., Atlanta, GA; [4]Biomed. Engin., Emory Univ. and GA Tech., Decatur, GA

Abstract: Over the past decade, dynamical systems tools have provided a powerful lens for understanding how computations arise from the interactions of neuronal populations. However, these tools have primarily been applied to study dynamics in continuous-valued, rate-based neural networks. Yet, mechanistically, biological computations are performed mostly by discrete, neuronal spiking. Spiking neural networks (SNNs) are an alternative model class that more closely mirrors the architecture of biological neural circuits. However, because SNNs discretely spike, existing tools for dynamical systems analyses, such as fixed point finding, cannot be applied to these networks due to computational intractability.
Here, we develop analytical tools for probing dynamics in SNNs. Specifically, to enable fixed point and flow field analyses, we construct a differentiable rate approximation of an SNN, approximating each neuron's spiking with a firing rate from a smoothed version of the analytical frequency-current curve. Critically, the rate approximation is not trained: it inherits the trained SNN's recurrent weight matrix, which governs the SNN's dynamics. We validate the approach on a family of SNNs built from leaky integrate-and-fire (LIF) neurons, each trained to produce a sine wave at a different target frequency (3, 4, 5, 6, 7 Hz). We hypothesized that the SNN's dynamical solution would be an attractive limit cycle centered around an unstable fixed point. After training, the SNNs accurately reconstruct the target sinusoidal dynamics, with the rate approximation recovering the oscillatory structure as well. In PC space, flow fields of the rate approximation revealed a limit cycle with minimal flow at its center, suggesting a fixed point. Using gradient-based methods in the full dimensional state space, we identified a single, unstable fixed point (dominant eigenvalue $|\lambda| > 1$ across all networks; 1.0006 - 1.0015) at the center of the limit cycle, consistent with our hypothesis. We found the rotational frequency of the dominant

eigenvalue was highly correlated with the target frequency (r = 0.9924). This work shows that fixed-point analysis, an analysis previously restricted to rate-based RNNs, can be extended to trained spiking networks, allowing us to reverse-engineer the solutions they learn and link more biologically realistic models to the dynamical-systems view of neural computation. Future work will aim to uncover how SNNs architect dynamical solutions in more complex tasks (e.g. 3 bit flip flop).

Disclosures: N. Govindarajan: None. **A. Vermani:** None. **C. Versteeg:** None. **N. Au Yong:** None. **C. Pandarinath:** C. Other Research Support (receipt of drugs, supplies, equipment or other in-kind support); Research Scientist, Meta.

Poster

PSTR160: From *In Vitro* Cellular Imaging and Simulations to Neural Activity Mapping

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR160.14/LL75

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

Support: NSF Grant 2117997

Title: Reconstructing and Forecasting High-Density Neural Spiking Activity Using Generative Diffusion Models

Authors: *K. JONES[1], H. FANG[2], R. CANFIELD[3], T. OUCHI[2], K. M. PERKS[4], A. L. ORSBORN[2];
[2]Electrical & Computer Engin., [3]Bioengineering, [4]Grad. Program in Neurosci., [1]Univ. of Washington, Seattle, WA

Abstract: Modeling relationships between neural spiking activity and behavior is essential for developing methods that can generate biologically plausible neural data. Synthetic data can supplement resource intensive experiments to improve our understanding of brain-behavior relationships, and advance engineering applications like brain-computer interfaces. Previous work used various generative algorithms on multielectrode spiking datasets to reconstruct neural activity time series and model neural-behavior relationships. These approaches have not been tested on neuron-level spiking activity when the behavior covariates are used to guide (or "condition") neural generation. Furthermore, few have extended the generative reconstruction to future neural forecasting. We address these challenges by proposing a new latent diffusion modeling framework and evaluating its performance on a novel dataset of high-density spiking activity recorded as monkeys perform motor behaviors. Our modeling approach includes two main components: an autoencoder for latent projection and reconstruction, and a diffusion transformer for forward noise and backward denoising within the latent spaces. We tested our model on spiking activity from frontal motor cortices (PMd, M1) measured with Neuropixels probes. Neural activity was recorded alongside eye and arm movements as monkeys performed point-to-point reaches from a central location to eight target locations. We found our model

successfully projected Neuropixel data into eight separable directional latent trajectories while generating behaviorally relevant spiking data. Our model also showed better held-out neural forecasting performance when compared to traditional latent diffusion architectures. Our results introduce diffusion models as a viable neural synthesis framework and enable future conditional high-density spiking data generation.

Disclosures: K. Jones: None. **H. Fang:** None. **R. Canfield:** None. **T. Ouchi:** None. **K.M. Perks:** None. **A.L. Orsborn:** F. Consulting Fees (e.g., advisory boards); Meta Reality Labs, EpiaNeuro.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.01/LL76

Topic: J.07. Data Analysis and Statistics

Title: A model-based alternative to cluster-based permutation tests for the analysis of time-resolved data

Authors: *L. NALBORCZYK[1], P. BÜRKNER[2];
[1]Aix Marseille Univ, CNRS, LPL, Aix-en-Provence, France; [2]Dept. of Statistics, TU Dortmund Univ., Dortmund, Germany

Abstract: A central goal in cognitive neuroscience is to determine whether, when, and where neural responses differ across conditions or groups. Standard analyses of time-resolved M/EEG data typically rely on mass-univariate tests with multiple-comparison correction, often using cluster-based permutation methods. Although these methods control error rates, they do not support precise inference about effect onset, offset, or location, because inference is made at the cluster level rather than at the level of individual time points. We propose a model-based alternative based on Bayesian generalised additive multilevel models (BGAMMs). The approach models neural responses as smooth functions over time, accounts for temporal dependencies and between-participant variability, and yields posterior odds that an effect is above zero, or above chance, at each time point. We benchmarked the method on simulated EEG data with known ground-truth onset and offset, comparing it with raw pointwise tests, FDR and FWER corrections, cluster-mass permutation tests, threshold-free cluster enhancement, and changepoint detection across 10,000 simulated datasets. BGAMMs showed the lowest bias and error for both onset and offset estimation, with near-unbiased temporal estimates, whereas pointwise and weakly corrected procedures were overly lenient and cluster-based approaches were less temporally precise. We then applied the method to empirical MEG decoding time courses from 32 participants and assessed stability using repeated split-half subsets. The BGAMM approach produced the most stable onset/offset estimates, that varied systematically with subset similarity. These results suggest that Bayesian additive multilevel modeling provides a practical and temporally precise framework for population-level inference on time-resolved neural effects,

complementing existing cluster-based approaches when temporal localisation is theoretically important. To facilitate adoption and reproducibility, the method is implemented in the open-source R package neurogam: https://github.com/lnalborczyk/neurogam.

Disclosures: L. Nalborczyk: None. **P. Bürkner:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.03/LL78

Topic: J.07. Data Analysis and Statistics

Title: First Digit Distributions Reveal Highly Reproducible Benford Conformity in EEG and MEG Power Spectra

Authors: *R. Y. SHEN;
Fischell Dept. of Bioengineering, Univ. of Maryland, College Park, MD

Abstract: Benford's law predicts a logarithmic distribution of first significant digits in many naturally occurring datasets. Prior studies have evaluated Benford conformity in time-domain EEG signals across anesthesia states and Alzheimer's disease; however, these small-sample investigations reported contradictory findings for normal brain function. We analyzed three publicly available, preprocessed datasets from healthy human participants: two EEG datasets (A: OpenNeuro accession no. ds004519, 40 participants, 62 channels, 1 run; B: ds004588, 42 participants, 19 channels, 1 run) and one MEG dataset (C: ds003633, 11 participants, 272 channels, 8 runs), totaling >16 billion data points. For each participant, channel, and run, we extracted first digit distributions from EEG/MEG recordings, time derivatives, power spectra, and five frequency bands (delta, theta, alpha, beta, gamma). The first digit distributions for dataset A are shown in Figure 1a-c. Conformity to Benford's law was quantified using Nigrini's mean absolute deviation (MAD) test. Across datasets, time-domain EEG/MEG signals showed nonconformity (mean MAD > 0.015), with MAD scores of 0.0178 ± 0.0025 (A, mean ± SD, n = 40 x 62 x 1), 0.0186 ± 0.0033 (B, n = 42 x 19 x 1), and 0.0201 ± 0.0021 (C, n = 11 x 272 x 8) for EEG/MEG recordings and 0.0163 ± 0.0033 (A), 0.0157 ± 0.0022 (B), and 0.0218 ± 0.0019 (C) for time derivatives. In contrast, power spectra showed close conformity (mean MAD < 0.006) in all datasets (MAD = 0.0039 ± 0.0013 (A), 0.0023 ± 0.0008 (B), and 0.0035 ± 0.0012 (C)). Topographic mapping revealed widespread nonconformity across sensors for time-domain signals, strikingly contrasting with near-uniform, close conformity for the power spectra (e.g., Figure 1d-f, dataset A), and all individual EEG/MEG frequency bands showed close or acceptable conformity. Our results identify a highly reproducible Benford conformity baseline in healthy brain EEG and MEG power spectra, suggesting that deviations from frequency-domain Benford behavior may provide simple, scalable markers for pathological brain states.

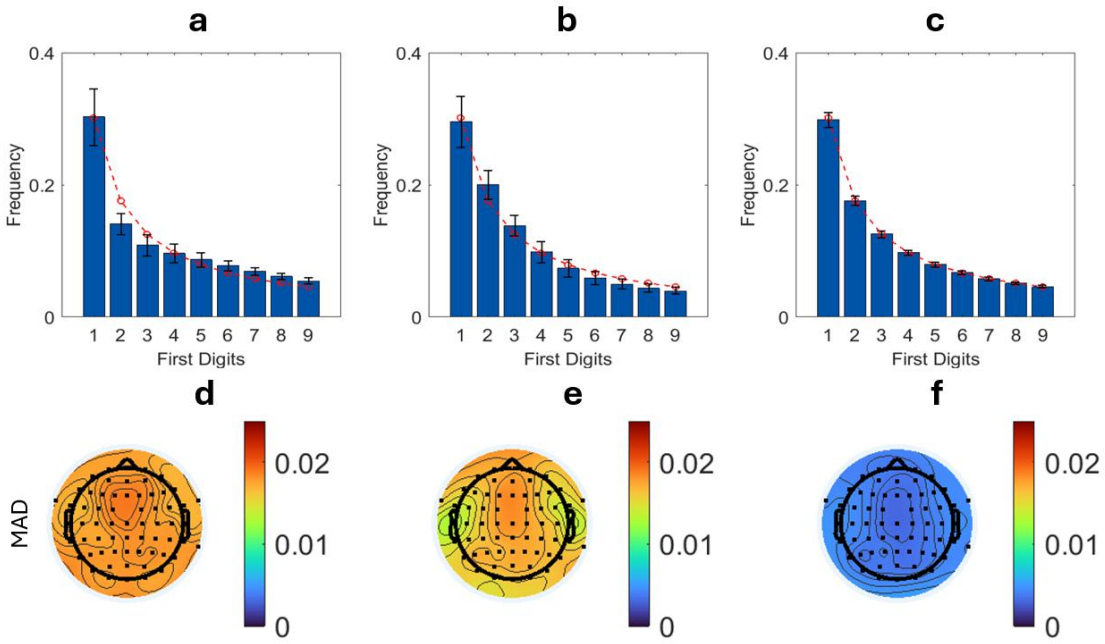


Figure 1. (a–c) First digit distributions in EEG recordings, time derivatives, and power spectra of dataset A (n = 40 × 62, error bar: ±1 SD). o: Benford distribution. (d–f) Corresponding topographic maps of mean MAD scores.

Disclosures: R.Y. Shen: None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.04/Web Only

Topic: J.07. Data Analysis and Statistics

Support: Signant Health

Title: Longitudinal Rater-Level Persistence of PANSS Data Quality Concerns in Schizophrenia Clinical Trials

Authors: *D. G. DANIEL[1], X. WANG[2], A. KOTT[3];
[1]Signant Hlth., McLean, VA; [2]Signant Hlth., Blue Bell, PA; [3]Sci. and Med., Signant Hlth., Prague, PA

Abstract: *Introduction*In clinical trials aberrant symptom rating patterns may contribute to non-specific variance, signal degradation and trial failure. Data analytic techniques that identify specific raters with persistently aberrant rating patterns across studies would facilitate remediation and inform future rater selection. This study evaluates cross-protocol longitudinal stability of data quality concerns using the primary rating scale in schizophrenia trials-the PANSS.

*Methods*Data from 887 PANSS raters across 18 schizophrenia trials (47,664 ratings) were analyzed. Two concerns were assessed: identical 30/30 PANSS item ratings at consecutive visits and large score changes (≥10, ≥15, ≥20 points) from the prior visit. Generalized Estimating Equations (GEE) examined whether data concerns in prior protocols predicted recurrence across 780 rater-protocol transitions (375 raters), using cumulative (any prior protocol) and lag-1 (immediately preceding protocol only) definitions and adjusting for number of prior protocol participations. A three-level logistic model decomposed variance into rater-, site-, and residual-level components using latent variable ICC approach.
*Results*Identical ratings showed strong cross-protocol persistence (cumulative OR=5.11, 95% CI 2.59-10.06; lag-1 OR=7.77, 95% CI 3.82-15.77; both p<0.0001). The likelihood increased with each additional prior protocol containing this concern (OR=1.36 per additional flagged protocol). Variance decomposition attributed 82.5% of latent variance to between-rater differences (ICC=0.825). Large score changes were primarily driven by within-rater residual variance (68-83%), consistent with true patient variability rather than rater effects; modest persistence was observed only at higher thresholds. Increasing ICC (0.17→0.89) indicated that less frequent concerns (≥20-point changes and identical ratings) are more strongly associated with rater-specific behavior.
*Discussion*Identical consecutive PANSS ratings represent a stable, rater-level data quality concern with strong cross-protocol persistence, whereas large score changes largely reflect clinical variability. These findings suggest that longitudinal, rater-level performance tracking—beyond within-protocol site monitoring—is feasible. Incorporating cross-protocol rater history may strengthen risk-based quality management in schizophrenia trials.

Disclosures: D.G. Daniel: E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signant Health. F. Consulting Fees (e.g., advisory boards); Signant Health. **X. Wang:** A. Employment/Salary (full or part-time):; Signant Health. **A. Kott:** A. Employment/Salary (full or part-time):; Signant Health. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Signant Health.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.05/LL79

Topic: J.07. Data Analysis and Statistics

Title: BMI-related microstructural alterations in prepubertal population: A QA-based connectometry analysis.

Authors: *Y. ROJAS-LEMUS[1], S. HIDALGO-TOBON[2], B. DE CELIS ALONSO[3], B. ROMERO BAIZABAL[4], P.-W. SO[5];
[1]Univ. Autonoma Metropolitana Iztapalapa, Iztapalapa, Mexico; [2]Fisica, UAM-Hospital Infantil de Mexico Federico Gomez, Ciudad DE Mexico, Mexico; [3]Fac. of Physical and Mathematical

Sci., Benemerita Univ. Autonoma De Puebla, Puebla, Mexico; [4]Hosp. Infantil de Mexico Federico Gomez, MEXICO, Mexico; [5]Neuroimaging, King's Col. London, London, United Kingdom

Abstract: Obesity represents a major public health issue in Mexico due to its high prevalence and its role as a risk factor for the leading causes of morbidity in the country [1]. This chronic metabolic disorder is associated with functional and structural changes in the adult brain [2,3]; thus, physical activity and nutritional guidance may not be the only approaches for treatment and prevention. Understanding how this condition affects pediatric brain structure and function may help healthcare professionals develop diversified strategies to reduce its prevalence in adulthood [4,5].This study presents a comparative exploratory diffusion-MRI QA-connectometry analysis to identify BMI-related alterations in white matter (WM) tracts in a cohort of 137 prepubertal subjects (n=47 with obesity, n=28 with overweight, n=62 controls; Tanner stage I; males [100%], ages 6-11 years). Diffusion-MRI data were acquired using a 3T scanner (SIEMENS SKYRA; 2D-EPI; TE=106 ms; TR=3200 ms; HARDI, 128 dir.; b=10000 s/mm^2, pix.res.=0.65, s. thick.=5.2 mm). Tract reconstruction was performed using DSI-studio (QSDR; output res.=3 mm isotropic). Intragroup analyses evaluated correlations between quantitative anisotropy (QA) and BMI using nonparametric Spearman partial correlations adjusted for age (T-score > 2.5; FDR < 0.05 with 4000 permutations). The research protocol was approved by the Ethics Committee of the Hospital Infantil de México Federico Gómez (HIM/2016/105) and adhered to the principles of the Declaration of Helsinki.Intragroup BMI-related analyses in pediatric subjects revealed the most extensive QA variations in WM tracts in the overweight group (74 tracts) compared with the obesity group (17 tracts) and the control group (60 tracts). The main involvement included the left inferior fronto-occipital fasciculus, corpus callosum tapetum, forceps minor, left uncinate fasciculus, and anterior commissure, subserving interhemispheric communication, socioemotional regulation, associative learning, and reward processing.Motivation and reward circuits appear particularly affected during the overweight stage, suggesting stage-specific neurodevelopmental dynamics in white matter organization.References:1. INEGInforma. *EDR. 2026*; 26(2).2. Gómez-Apo et al. J Obes 2021;(1):6613385.3. Raji et al. Hum Brain Mapp. 2010;31(3):353-364.4. Ronan et al. Cereb Cortex. 2020;30(4):2519-2528.5. Bauer et al. Pediatr Obes. 2015;10(3):196-204.

Disclosures: Y. Rojas-Lemus: None. **S. Hidalgo-Tobon:** None. **B. De Celis Alonso:** None. **B. Romero baizabal:** None. **P. So:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.06/LL80

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant NS124564
NIH Grant NS131069

NIH Grant NS127849
NIH Grant NS096761
NIH Grant EB029365
NSF GRFP DGE2140739

Title: Temporal Leakage in Offline Classification of EEG-Based Brain-Computer Interfaces

Authors: *J. H. ZHANG[1], J. KOSNOFF[1], H. WANG[1], B. HE[1,2];
[1]Dept. of Biomed. Engin., [2]Neurosci. Inst., Carnegie Mellon Univ., Pittsburgh, PA

Abstract: Brain-computer interfaces (BCIs) enable communication between the brain and external devices, offering a promising approach for restoring and augmenting motor function [1]. Electroencephalography (EEG)-based BCIs, in particular, provide a safe and accessible noninvasive solution. In offline analysis, continuous recordings are commonly segmented into non-overlapping time windows and treated as independent samples for model training. However, temporal nonstationarity may introduce data leakage between windows close in time, leading to overestimation of model performance under improper data splitting.

In this study, we evaluated the impact of data-splitting strategies on temporal leakage across four publicly-available motor imagery EEG datasets. EEG signals were segmented into 500ms and 1000ms long non-overlapping windows and classified using both EEGNet and common spatial patterns with shrinkage linear discriminant analysis (CSP-sLDA).

Performance was evaluated using four data-splitting strategies with increasing temporal separation between training and testing samples: an interleaved k-fold split that alternated neighboring windows between training and testing sets, a random k-fold split, a blocked k-fold split that preserved local temporal structure, and a fully chronological split in which earlier data were used for training and later data were used for testing. The interleaved split serves as a "worst-case scenario" for random k-fold where training and testing windows are always very close in time. The chronological split serves to replicate how models are trained and tested in online BCI experiments.

Splitting strategies that did not preserve temporal ordering (i.e., interleaved k-fold and random k-fold) consistently produced significantly higher test accuracies—up to 11.5%—than those that did (i.e., blocked k-fold and chronological) across datasets, models, number of folds, and window sizes (two-tailed paired t-tests, $p < 0.05$).

These findings demonstrate that temporal dependencies in EEG-BCI data can lead to overestimation of model performance. We recommend that future offline EEG-based BCI studies account for temporal structure when designing validation protocols to obtain more realistic performance estimates that better reflect online BCI applications.

[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,* 18, 26-49.

Disclosures: J.H. Zhang: None. **J. Kosnoff:** None. **H. Wang:** None. **B. He:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.07/LL81

Topic: J.07. Data Analysis and Statistics

Support: Pennsylvania Department of Health under Award No. 4100077082.

Title: Influence of correlational and parcellation methods on structure-function coupling in neurotrauma

Authors: *L. BAIRD[1], I. PESATI[2];
[1]Penn State Univ., State College, PA; [2]The Pennsylvania State Univ., Cupertino, CA

Abstract: The ultimate goal in many investigations of structure-function relationships in human brain networks is to uncover relationships that yield valuable clinical insights towards treatment outcomes for various brain disorders. MRI-based structure-function coupling (SFC) combining resting-state fMRI and diffusion tensor imaging (DTI) data may serve as a clinically-relevant metric, however, significant methodological variation in the calculation of SFC poses challenges for evaluating its translational potential. The current study aims to assess the influence of varying macroscale parcellation schemes and correlational methods on SFC measurements in both healthy aging and msTBI-exposed populations. In cohort of 84 participants (nTBI = 43, nControl = 41; nMale = 54, nFemale = 30) over 50 years of age (Mage = 64.17, SDage = 7.61) with a history of TBI, we evaluate the performance of SFC against a random permutation model in two established brain networks - the visual network and the default mode network - across multiple brain atlases (Schaefer 100, 400, 700 and 1000, Brainnetome and Glasser). We also test differences in SFC between two common correlational techniques, Pearson's r and Spearman's rho. Results from the random permutation model yielded inconsistent results across atlases and networks; empirical estimates of SFC were significantly different from the random permutation model in three atlases for the visual network (Schaefer 400, 700 and 1000) in the healthy aging group. In the default mode network, empirical estimates of SFC were different from the random permutation model in the Schaefer 400 atlas in the healthy aging group, and in the Schaefer 700 and Brainnetome atlases for the msTBI group. Comparisons of correlational techniques show a more pronounced effect of correlational technique on SFC calculations in the visual network when compared to the default mode network. No group differences in SFC were detected between the healthy aging and msTBI groups, regardless of atlas or correlational technique. These results suggest that SFC is highly sensitive to the selection of parcellation schemes and correlational technique and indicate a need for consistent standards in the field of SFC literature.

Disclosures: L. Baird: None. **I. Pesati:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.08/LL82

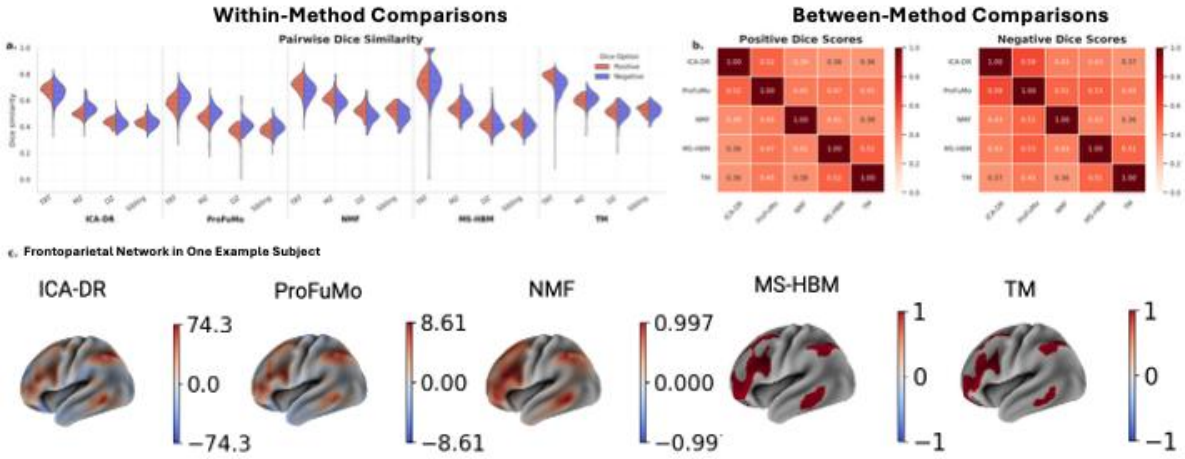
Topic: J.07. Data Analysis and Statistics

Support: NIH Grant R25NS130965
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other ABCD grants unable to fit in box above: U01DA041148, U01DA041093, U01DA041089, U24DA041123, U24DA041147

Title: Precision functional networks in the human brain: establishing correspondence across methods

Authors: *A. CROWN, S. NARANJO RINCON, K. HAMILTON, H. MODI, L. LUO, S. JARUKASEMKIT, J. BIJSTERBOSCH;
Washington Univ. Sch. of Med. in St Louis, St Louis, MO

Abstract: Resting-state functional MRI network topography can be used to study individual differences in functional organization that have been shown to covary with behavioral and clinical information (Bijsterbosch et al 2018; Lynch et al 2024; Wang et al 2015). Group and subject-level spatial topography maps are estimated via precision functional mapping (PFM) methods, but the consistency of network boundaries across PFM methods is unknown. We compared five PFM methods using the 6.1 release of the Adolescent Brain Cognitive Development cohort to investigate methodological and individual differences in network topography boundaries. After screening for motion and presence of three imaging sessions, we included N=3,050 subjects plus a held-out template group of N=100 used to define group priors. PFM methods included Independent Components Analysis and Dual Regression (ICA-DR), Probabilistic Functional Modes (ProFuMo), Non-Negative Matrix Factorization (NMF), Multi-Session Hierarchical Bayesian Modeling (MS-HBM), and Template Matching (TM). Methods were independently performed at a 14-network dimensionality. After subtracting the group mean, Sørensen-Dice scores were calculated separately on vertices where the subject's network was larger (positive dice score) or smaller (negative dice score) than the group. Ward's hierarchical clustering on group template networks (non-demeaned) revealed 9 out of 14 networks with close correspondence in all PFM methods (dice 0.42-0.93), which were included in further analyses. All PFM methods showed high test-retest reliability and similarity between monozygotic (MZ) and dizygotic (DZ) twins (Fig. 1A). When comparing network boundaries between PFM methods, the highest similarity was observed between ICA-DR and ProFuMo and between TM and MS-HBM (Fig. 1B), and similar network features were qualitatively observed at the subject level (Fig. 1C). These results demonstrate that despite large differences in methodological approaches, these PFM methods capture similar network topographies and individual differences.



Disclosures: A. Crown: None. **S. Naranjo Rincon:** None. **K. Hamilton:** None. **H. Modi:** None. **L. Luo:** None. **S. Jarukasemkit:** None. **J. Bijsterbosch:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.09/Web Only

Topic: J.07. Data Analysis and Statistics

Title: Posterior-Biased Delta Power at Term-Equivalent Age in Ex-Preterm Infants Compared With Term-Born controls

Authors: *S. SHIRAKI[1], D. ZAFER[2], H. HAYASHI[3], S. HAYASHI[4], H. RIN[5], C. ISHIKAWA[6], Y. KITASE[7];
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Abstract: Survivors of preterm birth remain at risk for later neurodevelopmental impairment, yet it is unclear whether neonatal EEG topography fully converges with that of term born infants by term-equivalent age (TEA). We tested whether ex-preterm infants show residual, band-specific posterior delta-power differences at TEA. We retrospectively analyzed clinically indicated EEGs recorded at ≥37 weeks postmenstrual age from 24 ex-preterm and 65 term-born infants. Major congenital anomalies, therapeutic hypothermia, sedation during EEG, severe intraventricular hemorrhage, cystic periventricular leukomalacia, and visually apparent background suppression were excluded. Artifact-free epochs from natural-sleep recordings were analyzed using Persyst Advanced review. Absolute delta power (0.53-4 Hz) was partitioned into five sub-bands across eight bipolar mintages. Group differences were assessed using Mann-Whitney U test with false

discovery rate (FDR) correction across 40 pair-by-band contrasts, and effect sizes were summarized by Cliff's δ. To account for recording-age differences, log-transformed power was also modeled with group and postmenstrual age as covariates. Ex-preterm infants showed a frequency- and region-dependent tendency toward higher delta power, with the largest effect-size differences in posterior and right-posterior montages. Low-delta activity was relatively elevated across posterior regions, whereas higher-delta activity showed a more focal right-occipital/posterior emphasis. Similar posterior-biased patterns were observed after post menstrual-age adjustment, but confidence intervals often included zero and no contrast survived FDR correction. Thus, these findings should be interpreted as exploratory evidence of a posterior, spectrally unbalanced delta profile rather than definitive proof of group differences. Region- and band-resolved qEEG may provide a practical bedside framework for detecting residual functional brain-activity patterns at TEA in infants born preterm. External validation, standardized sleep-state assessment, EEG-MRI integration, and longitudinal neurodevelopmental follow-up are needed to determine whether this posterior delta profile represents a reproducible biomarker of later vulnerability.

Disclosures: S. Shiraki: None. **D. Zafer:** None. **H. Hayashi:** None. **S. Hayashi:** None. **H. Rin:** None. **C. ishikawa:** None. **Y. Kitase:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.10/Web Only

Topic: J.07. Data Analysis and Statistics

Support: National Research Foundation of Korea RS-2026-25483830
National Research Foundation of Korea RS-2023-00265824

Title: Subject-Independent Prediction of Motor Function Using an EEG Foundation Model in Older Adults

Authors: *H. KIM, H. KIM, G. KWON, J. LEE;
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Abstract: Resting-state EEG provides non-invasive access to neural dynamics underlying motor function, making it a promising tool for passive clinical monitoring in aging populations. Predicting continuous clinical scores from EEG remains challenging due to limited labeled data, high inter-subject variability, and the need for subject-independent evaluation to prevent data leakage. We hypothesized that a foundation model-based approach, leveraging pre-training on large-scale EEG data, would generalize better to unseen subjects and investigated its ability to predict the Timed Up and Go (TUG) score from resting-state EEG in older adults, benchmarked against conventional deep learning baseline models. A total of 119 adults aged 57 to 84 years were included. Resting-state EEG was recorded in a continuous 10-minute session consisting of

Eyes-Open (EO) followed by 5 minutes of Eyes-Closed (EC), and the full sequential recording (EO+EC) was used as model input. 19-channel EEG data were preprocessed using band-pass filtering (0.5 - 45 Hz), notch filtering (60 Hz), resampling to 200 Hz, ICA-based artifact removal (ICLabel), and automated epoch rejection (Autorejection). We adopted LaBraM, an EEG foundation model pre-trained on large-scale multi-session EEG, as the backbone of a transformer architecture and fine-tuned it for subject-level TUG regression by replacing the task head with a regression layer and applying Low-Rank Adaptation (LoRA). Performance was compared against EEGNet, ShallowConvNet, and DeepConvNet under 10-fold group cross-validation with a subject-independent split. Our LaBraM-based model achieved the highest coefficient of determination (R2 = 0.373) for TUG prediction, outperforming all conventional baseline models: EEGNet (R2 = -1.901), ShallowConvNet (R2 = 0.231) and DeepConvNet (R2 = -1.298). These findings support our hypothesis and demonstrate the feasibility of motor function prediction from resting-state EEG using a fine-tuned foundation model. The superior performance of our model likely stems from generalized EEG representations acquired through large-scale pre-training on diverse multi-session data, which alleviated the need to learn low-level features from the limited clinical dataset. Furthermore, LoRA-based fine-tuning preserved these pre-trained representations while suppressing overfitting under subject-independent evaluation. This approach may contribute to scalable, passive motor assessment tools for aging populations.

Disclosures: H. Kim: None. **H. Kim:** None. **G. Kwon:** None. **J. Lee:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.11/LL83

Topic: J.07. Data Analysis and Statistics

Support: NIH Grant UH3 NS135168

Title: Machine Learning Based Phenotyping of the Response to Mindfulness for Pain

Authors: *B. NEPHEW[1], J. A. KING[2];
[2]Peterson Family Dean of Arts & Sciences, Professor of Biol. & Biotech., [1]Worcester Polytechnic Inst., Worcester, MA

Abstract: Millions of people each year suffer from chronic low back pain (cLBP), which adversely affects their physical and mental health. While non-pharmacological interventions such as mindfulness are known to be effective in treating cLBP, not all patients experience the same benefit. Determining who these treatments might work best for is difficult, as there are no reliable predictors of the response to mindfulness for cLBP. The objective of the current study was to apply predictive machine learning to data collected from clinical trials of mindfulness for cLBP to identify phenotypes characterizing those who did and did not respond to the intervention. Various machine learning techniques were used to identify key characteristics of

responders and non-responders. The top three phenotypes for each were able to identify responders and non-responders with 92-100% precision. Results from this machine learning based phenotyping can guide clinician and patient decision-making to maximize clinical efficiency, patient outcomes, and resource use as well as inform research and development of mindfulness-based treatments for pain.

Disclosures: B. Nephew: None. **J.A. King:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.12/LL84

Topic: J.07. Data Analysis and Statistics

Title: Intrinsic cortical BOLD dynamics link dynamic motifs to neurochemical architecture and behaviors

Authors: *J. XIAN, Y. WANG, W. YIN, W. LIN;
Dept. of Radiology, Univ. of North Carolina, Chapel Hill, NC, USA, Chapel Hill, NC

Abstract: Intrinsic cortical BOLD dynamics link dynamic motifs to neurochemical architecture and behaviors**Introduction.** Human cortical organization is usually described through inter-regional BOLD connectivity, yet each region also possesses intrinsic temporal dynamic BOLD signals that may form a complementary organizing principle. **Methods.** Using resting-state fMRI from the Human Connectome Project, we parcellated the cortex and assessed each region's time series with highly comparative time-series analysis (HCTSA), extracting thousands of multiscale temporal features. A proxy-based contrastive model learned region-specific HCTSA features, identifying regions with similar HCTSA features across individuals and scanning sessions while repelling different regions (Fig. a). We validated the representation in held-out subjects, unseen sessions, and an independent cohort, and compared it against other commonly used dimensionality-reduction and feature-selection baselines.**Results.** The learned latent space recovered region identity in unseen individuals well above chance (accuracy=0.184; chance=0.005, Fig. b). Regional identity, rather than subject or session, dominated the representation. Cross-subject similarity was the highest within the same region, followed by within a network, and lowest across networks (Fig. c). This structure organized into six mesoscale dynamic motifs with coherent but distributed cortical patterns that only partially matched canonical networks (Fig. d). These motifs spanned across 4 continuous dynamic axes (timescale, distributional shape, local-switching/model-structured dynamics, asymmetry) that mapped onto neurotransmitter maps, cognitive terms, and cortical gradients (Fig. e). Individual deviations within this motif architecture tracked behaviors, with different behaviors associated with the switching of regions between distinct dynamic axes (Fig. f-h).**Conclusions.** Intrinsic temporal dynamics constitute a learnable, motif-based architecture of human cortical organization, bridging regional signal phenotypes, mesoscale motifs, neurobiology, and

behaviorally relevant individual differences.

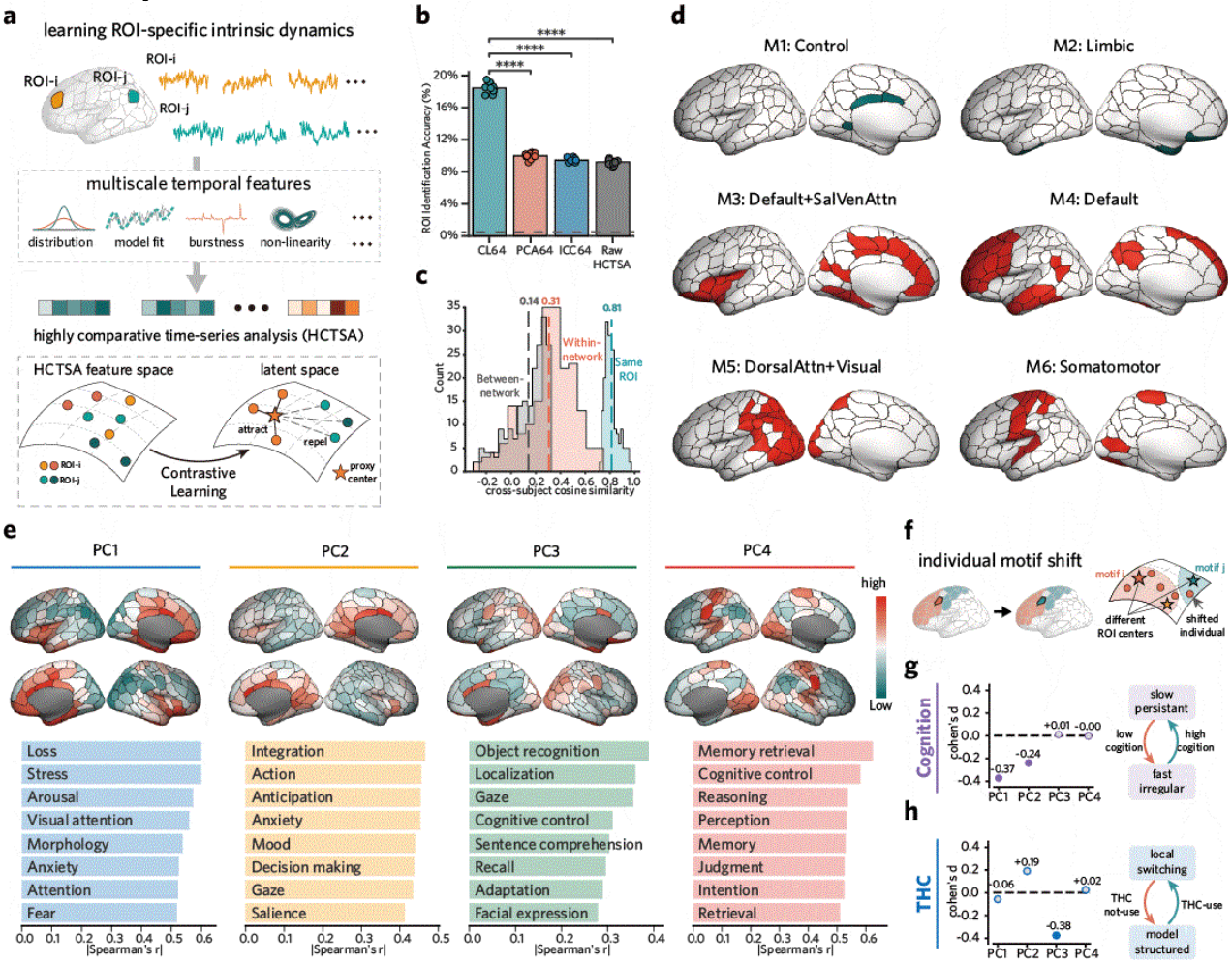


Figure. Intrinsic cortical BOLD dynamics reveal region-specific motifs and behaviorally relevant individual shifts.a, HCTSA+proxy contrastive learning embeds regional BOLD dynamics. b, Latent space identifies held-out regions above chance and baselines. c, Similarity follows region>network>cross-network. d,e, Six motifs vary along four dynamic PCs. f–h, Individual motif shifts relate to cognition and THC use.

Disclosures: J. Xian: None. **Y. Wang:** None. **W. Yin:** None. **W. Lin:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.13/LL85

Topic: J.07. Data Analysis and Statistics

Title: Phase-resolved Cortical Traveling Waves are Linked to Canonical Brain Maps

Authors: *Y. WANG[1], J. XIAN[2], W. YIN[3], X. LI[3], Y. ZHENG[4], W. LIN[5];
[1]Dept. of Radiology, Univ. of North Carolina, Chapel Hill, NC; [2]Dept. of Radiology, Univ. of North Carolina, Chapel Hill, NC, USA, Chapel Hill, NC; [3]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Lampe Joint Dept. of Biomed. Engineering, Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Univ. North Carolina @ Chapel Hill, Chapel Hill, NC

Abstract: Large-scale cortical activity is shaped by both synchronous interactions and organized propagation across the cortex. Although traveling waves have been observed in human brain activity, it remains unclear how dominant traveling-wave modes relate to canonical cortical maps, including receptor distributions, microstructural features, and functional gradients.We applied complex principal component analysis (CPCA) to resting-state fMRI data from the Human Connectome Project to identify dominant phase-resolved propagation modes. For each CPCA component, we reconstructed cortical activation maps across phase bins, summarized their network-level distributions, reconstructed functional connectivity, and related these maps to multimodal cortical annotations from neuromaps.The first three CPCA components revealed distinct propagation modes with an organized inter-network structure. CPCA1 separated sensory-attention systems (visual (V), somatomotor (SM), dorsal attention (DA), and ventral attention (VA) networks) from frontoparietal (FPC) and default-mode (DM) networks (Fig. a). CPCA2 contrasted SM, DM, and limbic networks with VA and FPC networks, while V and DA networks occupied intermediate phases (Fig. b). CPCA3 further separated VA and V networks from the remaining systems (Fig. c). Phase-resolved reconstructed activation maps showed widespread FDR-significant associations with neuromaps annotations (Fig. d). CPCA1 aligned most strongly with the principal functional connectivity gradient, reflecting the sensory-association axis; CPCA2 was strongly related to the second and third functional connectivity gradients; and CPCA3 was associated with the second and fourth functional connectivity gradients as well as the MEG alpha map. These findings indicate that distinct traveling-wave modes are associated with distinct functional and neurophysiological axes of cortical organization.Cortical traveling waves reflect organized phase-resolved propagation modes with systematic correspondence to canonical cortical annotations. This work links inter-network phase structure, reconstructed functional coupling, and multimodal brain-map organization, extending the study of large-scale

cortical organization from static spatial relationships to phase-resolved propagation dynamics.

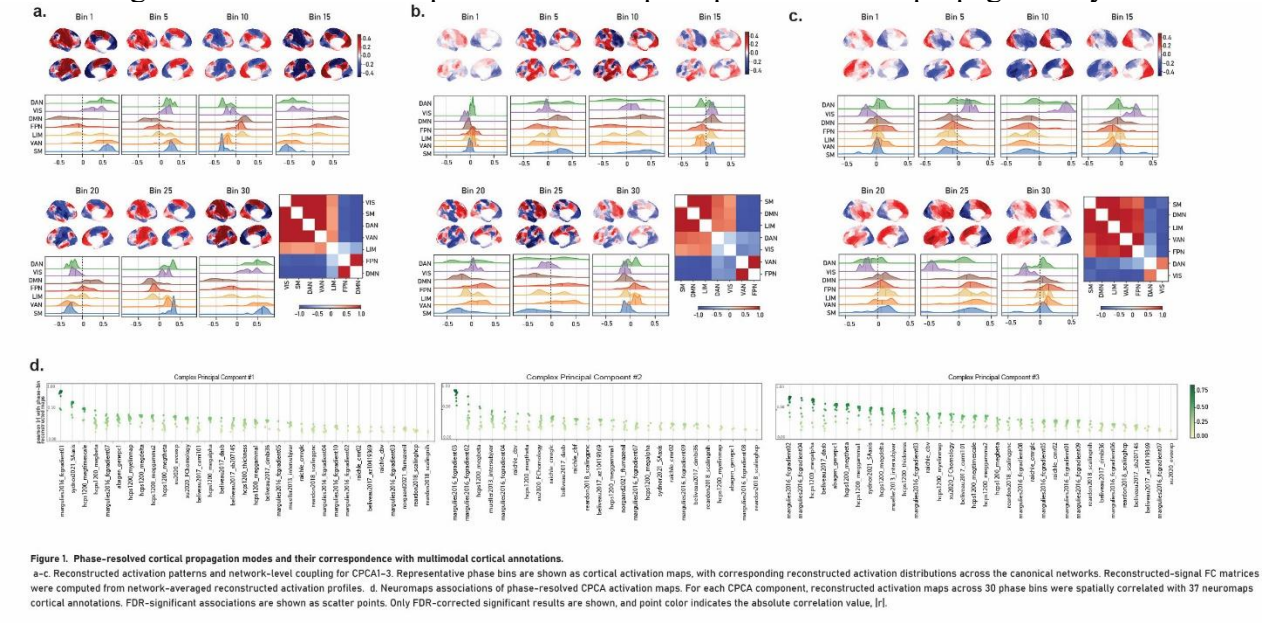


Figure 1. Phase-resolved cortical propagation modes and their correspondence with multimodal cortical annotations.
a–c. Reconstructed activation patterns and network-level coupling for CPCA1–3. Representative phase bins are shown as cortical activation maps, with corresponding reconstructed activation distributions across the canonical networks. Reconstructed-signal FC matrices were computed from network-averaged reconstructed activation profiles. d. Neuromaps associations of phase-resolved CPCA activation maps. For each CPCA component, reconstructed activation maps across 30 phase bins were spatially correlated with 37 neuromaps cortical annotations. FDR-significant associations are shown as scatter points. Only FDR-corrected significant results are shown, and point color indicates the absolute correlation value, |r|.

Disclosures: Y. Wang: None. **J. Xian:** None. **W. Yin:** None. **X. Li:** None. **Y. Zheng:** None. **W. Lin:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.14/LL86

Topic: J.07. Data Analysis and Statistics

Support: NSTC 114-2410-H-006-117
NSTC 113-2410-H-006-090

Title: An Adaptable Deep-Learning Framework for Whole-Brain Decoding and Perturbation-Based Interpretation of Task-fMRI

Authors: *H.-Y. HSIAO, D.-Y. CHEN;
Natl. Cheng Kung Univ., Tainan, Taiwan

Abstract: Task-based functional magnetic resonance imaging (fMRI) is widely used to probe the neural substrates of cognition, yet most decoding pipelines are confined to single subjects or ROI-centric classifiers, limiting cross-subject comparison of model-derived interpretations. We developed an integrated and adaptable deep multivariate pattern analysis framework that learns a shared whole-brain decoder from pooled trial-level beta maps while preserving subject-specific metadata for validation. The architecture incorporates multiple output heads to model distinct experimental or subject-related factors, enabling simultaneous prediction of task conditions and

other covariates. The framework pools data across participants into a shared decoding model while retaining subject-level information for validation and interpretation. This design provides a common basis for comparing perturbation-derived regional effects, while allowing subject-level grouping when evaluating performance. In human task-fMRI data, the shared decoder distinguished experimental conditions from whole-brain activation patterns. When applied to rat task-fMRI, the same pipeline remained effective for condition decoding, demonstrating adaptability across species. To interpret regional contributions, we introduced perturbation-based virtual-lesion analyses that quantify changes in model outputs, such as class evidence, predictive uncertainty, or decision structure when specific voxel clusters are occluded. This provides a model-level estimate of regional functional reliance during decoding. Together, these results support the deep-learning framework as a flexible approach for whole-brain decoding and interpretable model assessment. The framework provides a common modeling space for examining distributed representations and coordinated contributions of large-scale brain networks across participants and experimental conditions.

Disclosures: H. Hsiao: None. **D. Chen:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.15/LL87

Topic: J.07. Data Analysis and Statistics

Support: Royal Academy of Engineering Research Fellowship

Title: Out-of-distribution detection for EEG

Authors: *P. BOMATTER, H. GOUK;
Univ. of Edinburgh, Edinburgh, United Kingdom

Abstract: The clinical application of machine learning methods for electroencephalography (EEG) is hindered by a critical vulnerability: models can fail catastrophically, and with high confidence, when encountering cases that differ substantially from their training data. We designed a suite of signal perturbations to systematically evaluate methods for the detection of such out-of-distribution (OOD) cases. Our benchmark of relevant approaches spanning both methods that operate directly on the classification model (Maximum Softmax Probability (MSP), Energy Score, Out-of-Distribution Detector for Neural Networks (ODIN), Activation Shaping (ASH)) and methods that utilise a separate generative model of the training distribution (likelihoods, Typicality, Density of State Estimation (DoSE), Signal in the Noise (SITN)) reveals that the former group of methods is largely ineffective for EEG OOD detection (rarely exceeding an AUROC of 0.55), whereas in particular SITN achieves excellent results, frequently achieving near-perfect detection (AUROC > 0.9) at moderate to high perturbation severity levels. We further assessed the impact of OOD detection on downstream performance in a clinical

prediction task (pathology prediction on the TUAB dataset, N=2329 patients) and find that prediction accuracy drops considerably for OOD data (e.g. from 80.5% to 54.6% under severe sampling rate perturbations), underscoring the value of reliable OOD detection. Furthermore, we find that while the first group of methods fails to separate in- and out-of-distribution samples, these methods provide superior signal for downstream model performance on in-distribution data. Preliminary experiments confirmed that combining methods from both groups, it is possible to leverage their complementary capabilities—the generative model-based approaches to flag OOD data, and the classifier-based approaches to further flag in-distribution samples with high model uncertainty, both of which are valuable to prevent model failure in practical applications. Overall, our study provides actionable guidance on how to do OOD detection for EEG machine learning applications, demonstrates the critical value of using these methods in a clinically relevant setting, and offers the first benchmark for EEG OOD detection to support future work in this area.

Disclosures: P. Bomatter: A. Employment/Salary (full or part-time):; Neuronostics. **H. Gouk:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.16/LL88

Topic: J.07. Data Analysis and Statistics

Support: Croatian Science Foundation Grant No. IP-2022-10-8493 (Uniqueness in development of interneurons in human prefrontal cortex during fetal life and first postnatal year—implications in pathogenesis of schizophrenia and autism, PI: Zdravko Petanjek)
National Recovery and Resilience Plan (NRRP) institutional project No. 10106-25-2973 (Digital Morphometry and Molecular Profiling of the Cerebral Cortex Using Machine Learning, DIMOPRO, PI: Ivan Banovac)

Title: Defining von Economo neurons: axon initial segment and the morphometric signature

Authors: *M. PRKAČIN[1,2], N. JOVANOV MILOSEVIC[1,3], Z. PETANJEK[1,2], I. BANOVAC[1,2]; [1]Croatian Inst. for Brain Res., [2]Dept. of Anat. and Clin. Anat., [3]Dept. of Biol., Univ. of Zagreb, Sch. of Med., Zagreb, Croatia

Abstract: von Economo neurons (VENs) are specialized projection neurons. In the human brain, VENs are predominantly located in layer Vb of the frontoinsular (FI) and anterior cingulate cortex (ACC). They are characterized by extreme elongation of the cell body, resulting in a distinctive rod- or stick-shaped morphology, and by an axon initial segment (AIS) that characteristically develops at the basal dendrite. Despite their distinctive morphology, disagreement persists over the criteria used to classify neurons as VENs. To address this issue,

we analyzed morphometric data from more than 90,000 neurons, including 46 manually identified VENs. Using a neural network-based machine learning approach, we evaluated multiple morphometric parameters and found that cell body Area and Aspect Ratio were the most informative features for VEN identification. We determined that an Area × Aspect Ratio value of 1681 or greater achieved 100% specificity while maintaining sensitivity above 95%. Based on these findings, we developed an algorithm for VEN detection that provides an objective framework for identifying VENs in histological samples. Because morphometric analyses were based on NeuN-defined somatic reconstructions, AIS origin was evaluated qualitatively using NeuN/Ankyrin G double-labeling and proposed as a complementary criterion for resolving borderline cases and validating VEN-like neurons outside their typical areal and laminar distribution. Our analysis suggests that a combination of the Area × Aspect Ratio metric, areal and laminar distribution, and AIS subcellular topography is highly informative for VEN identification. Our findings provide a practical framework for the objective identification of VENs and may help reduce inconsistencies in their classification across studies.

Disclosures: M. Prkačin: None. **N. Jovanov Milosevic:** None. **Z. Petanjek:** None. **I. Banovac:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.17/LL89

Topic: J.07. Data Analysis and Statistics

Support: NIH ZIAMH002783

Title: Spatially resolved similarity mapping pinpoints areas of reliable and distinct information across the cortical surface

Authors: *J. FASKOWITZ[1], P. BANDETTINI[2], J. GONZALEZ-CASTILLO[2];
[1]NIH, BETHESDA, MD; [2]Section on Functional Imaging Methods, Natl. Inst. of Mental Hlth., Bethesda, MD

Abstract: A primary goal in human brain mapping is to uncover spatially cohesive patterns of data that aid in the understanding of distributed brain functioning. Toward this aim, feature maps indexing neurophysiology or functional connectivity can be constructed using magnetic resonance imaging (MRI). To interpret these maps, researchers commonly compare such data to a canonical reference, a different modality, or even a different subject, by correlating data against each other. Recently, we have described how the commonly used Pearson correlation can be "unwrapped" to reveal the frame-by-frame similarity when comparing time series. Here, analogously, we apply the same mathematic unwrapping to reveal the vertex-by-vertex, or voxel-by-voxel, similarity when comparing spatial maps. This operation highlights locations that exert disproportionate influence on overall map similarity, as summarized by Pearson's *r*, with spatial

precision. Here we demonstrate how spatially rendered similarity can enhance comparisons commonly performed as part of brain mapping analyses. In this study, we use MRI features derived from both functional (resting-state) and structural (T1-weighted, T2-weighted) imaging acquisitions of the Human Connectome Project (N=352 subjects). Myelin maps were compared to the canonical principal functional gradient, validating a known relationship. By unwrapping this comparison for each subject, we observe how spatial similarity loads onto primary sensory cortex, suggesting that this relationship is driven largely by unimodal areas (e.g., visual cortex). Further, we performed a test-retest analysis of various resting-state features such as signal variance and functional connectivity degree, showing how different features are reliable in different parts of cortex. Furthermore, we extended this reliability analysis by comparing intra- versus inter-subject similarity, to highlight areas of individual uniqueness, concentrating along the temporal lobes. Overall, rendering spatial similarity maps provides us with information beyond the familiar Pearson's *r* value. They can reveal hotspots that drive similarity to an atlas or the distributed patches that make subjects unique. Further work will focus on further extracting individual-specific insights from these spatial similarity patterns.

Disclosures: J. Faskowitz: None. **P. Bandettini:** None. **J. Gonzalez-Castillo:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.18/LL90

Topic: J.07. Data Analysis and Statistics

Support: R01 MH125479
R01 EB008374
R01 MH133836
R01 EB035160

Title: Early Structure-Function Coupling Differentiation in Gyri and Sulci of the Infant Cortex

Authors: *J. MAO[1], K. HUYNH[2], S. AHMAD[3], K. THUNG[4], P.-T. YAP[5];
[1]Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [2]Radiology, Univ. of North Carolina Chapel Hill, Chapel Hill, NC; [3]Dept. of Radiology and BRIC, [4]The Univ. of North Carolina at Chapel Hill, Chapel Hill, NC; [5]Radiology, Univ. of North Carolina, Chapel Hill, NC

Abstract: Gyri and sulci differ in cytoarchitecture and connectivity, but how their structure-function relationships diverge during development remains unknown. Structure-function coupling (SFC) quantifies the correspondence between structural and functional connectivity; however, conventional parcellation-based approaches average across cortical folds and cannot distinguish gyral from sulcal connections. Using a vertex-wise, surface-based analysis of data from the Baby Connectome Project, we mapped SFC across the infant cortex to determine how gyri and sulci differentially develop during the first years of life.

Surface vertices were classified by mean curvature into sulcal pits, gyral crowns, or transition zones. Connections between gyral and sulcal vertices were further categorized as gyro-gyral, gyro-sulcal, or sulco-sulcal. For each connection type, we computed the mean tract length using diffusion MRI tractography and quantified SFC. Developmental trajectories of SFC were then modeled using generalized additive mixed models (GAMMs).

From birth to 5 years of age, gyro-gyral connections exhibited the longest mean tract lengths and strongest SFC with an initial increase followed by a decrease, whereas gyro-sulcal and sulco-sulcal connections showed shorter tract lengths and a stabilizing, downward trend. Across connection types, longer tracts were associated with stronger coupling ($r = 0.24$; mixed-effects standardized $\beta = 0.271$, $p < 0.001$). Gyral coupling was strongest in unimodal cortical regions, consistent with rapid, stimulus-driven functional responses supported by direct structural connectivity. Gyro-sulcal connections showed the weakest coupling (Cohen's $d = 5.6\text{-}6.1$, $p < 0.001$).

These results suggest gyri act as global communication hubs, exchanging information with remote gyri and neighbouring sulci, while sulci form shorter-range connections that are more functionally segregated. Critically, this division is already taking shape in the first years of life, pointing to folding as an early organising principle of cortical communication.

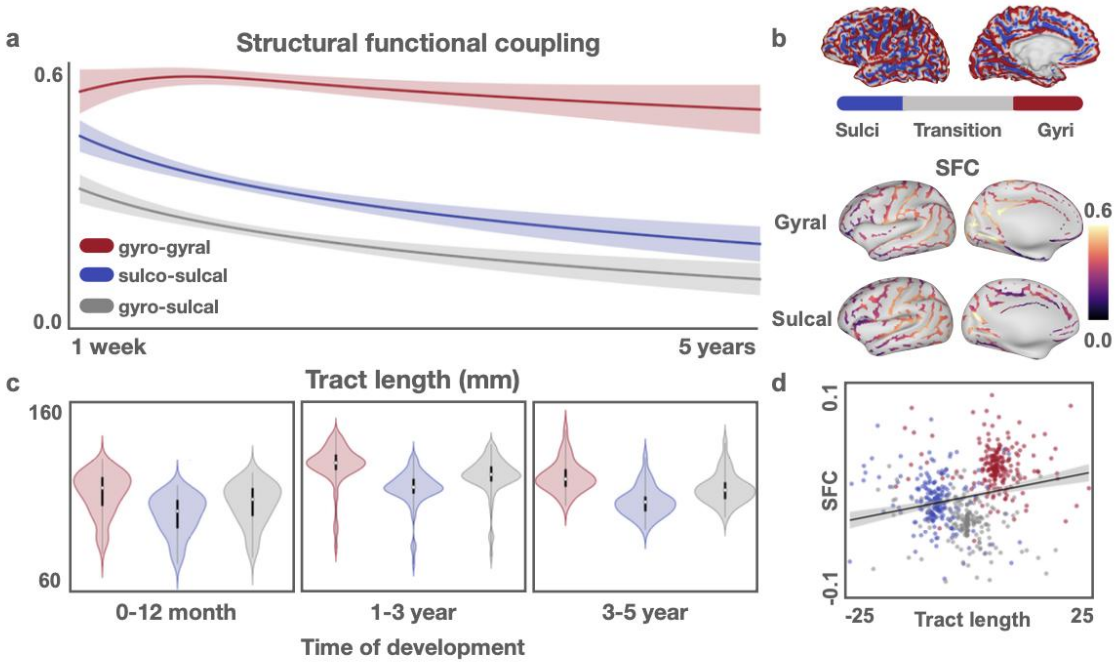


Figure 1.Structure–function coupling (SFC) and tract length across gyral and sulcal connection types during early development. **(a)** Developmental trajectories of SFC from birth to 5 years (GAMM fits ± 95% CI). **(b)** Top: cortical partition into sulci, transition zones, and gyri. Bottom: SFC at 5 years for gyral and sulcal vertices in the left hemisphere. **(c)** Across-subject distributions of mean tract length, with interquartile ranges indicated. **(d)** Relationship between tract length (zero-centered) and SFC (zero-centered) across connection classes.

Disclosures: J. Mao: None. **K. Huynh:** None. **S. Ahmad:** None. **K. Thung:** None. **P. Yap:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.19/LL91

Topic: J.07. Data Analysis and Statistics

Support: National Institutes of Health (NIH)/National Institute of Drug Abuse (NIDA) (R34-DA061924 to M.Z
Data Collection was supported National Science Foundation (NSF, IIS 1907807 to G.B., R.S)
Engineering Distinguished Scholar Fellowship of Michigan State University (to P.A)
P.E.O. International Peace Scholarship Award (to P.A)

Title: Topological Data Analysis Captures Complexities in Movement during Human Social Interaction from Motion Capture Data

Authors: *P. AKATUHWERA[1], G. BENTE[2], R. SCHMÄLZLE[2], M. ZHANG[1,3];
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Abstract: Interpersonal interaction depends strongly on nonverbal behavior. Nonverbal behavior has often been studied using subjective ratings or manual coding. Such manual processing can be labor-intensive for time-intensive coding of behavioral dynamics. More recently, motion capture enabled the tracking of full-body movements at high time resolution more efficiently. Nevertheless, most studies remain reliant on time-aggregated measures, leaving much of the richness in motion capture data untapped. Meanwhile, Topological Data Analysis (TDA) was introduced to capture finer dynamics in social interaction based on time-intensive subjective ratings of interpersonal dynamics, but its applicability to motion capture data is unclear. In the present study, we examine the suitability of Temporal Mapper, a TDA tool initially developed to characterize the complex brain dynamics as a transition network from time-series data. The transition network includes two main components: the nodes, which represent stable states, and the edges, which represent transitions from one state to another. In this study, we aim to examine whether Temporal Mapper can characterize complex interpersonal dynamics from motion capture data alone, producing meaningful visualizations and discriminating between distinct types of social interaction. We use a sample of 30 dyads from an existing 3D motion capture dataset. Each dyad engaged in two sessions of interaction, namely, casual chat and conflict interaction. Raw data were converted into 22-dimensional joint-angle rate-of-change time series, including 11 joint angles for each person in a dyad, which was further used to construct transition networks using Temporal Mapper. Nodes were classified into symmetric interaction (both persons inactive, both persons active) and asymmetric interaction (either Person 1 Active or Person 2 Active). Compared to casual chat, conflict interaction exhibits a significantly greater number of nodes and edges in asymmetric interactions but a lower number of nodes and edges in symmetric interactions. We also found a significantly lower cycle count in conflict conditions compared to the casual chat in the whole transition network. These results suggest that, during conflict, asymmetric interaction states become more dominant and the overall behavioral dynamics follow fewer, more repetitive patterns. Our findings show that the Temporal Mapper can capture the complex dynamic structure in high-dimensional motion capture data. This work

introduces a novel framework for unraveling the hidden structure in nonverbal behavior from the rich motion capture data.

Disclosures: P. Akatuhwera: None. **G. Bente:** None. **R. Schmälzle:** None. **M. Zhang:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.20/LL92

Topic: J.07. Data Analysis and Statistics

Support: The VA Office of Academic Affiliations (OAA) Fellowship program
VA CSR&D Grant 1 I01 CX002182-01

Title: Long-term follow-up of brain atrophy in veterans with Chronic Multisymptom Illness: a longitudinal imaging study

Authors: *Y. ZHANG[1], Y. RAHIMPOUR[1,2], J. W. ASHFORD, Jr.[1,2], P. J. BAYLEY[1,2], A. J. FURST[1,2];
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Abstract: BACKGROUND: Chronic Multisymptom Illness (CMI) is characterized by a constellation of persistent, medically unexplained symptoms, including fatigue, pain, and cognitive difficulties, primarily affecting veterans. Cross-sectional studies demonstrate that veterans with CMI exhibit a reduction in brainstem volume when compared to healthy controls. The objective of this study was to elucidate the temporal progression of regional brain atrophy rates in veterans with CMI in comparison to healthy civilians. MATERIALS AND METHODS: This pilot study included six male veterans with CMI (baseline age = 48.8 ± 12 years), comprising three individuals who served in the Iraq/Afghanistan War, two from the 1990-91 Gulf War, and one from the Vietnam War. These veterans underwent baseline and follow-up MRI scans at an average interval of three years. Additionally, eight healthy male civilians (HC, baseline age = 54.6 ± 11 years) who were examined with baseline and follow-up MRI scans approximately four years apart, were collected from a public research data repository. Imaging analysis was conducted using a FreeSurfer longitudinal processing pipeline to measure the volumes of the brain cortex, 15 subcortical regions and three brainstem segments at both time points. A linear mixed-effects model was used to compare the differences in the annual rate of volume changes between the CMI and HC groups. This model incorporated group and duration in years as fixed effects, subjects as random effects, and age as a covariate, given that the HC group was slightly older than the CMI group (mean age difference = 6.3 years, $p = 0.2$). RESULTS: Both the CMI and HC groups exhibited increased rates of atrophy in the supratentorial regions with advancing age. Specifically, the average rate of hippocampal atrophy was 0.7% per year for the HC group, versus 1.1% per year for the CMI group. In contrast,

brainstem atrophy rate in the HC group was less pronounced, averaging 0.3% per year, whereas veterans with CMI exhibited a continuous acceleration in brainstem atrophy rates, averaging 1.2% per year. Compared to the HC group, the CMI group showed significantly higher rates of atrophy in the whole brainstem (t = -4.6, $p < 0.001$), midbrain (t = -3.7, p = 0.003), medulla (t = -2.1, p = 0.03) and putamen (t = -3.6, p = 0.005). No differences were observed in the annual atrophy rates between HC and CMI in other brain regions, including the hippocampus (t = -1.0, p = 0.4). CONCLUSION: These preliminary findings indicate that CMI is associated with a rate of atrophy that exceeds what is generally observed in normal aging, particularly in the brainstem.

Disclosures: Y. Zhang: None. **Y. Rahimpour:** None. **J.W. Ashford:** None. **P.J. Bayley:** None. **A.J. Furst:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.21/LL93

Topic: J.07. Data Analysis and Statistics

Title: Effectiveness of middle meningeal artery embolization in young adults for chronic subdural hematomas

Authors: *O. WALKER[1,2], L. PRZEPIORKA[1], A. SIDDIQUI[1];
[1]Univ. at Buffalo Neurosurg., Buffalo, NY; [2]Univ. at Buffalo, Buffalo, NY

Abstract: Although chronic subdural hematomas (CSDHs) predominantly affect elderly patients, they infrequently occur in younger individuals. Management strategies include surgical drainage and middle meningeal artery embolization (MMAE). However, the use and outcomes of MMAE in younger patients remain understudied. This study evaluated the effectiveness and outcomes of MMAE in young adults with CSDH. In this single-center, retrospective study, patients aged 40 years or younger diagnosed with CSDH were reviewed for clinical presentation, demographics, relevant medical history, outcomes, and recurrence. Five patients (2 males, 40%) with CSDH were identified, with a median age of 25 years (IQR: 21-32). Three patients (60%) had a history of cranial trauma, and 3 (60%) were symptomatic at presentation: one had headaches, neck pain, blurry vision, nausea, vomiting, and numbness; the second had dizziness and disorientation; and the third had headaches, nausea, vomiting, and blurry vision. Three patients (60%) underwent subdural evacuating port system placement prior to MMAE during the same hospitalization. One patient had prior CSDH evacuation with interval resolution before sustaining repeat trauma 2 months preceding the index procedure. Median pre-procedural hematoma volume was 30.1mL (IQR: 20.05-82.1 mL), with a median midline shift of 5 mm (IQR: 3.5-7.5 mm). All MMAE procedures were performed under moderate conscious sedation and achieved technical success without complications. No underlying vascular malformations or coagulopathies were identified. At 3-month follow-up, among the 3 initially symptomatic patients, 2 had complete symptom resolution, and 1 had partial improvement, with headaches,

fatigue, and nausea remaining. Median hematoma volume at 3 months was 0.7 mL (IQR: 0.025-2.53 mL), with resolution of midline shift in all patients. Median modified Rankin Scale score at 3 months was 1 (IQR: 0-1). No patients required repeat CSDH treatment. Our experience suggests that MMAE may be an effective treatment option for CSDH in young adults, with favorable radiographic and clinical outcomes. No underlying vascular malformations or coagulopathies were identified in this group, although larger studies are needed to further characterize predisposing factors in younger patients.

Disclosures: O. Walker: None. **L. Przepiorka:** None. **A. Siddiqui:** 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.; Co-I for NSF 2304388 STTR Phase II: An AI-Enhanced Angiographic System to Guide Endovascular Treatment of Intracranial Aneurysms, Co-PI NIH OT2NS129366 / Medical University of South Carolina StrokeNet Thrombectomy Endovascular Platform (STEP), PI for Brain Aneurysm Foundation study titled Exploring the Relationship between Imaging- and Blood-Based Aneurysm Biomarkers and the Pathobiology of the Aneurysm Wall, PI for University of Cincinnati / NINDS FASTEST: rFVIIa for Acute Hemorrhagic Stroke Administered at Earliest Time Trial. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); 3N Endovascular, Adona Medical, Inc., Basecamp Vascular SAS, Bend IT Technologies, Ltd., BlinkTBI, Inc, Borvo Medical, Inc., CerebrovaKP, Code Zero Medical, Inc., Cognition Medical, Collavidence, Inc., Contego Medical, Inc., CVAID Ltd., CygnusMed, E8, Inc., Endostream Medical, Ltd (Sold 2025 to Kaneka), FreeOx Biotech, SL, Galaxy Therapeutics, Inc., Hyperion Surgical, Inc., Imperative Care, Inc., InspireMD, Ltd., Instylla, Inc., IRRAS, AB, Launch NY, Inc., Neurolutions, Inc., Neurovascular Diagnostics, Inc., NeXtGen Biologics, Peijia Medical, PerFlow Medical, Ltd., Physician X, LLC, Piraeus Medical, Inc., Prometheus Therapeutics, Inc., PUMA Venture Capital Fund I, LP, Q'Apel Medical, Inc., QAS.ai, Inc., Radical Catheter Technologies, Inc., ReNiva, Inc., Rist Neurovascular, Inc. (Purchased 2020 by Medtronic), Sense Diagnostics, Inc., Serenity Medical, Inc., Sim & Cure, Spinnaker Medical, Inc., Stent'Up, Synchron, Inc., Tegus Medical, GmbH, T.G. Medical, Inc., Tulavi Therapeutics, Inc., Vastrax, LLC, Viseon, Inc., Viz.ai, Whisper Medical, Inc., Willow Medtech, Inc.. F. Consulting Fees (e.g., advisory boards); Abbott Laboratories, Acandis GmbH, Asahi Intecc Co. Ltd., Canon Medical Systems USA, Inc., Carotix Medical, LLC, CerebrovaKP, Cerenovus, Contego Medical, Inc., Cordis, Endostream Medical, Ltd (recently sold to Kaneka), FreeOx Biotech, SL, Hyperfine Operations, Inc., Imperative Care , InspireMD, Ltd., Integra LifeSciences Corporation, IRRAS AB, Medtronic, Minnetronix Neuro, Inc., Medical Microinstruments, Inc., Peijia Medical, Penumbra, Inc. Perflow Medical, Ltd., Piraeus Medical, Inc., Prometheus Therapeutics, Inc., Q'Apel Medical, Inc., Serenity Medical, Inc., Shockwave Medical, Inc., Sirtex Medical, Inc., Stryker Neurovascular., Synchron Australia Pty Ltd., Tegus Medical, GmbH, T.G. Medical, Inc., Terumo Neuro (Formerly MicroVention), Unity Medical, Inc. Vastrax, LLC, Vesalio, Viz.ai, Inc., WL Gore; National PI/Steering Committees: Cerenovus EXCELLENT and ARISE II Trial; Medtronic ARTISSE IDE, SWIFT PRIME, VANTAGE, EMBOLISE and SWIFT DIRECT Trials; Terumo Neuro (formerly MicroVention) FRED Trial & CONFIDENCE Study; MUSC POSITIVE Trial; Penumbra 3D Separator Trial, COMPASS Trial, INVEST Trial, MIVI neuroscience EVAQ Trial; Rapid Medical SUCCESS Trial; InspireMD C-GUARDIANS IDE Pivotal Trial; Patents: Patent No. US 11,464,528 B2, Date: October 11, 2022, CLOT RETRIEVAL SYSTEM FOR REMOVING OCCLUSIVE CLOT

FROM A BLOOD VESSEL, Applicant and Assignee: Neuravi Limited (Galway), Role: Co-Inventor.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.22/LL94

Topic: J.07. Data Analysis and Statistics

Support: National Research Foundation of Korea RS-2026-25483830
National Research Foundation of Korea RS-2023-00265824

Title: Voxel-wise Weighted Multi-view Fusion for Synthesizing Fractional Anisotropy Maps from T1-Weighted MRI

Authors: *G. KWON, H. KIM, H. KIM, J. LEE;
Kumoh Natl. Inst. of Technol., Gumi, Korea, Republic of

Abstract: Deep learning-based image synthesis enables the generation of one modality from another, reducing acquisition time. To reduce the acquisition burden of diffusion tensor imaging (DTI), fractional anisotropy (FA) maps were synthesized from T1-weighted MRI (T1). Although FA synthesis commonly relies on the axial plane alone, the variable orientation of white matter tracts causes axial stacking to underrepresent tracts not aligned with this plane. Adding coronal and sagittal views and fusing the three may better capture white matter by accounting for these orientation differences. Single views, two-view fusions, simple averaging (avg), and a voxel-wise weighted fusion were compared to identify which fusion best approximates FA across white matter tracts. T1-FA pairs from cognitively normal ADNI participants were used: 889 scans (n = 461), split into training (628, n = 323), validation (123, n = 68), and test (137, n = 70) sets (mean age 71.7 ± 7.5 years; 59.4% women). Three U-Net generators, one per plane (axial, coronal, sagittal), each mapped 2.5D T1 input (three consecutive slices) to FA. At each voxel, a multiple linear regression was fitted on the training set with the three synthesized FA values as predictors and real FA as response; the voxel-wise coefficients (β) were applied to the test set (reg). Single views, two-view fusions, averaging (avg), and reg were compared by (1) MAE, RMSE, PSNR, and SSIM at whole-brain and white matter levels, (2) voxel-wise difference maps (|Real - Synthetic|), and (3) Johns Hopkins University white matter atlas tract-based mean FA (paired t-test). The voxel-wise weights estimated by reg were non-uniform, favoring the axial and coronal views over the sagittal (whole brain: axial 0.409, coronal 0.389, sagittal 0.202; white matter: 0.387, 0.412, 0.201). All multi-view fusions outperformed the single views, and reg achieved the best values across all metrics (whole brain: PSNR 24.91, SSIM 0.84; white matter: PSNR 22.92, SSIM 0.83), together with the smallest difference-map errors at both the whole-brain and white matter levels. This advantage carried over to the tract level, where reg most closely approximated the real FA among all methods in the Alzheimer's disease-relevant tracts: the fornix, cingulum (cingulate gyrus), and cingulum (hippocampus). This study evaluated whether a voxel-wise

weighted fusion reflecting orientation differences across tracts best fused the three views. Although reg and avg differed only slightly in the global metrics, reg showed a consistent advantage in the difference maps and the tract-level analysis, recovering the real FA most accurately.

Disclosures: G. Kwon: None. **H. Kim:** None. **H. Kim:** None. **J. Lee:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.23/Web Only

Topic: J.07. Data Analysis and Statistics

Support: National Research Foundation of Korea RS-2026-25483830
National Research Foundation of Korea RS-2023-00265824

Title: Toward a Better Age Covariate in Parkinson's Disease: Brain Age Estimated Using Deep Learning on Brain Imaging

Authors: *H. KIM, G. KWON, H. KIM, J. LEE;
Kumoh Natl. Inst. of Technol., Gumi, Korea, Republic of

Abstract: In neurodegenerative diseases such as Parkinson's disease (PD), age is a major factor associated with dysfunction and clinical progression. Therefore, age is widely used as a key covariate and reference variable in PD biomarker studies to account for age-related variability and to improve the interpretation of disease-specific neurobiological changes. However, the actual degree of aging may differ from chronological age (CA) due to genetic, lifestyle, and environmental factors. Replacing CA with a biological age that reflects the subject's actual aging status could serve as a superior covariate and help discover more accurate biomarkers, as well as identify biomarkers whose significance may have been previously underestimated. Using 3,656 T1-weighted MRI scans from cognitively normal individuals collected from ADNI, AIBL, and MCSA, we trained a deep learning model to estimate brain age (BA) as a proxy for biological age. We then performed BA inference on T1-weighted MRIs from 389 PD patients in PPMI. We analyzed the correlation of the UPDRS-III, which reflects motor symptoms in PD, with CA and BA. Rather than simply comparing CA and BA, we fitted a linear regression based on CA and progressively selected subjects with the largest residuals to apply BA. In Pearson correlation analyses with UPDRS-III, CA yielded $r=0.119$, $p=0.019$, whereas BA yielded $r=0.185$, $p<0.001$. When BA was applied to subjects in the top 25% of CA-based regression residuals (n=97), and CA was retained for the remainder, the correlation was $r=0.177$, $p<0.001$; applying BA to the top 50% (n=194) yielded $r=0.192$, $p<0.001$, and to the top 75% (n=289) yielded $r=0.185$, $p<0.001$. Notably, selectively applying BA to the top 50% produced a stronger correlation than applying BA to all subjects. These findings suggest that T1-weighted MRI-based BA is preferable to CA, and that selectively replacing age rather than applying the replacement to all subjects may yield

more meaningful analyses. Future work will focus on improving the precision of BA estimation through refined selection criteria and model training, and on investigating biomarker discovery using BA as a covariate.

Disclosures: H. Kim: None. **G. Kwon:** None. **H. Kim:** None. **J. Lee:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.24/LL95

Topic: J.07. Data Analysis and Statistics

Title: A Reproducible Framework for Target Curation, Prioritization, and Population-Scale Clinical Journey Visualization across Migraine Subtypes using UK Biobank Data

Authors: R. BETTADAPURA[1], *V. CHAKRABORTY[1], R. PAIT CHOWDHURY[1], K. MANOKARAN[1], A. GANAPATHY[1], P. GARG[1], J. JACOB[1], A. VASANTHAKUMAR[2], R. CHEN[2];
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Abstract: Background: Migraine is a highly prevalent and disabling neurological disorder that is a leading contributor to headache-related disability globally. Migraine prevalence increased by 58% in 1990 to 2021, reaching 1.16 billion cases, highlighting the need to integrate curated biological evidence with population-scale longitudinal datasets.
Methods: We developed a replicable two-phase framework combining systematic literature curation with scalable biobank harmonization and visualization.
Phase 1: Systematic Target Curation and Competitive Intelligence
We implemented an LLM-assisted prioritization workflow followed by expert curation and scientific review for structured extraction of multi-layered evidence, including genetic, functional, mechanistic, and druggability attributes. The systematic curation of 1,109 published studies (2020-2025) identified 650 unique targets and six major Mechanisms of Action (MoA) categories. The trigeminovascular pathway emerged as the dominant MoA hub. Targets were prioritized using a multi-criteria scoring framework, supported by convergent MoA, drug, and GWAS evidence, resulting in 64 high-confidence genes, including CALCA, CACNA1A, and TRPA1.
Phase 2: Clinical Journey Visualization Platform
To translate curated evidence into population-scale exploration, we developed a secure web-based Clinical Journey Visualization Portal. The platform ingests raw UK Biobank data and performs automated preprocessing, including unit harmonization and clinical code mapping (ICD-10 and OPCS-4), enabling longitudinal restructuring of large-scale datasets. The system supports cohorts up to ~290,000 participants and processes datasets (~5 GB; 62.9M rows; 968 columns) in ~35-40 min, while typical disease cohorts (≤10,000 participants) are processed in ~2-3 min. The portal enables cross-cohort comparison through cohort summaries, treatment

transition Sankey charts, and participant-level multi-layer timelines (swimlanes) integrating diagnoses, medications, procedures, and clinical events in a single dashboard.
Results and Ongoing Work: Using this framework, we established well-characterized migraine cohorts across UK Biobank. These cohorts support integrated visualization and downstream genomic and proteomic biomarker analyses currently underway.
Conclusion: We present a scalable framework integrating curated biological evidence with longitudinal biobank data and clinical visualization. Applied to migraine, it enabled target prioritization, cohort characterization and is designed for extension to other disorders, supporting biomarker discovery and translational research.

Disclosures: R. Bettadapura: None. **V. Chakraborty:** None. **R. Pait Chowdhury:** None. **K. Manokaran:** None. **A. Ganapathy:** None. **P. Garg:** None. **J. Jacob:** None. **A. Vasanthakumar:** None. **R. Chen:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.25/Web Only

Topic: J.07. Data Analysis and Statistics

Support: National Science and Technology Council (Taiwan)

Title: Quantitative Stability and AI-Induced Bias of DnCNN and Transformer Denoising Models for Structural MRI

Authors: *S. GU-YI;
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Abstract: Denoising is widely assumed to improve MRI quality without affecting downstream biological interpretation. In this study, we challenge this assumption by focusing on two representative deep learning models: DnCNN and Transformer-based architectures. Using 105 high-resolution structural MRI datasets, we systematically quantify how these models alter probabilistic inference, spatial consistency, and morphometric outcomes.All datasets underwent identical preprocessing including bias correction, segmentation, and spatial normalization using SPM. Quantitative evaluation incorporated both image-quality metrics (SSIM, MAD, CNR, sharpness) and probabilistic/spatial metrics, including entropy, coefficient of variation (CV), center-of-mass (COM) displacement, and deformation field burden.
Both DnCNN and Transformer models introduced structured, non-random signal alterations. Transformer-based models exhibited stronger low-frequency bias-field modulation, while DnCNN showed comparatively moderate but consistent redistribution. At the probabilistic level, entropy decreased across all methods, accompanied by shifts in maximum tissue probability distributions. Segmentation variability increased substantially, with CV rising by approximately 30-50% in gray matter regions.

Group-level analysis further demonstrated systematic morphometric bias. Mean absolute difference between method and raw images remained consistently elevated (~0.018-0.022), indicating persistent deviation. Paired t-test analysis revealed extensive suprathreshold voxel burden, with RAW>METHOD differences reaching ~7×10^5-9×10^5 voxels, while METHOD>RAW remained substantially lower (~1×10^5-2×10^5), indicating directional bias. Peak T-values ranged from ~40 to >70 across contrasts, confirming strong statistical effects. Spatial analysis showed measurable COM displacement and deformation-field differences, with Y-field displacement burden differing across methods, indicating altered anatomical alignment. These effects were consistently observed across all 105 subjects.
Collectively, these findings demonstrate that DnCNN and Transformer-based denoising act as implicit priors that reshape probabilistic structure, induce spatial deformation, and systematically bias morphometric estimates. This directly contradicts the assumption of preprocessing neutrality and establishes AI-based denoising as a primary source of variability in quantitative neuroimaging, with implications for structural MRI and neurodegenerative disease studies.

Disclosures: S. Gu-Yi: None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR161.26/LL96

Topic: J.07. Data Analysis and Statistics

Support: NIH R01EB033210

Title: Developing manual and automated ICA-based denoising for resting-state arterial spin labeling fMRI

Authors: *H. RAHIMZADEH, J. GUO;
UNIVERSITY OF CALIFORNIA RIVERSIDE, Riverside, CA

Abstract: Arterial spin labeling (ASL) fMRI offers advantages over blood-oxygen-level-dependent (BOLD) fMRI for resting-state networks, including quantitative cerebral blood flow, physiologically meaningful fluctuations, and localized activation maps. However, low signal-to-noise ratio and motion and physiological noise sensitivity limit these advantages. Unlike BOLD, few ASL denoising strategies exist. We evaluated manual ICA denoising and machine learning-based ICA automation for resting-state ASL. Two datasets were analyzed: a pCASL cohort split into a subset selected for manual ICA labeling and a reserved unlabeled subset (29/63 and 34/63), and a PASL cohort split similarly (15/40 and 25/40). All subjects underwent a basic pipeline: motion correction, ASL subtraction, MNI normalization, and smoothing. Within each subset, the basic pipeline was the reference. We tested 24-parameter motion regression, aCompCor, and ICA-based denoising through manual and automated paths. For manual ICA, MELODIC components from the manual-labeling subset were classified as Signal, Mix, or Noise

(1,201 total), and noise components were regressed out. For automated ICA, manually labeled component features were used to train Keep/Noise classifiers, which were applied to unlabeled subjects; predicted noise components were then regressed out. Manual and automated ICA were combined with aCompCor. Pipelines were compared separately in both subsets using FCC, brain-edge DVARS, median |QC-FC|, and QC-FC distance dependence. Relative to each subset's basic pipeline, manual ICA increased FCC from 3.725 to 4.655 and reduced brain-edge DVARS from 2.291 to 1.441 ($p<0.05$), with median |QC-FC| decreasing from 0.176 to 0.125 and distance dependence from 0.061 to 0.046. Among standalone denoising methods, ICA performed best on three of four metrics, whereas aCompCor yielded the highest FCC. Combining manual ICA with aCompCor improved performance (FCC 5.755, DVARS 1.102). Trained on manually labeled features, the random forest classifier achieved 80.5% accuracy and ROC-AUC 0.899 while preserving 97.2% of Signal components. Automated ICA increased FCC from 3.064 to 3.723 and reduced DVARS from 2.020 to 1.021 ($p<0.05$), with median |QC-FC| decreasing from 0.367 to 0.137 and distance dependence from 0.054 to 0.011. Combining automated ICA with aCompCor improved performance (FCC 4.458, DVARS 0.730). These findings show that manual and automated ICA denoising improve resting-state ASL fMRI beyond basic preprocessing. ICA and aCompCor provide complementary benefits, while machine learning enables scalable ASL-specific classification for functional brain network mapping.

Disclosures: H. Rahimzadeh: None. **J. Guo:** None.

Poster

PSTR161: Data Analysis and Statistics: Human Data I

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Program #/Poster #: PSTR161.27/MM1

Topic: J.07. Data Analysis and Statistics

Support: NIH 1R01NS134410-01

Title: Ultrasoft Fleuron transcortical probes move with the brain to provide stable neural data by eliminating pulsation-driven single-unit micromotion in pigs and humans

Authors: *O. E. ARMITAGE[1], **J. SWANN**[1], A. SPENCER[1], X. GONG[1], M. DENARDO[1], F. VASHAHI[1], S. NORRIS[1], H. HINTON[1], M. EL FAKIRI[1], R. HUANG[1], J. H. WANG[1], J. TASSERIE[1], R. ALBOUY[1], J. LIU[2], P. LE FLOCH[1], T. J. WILSON[4], P. HADAR[4], B. HSUEH[5], B. F. COUGHLIN[4], I. DAS[4], Z. WILLIAMS[3], G. P. DUNN[5], B. A. COSTINE-BARTELL[6], S. S. CASH[4], A. C. PAULK[7], A. FRANCIS[8], C. CANDANEDO[8], R. BERMUDEZ[8], C. COUTURIER[9];
[1]Axoft, Cambridge, MA; [2]Harvard Univ., Boston, MA; [3]Harvard Univ., Cambridge, MA; [4]Dept. of Neurology, Mass Gen. Brigham, Boston, MA; [5]Dept. of Neurosurgery, Mass Gen. Brigham, Boston, MA; [6]Neurosurg., Massachusetts Gen. Hosp., Charlestown, MA; [7]Massachusetts Gen. Hosp., Boston, MA; [8]The Panama Clin., Panama, Panama; [9]Neurol. and Neurosurg., McGill Univ., Montreal, QC, Canada

Abstract: Rigid laminar intracortical electrodes provide high signal quality but are fixed relative to the skull while the brain pulses with the cardiac and respiratory cycles, producing relative motion between the array and surrounding tissue. This micromotion causes the extracellular waveform of single neurons to translate across electrode contacts over the pulsation cycle, degrading spike sorting and chronic stability; which is today corrected post-hoc through registration (such as DREDge, Decentralized Registration of Electrophysiology Data). Herein we tested whether an ultrasoft probe would move with the tissue and eliminate this motion at its source to provide stable neural data. We recorded local field potentials (LFP) and single-unit activity with an ultrasoft transcortical laminar neural probe (160 μm inter-contact pitch) implanted in the cortex of pigs (n=4) and humans (n=7). In human recordings with known channel geometry, single units remained on the same contacts throughout the cardiac and respiratory cycle, with no detectable translation across contacts. Brain tissue motion was not registered directly, residual displacement in the compliant state was below the 150 μm contact pitch, as units did not appear on adjacent contacts. In a subset of pig recordings, (n=1) the probe was first anchored to a rigid substrate and then released, giving a within-subject comparison of fixed (rigid-like) and compliant states; probe motion was estimated with DREDge in the LFP frequency range (0.5-300 Hz). DREDge recovered a vertical displacement of the probe of ~1mm peak to peak (SD ~110μm) from the LFP band that returned to near zero (~35 μm) after release of the probe from the substrate. In pigs and humans, cortical surface motion, and ultrasoft probe motion within the brain, was confirmed by intraoperative microscope video. In one human recorded continuously across substrate release, motion-related LFP activity was present and quieted upon substrate release, consistent with loss of relative probe-tissue motion. Hence, we found an ultrasoft intracortical probe moves with the brain and eliminated pulsation-driven micromotion at its source, producing multi-channel stable neural data, without requiring post-hoc computational correction. Stable single-unit and LFP recordings in pigs and humans, together with the appearance and abolition of motion as the probe is anchored and released, indicate that probe compliance is the determining factor. These results have direct implications for chronic, high-fidelity single-unit recording in brain-computer interfaces, where data stability directly impacts decoding performance.

Disclosures: O.E. Armitage: A. Employment/Salary (full or part-time):; Axoft Inc. **J. Swann:** A. Employment/Salary (full or part-time):; Axoft Inc. **A. Spencer:** A. Employment/Salary (full or part-time):; Axoft Inc. **X. Gong:** A. Employment/Salary (full or part-time):; Axoft Inc. **M. DeNardo:** A. Employment/Salary (full or part-time):; Axoft Inc. **F. Vashahi:** A. Employment/Salary (full or part-time):; Axoft Inc. **S. Norris:** A. Employment/Salary (full or part-time):; Axoft Inc. **H. Hinton:** A. Employment/Salary (full or part-time):; Axoft Inc. **M. El Fakiri:** A. Employment/Salary (full or part-time):; Axoft Inc. **R. Huang:** A. Employment/Salary (full or part-time):; Axoft Inc. **J.H. Wang:** A. Employment/Salary (full or part-time):; Axoft Inc. **J. Tasserie:** A. Employment/Salary (full or part-time):; Axoft Inc. **R. Albouy:** A. Employment/Salary (full or part-time):; Axoft Inc. **J. Liu:** E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Axoft Inc. **P. Le Floch:** A. Employment/Salary (full or part-time):; Axoft Inc. **T.J. Wilson:** None. **P. Hadar:** None. **B. Hsueh:** None. **B.F. Coughlin:** None. **I. Das:** None. **Z. Williams:** None. **G.P. Dunn:** None. **B.A. Costine-Bartell:** None. **S.S. Cash:** None. **A.C. Paulk:** None. **A. Francis:** 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.; Axoft Inc. **C.**

Candanedo: 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.; Axoft Inc. **R. Bermudez:** 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.; Axoft Inc. **C. Couturier:** F. Consulting Fees (e.g., advisory boards); Axoft Inc.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.01/MM2

Topic: J.08. Methods to Modulate Neural Activity

Support: NIH Grant RF1NS122741

Title: Cells of the Motor Thalamus are Entrained by Transcranial AC stimulation of the Cerebellum

Authors: *Q. KANG[1], A. ROSHANI TALESH[2], T. ARAS[2], E. J. LANG[4], M. SAHIN[3]; [1]Dept. of Biomed. Engin., New Jersey Inst. of Technol., NEWARK, NJ; [2]Dept. of Biomed. Engin., [3]Biomed. Engin., New Jersey Inst. of Technol., Newark, NJ; [4]Neurosci., New York University, Grossman Sch. of Med., New York, NY

Abstract: Because the electric field generated by transcranial stimulation decreases exponentially by depth in the brain, modulation of cells is expected to be strongest in superficial regions. Nevertheless, neurons located in deeper structures may also be influenced indirectly through transsynaptic propagation of activity through neural projections. To examine this possibility, we investigated whether transcranial AC stimulation of the cerebellum (ctACS) can entrain neuronal activity in the motor thalamus, a major target of cerebellar output pathways.Experiments were performed in urethane anesthetized Sprague Dawley rats. Sinusoidal currents (1–400 Hz) were delivered transcranially through the skull via 2mm silver electrodes positioned over the cerebellum. Extracellular recordings were obtained from neurons in the ventral motor thalamus using tetrode electrodes. Single units were isolated offline, and spike entrainment was quantified using phase locking values (PLV) and preferred phases (PPh).A subset of motor thalamic neurons exhibited entrainment to ctACS despite electric field magnitudes at thalamic depths being far below levels expected to directly entrain neuronal activity. Entrainment occurred across a broad frequency range and peaked near 100–125 Hz. Spike histograms were frequently bimodal, with two peaks separated by approximately 180° within each stimulation cycle. The preferred phases shifted systematically with stimulation frequency, yielding an estimated propagation delay of 5.4 milliseconds that was consistent with transmission through the cerebello-thalamic pathway. The observed modulation is consistent with a disynaptic mechanism in which ctACS entrains Purkinje cells, which in turn modulate

cerebellar nuclear cells projecting to the motor thalamus.These findings demonstrate that transcranial stimulation can entrain neuronal activity in a deep brain structure through a multi synaptic pathway. The results support the feasibility of noninvasive modulation of subcortical structures through transsynaptic neural propagation and suggest that cerebellar tACS may provide a potential alternative approach for influencing thalamic networks traditionally targeted by deep brain stimulation.

Disclosures: Q. Kang: None. **A. Roshani Talesh:** None. **T. Aras:** None. **E.J. Lang:** None. **M. Sahin:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.02/MM3

Topic: J.08. Methods to Modulate Neural Activity

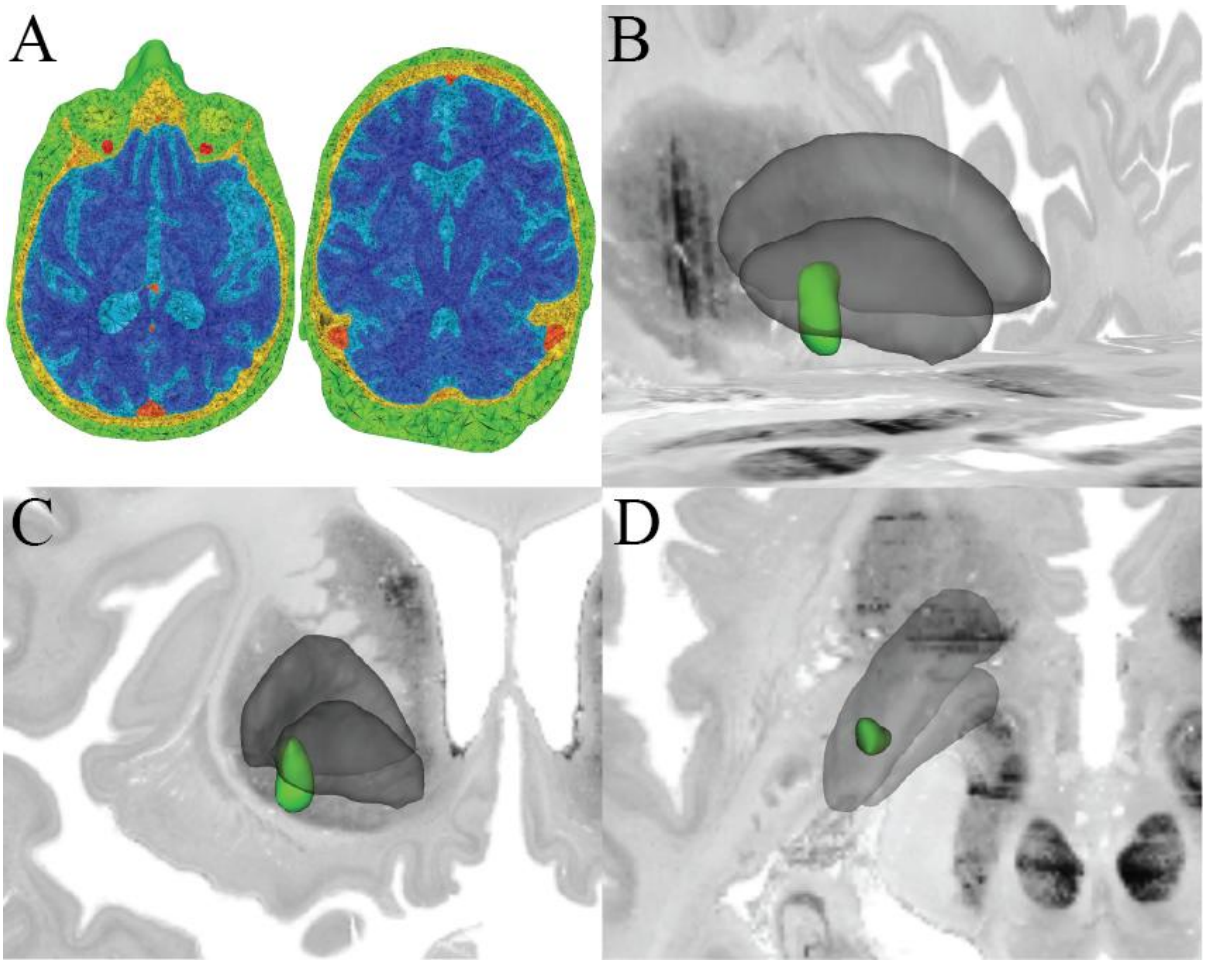
Support: NIH Grant R00NS137249

Title: Probabilistic deep brain stimulation sweet spots for alleviating depression in Parkinson's disease

Authors: *T. L. NAFZIGER[1], D. N. ANDERSON[2], P. COUTINHO[3], L. E. KENNEY[4], J. K. WONG[3], J. D. HILLIARD[5], K. D. FOOTE[5], D. BOWERS[6], G. M. PONTONE[3], C. DE HEMPTINNE[3], K. A. JOHNSON[1];
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Abstract: Deep brain stimulation (DBS) treatment of motor symptoms in Parkinson’s disease (PD) is highly effective. However, PD is associated with many nonmotor symptoms that are often insufficiently addressed by DBS. Depression can have a greater impact on quality of life in PD than motor symptoms and affects 30-35% of patients. Depressive symptoms before and after DBS treatment show mixed effects in both pallidal and subthalamic stimulation, and the underlying factors causing positive or negative outcomes remain unclear. The objective of this study was to identify DBS sweet spots in the pallidum for alleviating depression in PD and to identify the broader brain networks involved. We compared Beck Depression Inventory (BDI-II) score after 6 months of stimulation to preoperative baselines in 13 patients with PD (mean ± SD age of 68 ± 5.8, 46% female, 10 GPi, 3 STN). For each, we computed volumes of tissues activated (VTA) by modeling the activating function in patient-specific head models with their stimulation settings at 6 months. Each VTA was normalized to MNI152 space and used to perform voxel-wise t-tests to determine the location of sweet spots or sore-spots associated with

improvement or worsening of depressive symptoms, respectively. We identified a sweet spot in the ventral medial medullary lamina at the border of the globus pallidus internus (GPi) and externus (GPe) associated with improvement of depressive symptoms ($p<0.05$). Connectivity analysis using DISTAL atlas tractography shows this region largely projects to posterior parietal cortical networks, regions implicated in major depressive disorder. These findings suggest modulation of pallidal-parietal networks may underlie the antidepressive effects of pallidal DBS in PD and indicate potential lead trajectories near the GPi-GPe interface that could simultaneously alleviate both motor and depressive symptoms.



Disclosures: T.L. Nafziger: None. **D.N. Anderson:** None. **P. Coutinho:** None. **L.E. Kenney:** None. **J.K. Wong:** None. **J.D. Hilliard:** None. **K.D. Foote:** None. **D. Bowers:** None. **G.M. Pontone:** F. Consulting Fees (e.g., advisory boards); Dr. Pontone has consulted for Abbvie Inc and Cognition Therapeutics. **C. de Hemptinne:** None. **K.A. Johnson:** B. Contracted Research/Research Grant (principal investigator for a drug study, collaborator or consultant and pending and current grants). If you are a PI for a drug study, report that research relationship even if those funds come to an institution.; NIH R00NS137249.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.03/MM4

Topic: J.08. Methods to Modulate Neural Activity

Support: R00NS137249
UF Fixel-Eagles Pilot Award

Title: Basal ganglia spatio-spectral signatures of motor subtypes in Parkinson's disease

Authors: *D. KIM[1], V. LAVU[2], K. NORTH[1], J. WONG[3], J. HILLIARD[3], K. FOOTE[3], C. DE HEMPTINNE[3], K. A. JOHNSON[1];
[1]Univ. of Utah, Salt Lake City, UT; [2]Neurol., Univ. of Arkansas for Med. Sci., Little Rock, AR; [3]Univ. of Florida, Gainesville, FL

Abstract: Beta activity is a key electrophysiological marker in Parkinson's disease (PD), but it alone does not fully explain the heterogeneity of parkinsonian motor symptoms. The objective of this study was to investigate target-, frequency-, and symptom-specific local field potential (LFP) biomarkers of parkinsonian motor symptoms in the subthalamic nucleus (STN) and globus pallidus internus (GPi). We analyzed resting-state intraoperative LFP recordings from DBS leads in 165 hemispheres from 129 patients with PD: 51 STN hemispheres (27 left) from 40 patients (29 male; age 64.8 ± 7.7 years) and 114 GPi hemispheres (58 left) from 89 patients (61 male; age 66.1 ± 9.5 years). Bilateral baseline OFF-medication UPDRS-III subscores were used to quantify tremor, rigidity, bradykinesia, and postural instability/gait difficulty (PIGD). Power spectral density was analyzed across canonical frequency bands and correlated with each subscore using Pearson correlation. In STN, theta power showed significant positive correlations with rigidity, bradykinesia, and PIGD-related motor scores at dorsal contacts (rigidity C3: $p = 0.003$). Rigidity and PIGD additionally showed positive correlations with alpha activity at dorsal contacts (rigidity C2: $p = 0.015$), but STN tremor scores showed limited spectral correlations. In contrast, GPi theta and beta showed positive correlations with tremor scores at ventral contacts (theta C1: $p = 0.002$), whereas the other motor symptoms showed no significant spectral correlations. These findings suggest that distinct PD motor symptoms are associated with spatially localized and separable frequency- and target-specific oscillations within the basal ganglia, challenging beta as a universal biomarker. The STN-GPi spectral dissociation may reflect circuit-level differences in motor dysfunction. Future directions include imaging localization, periodic/aperiodic decomposition, and machine learning to identify multivariate spectral signatures across motor subtypes.

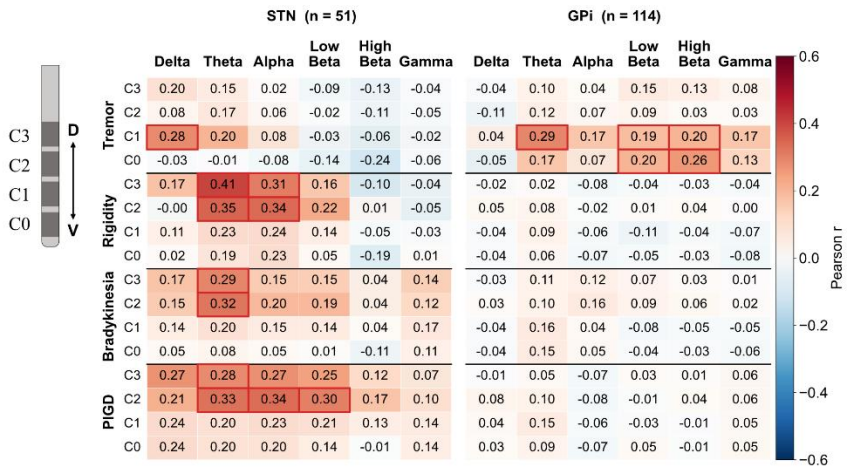


Figure 1. Contactwise correlations between spectral power and symptom severity.
Schematic of a DBS lead with four contacts (C0–C3), where C0 is the most ventral and C3 is the most dorsal. Pearson correlation heatmaps between resting-state LFP band power and bilateral baseline OFF-medication motor scores in STN (n = 51 hemispheres, left) and GPi (n = 114 hemispheres, right). Cell values represent Pearson's correlation coefficients (*r*), with color indicating the strength and direction of the correlation. Significant correlations ($p < 0.05$) are outlined in red.

Disclosures: D. Kim: None. **V. Lavu:** None. **K. North:** None. **J. Wong:** None. **J. Hilliard:** None. **K. Foote:** None. **C. de Hemptinne:** None. **K.A. Johnson:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.04/MM5

Topic: J.08. Methods to Modulate Neural Activity

Title: Novel Dual-Target Deep Brain Stimulation for Severe Post-Anoxic Chorea

Authors: *M. NOOR[1], C. W. JAMES[2], J. M. SCHWALB[1];
[1]Neurolog. Surgery, [2]Neurol., Indiana Univ. Sch. of Med., Indianapolis, IN

Abstract: Precision electrical neuromodulation demands tailoring stimulation to patient-specific anatomy, circuit pathology, and therapeutic goals, particularly when conventional targets are structurally compromised. Although emerging neuromodulation techniques such as optogenetics offer greater cell-type and circuit-level precision, they are not yet established in routine clinical neuromodulation in humans. Therefore, clinically approved neuromodulation approaches must leverage available technological capabilities to improve patient-specific circuit control. In the context of deep brain stimulation, design features such as long contact span, high contact count, and contact directionality can provide broader and more selective anatomical coverage, while independent stimulation programming allows differential modulation of distinct structures. Here, we report the case of a patient treated at our center using this approach for severe post-anoxic chorea, a challenging, refractory hyperkinetic movement disorder following hypoxic-ischemic

brain injury.
A young man developed severe, persistent choreiform movements following cardiac arrest related to an opioid overdose. Despite aggressive pharmacological therapy, his movements remained profoundly disabling, and neuroimaging demonstrated bilateral globus pallidus injury, making standard pallidal DBS infeasible. To address this challenge, a circuit-guided strategy was adopted to differentially modulate distinct nodes within the basal ganglia-thalamocortical motor network. Bilateral long-span, high-contact-count DBS leads were placed such that deeper contacts were positioned in the subthalamic region, while dorsal contacts were positioned in the ventral anterior thalamic region, which serves as a major relay for pallidal outflow. Independent stimulation programming enabled the use of low-frequency stimulation in the subthalamic region and high-frequency stimulation in the thalamic region. Within days of activation, the patient showed marked reduction in choreiform movement frequency and intensity, with substantial improvement in functional independence.
This case highlights how electrical neuromodulation can be tailored to an individual patient's anatomy and circuit dysfunction. Guided by a mechanistic understanding of DBS, extended contact coverage enabled dual-target engagement, while independent current control allowed target-specific stimulation frequencies. Together, these elements may provide a framework for patient-specific network modulation in selected patients with complex circuit dysfunction and damaged conventional targets.

Disclosures: M. Noor: None. **C.W. James:** None. **J.M. Schwalb:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.05/MM6

Topic: J.08. Methods to Modulate Neural Activity

Support: AMED (Grant Number: JP25wm0625325
JSPS KAKENHI (Grant Numbers: 23KK0146, 23K18275, 25K02548)

Title: Automated detection of evoked oscillatory responses after single-pulse electrical stimulation in human ECoG

Authors: *T. NAKAE[1,2], K. USAMI[3], K. KOBAYASHI[4], N. MUKAE[7], M. MATSUHASHI[5,8], Y. YAMAO[9], T. KIKUCHI[2], T. KUNIEDA[10], A. IKEDA[6], Y. ARAKAWA[2], R. MATSUMOTO[4];
[1]Mayo Clin., Rochester, MN; [2]Neurosurg., [3]Clin. Laberatory, [4]Neurol., Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [5]Epilepsy, Movement Disorder and Physiol., Kyoto Univ. Grad. Sch. of Med., Kyoto-Shi, Japan; [6]Epilepsy, Movement Disorder and Physiol., Kyoto Univ. Grad. Sch. of Med., Kyoto, Japan; [7]Neurosurg., Kyushu University, Grad. Sch. of Med. Sci., Fukuoka City, Japan; [8]Dept. of Med. Device Engin., Kobe Univ. Grad. Sch. of Med., Kobe, Japan; [9]Neurosurg.,

Natl. Hosp. Organization Kyoto Med. Ctr., Kyoto, Japan; [10]Neurosurg., Ehime Univ. Grad. Sch. of Med., Toon city, Japan

Abstract: Non-invasive brain stimulation, including TMS and tACS, has shown that the human cerebral cortex has frequency-specific oscillatory response properties. Using invasive subdural electrodes, we previously identified phase-reset-like oscillatory responses after single-pulse electrical stimulation (SPES) in human ECoG by visual inspection of averaged waveforms. Here, we developed an automated detection pipeline to validate this phenomenon using an objective and reproducible method.We analyzed routine cortico-cortical evoked potential (CCEP) recordings from 15 patients with focal epilepsy undergoing presurgical evaluation with subdural electrodes, excluding seizure-onset zone electrodes. Averaged waveforms were analyzed using time-domain oscillatory-shape correlation (TDOSC), which detects repeated waveform patterns by testing whether adjacent half-overlapping time windows show the polarity reversal expected for an oscillation. Candidate responses were classified into theta, alpha, and beta bands and mapped onto a standard cortical surface. TDOSC-derived maps were compared with maps based on visual inspection and with the distribution of spontaneous rhythms.TDOSC conservatively detected clear oscillatory responses and reproduced the frequency-specific topography observed by visual inspection. Theta responses were predominant in frontal regions, alpha responses in postcentral and temporal cortices, and beta responses around precentral and paracentral regions. These distributions resembled spontaneous rhythm topography and depended more on the recording site than the stimulation site, suggesting that SPES interacts with region-specific intrinsic oscillatory properties.These findings support TDOSC as a reproducible method for mapping stimulation-evoked oscillatory dynamics in human ECoG. Whereas early CCEP responses are often used as markers of direct cortico-cortical connectivity and delayed CCEP responses may reflect broader functional connectivity, synchronized evoked oscillations may provide a complementary marker of frequency-specific large-scale network organization, potentially involving cortico-subcortical loops.

Disclosures: T. Nakae: None. **K. Usami:** None. **K. Kobayashi:** None. **N. Mukae:** None. **M. Matsuhashi:** A. Employment/Salary (full or part-time):; The Department of Epilepsy, Movement Disorders and Physiology is the Industry-Academia Collaboration Courses supported by commercial enterprises.. **Y. Yamao:** None. **T. Kikuchi:** None. **T. Kunieda:** None. **A. Ikeda:** A. Employment/Salary (full or part-time):; The Department of Epilepsy, Movement Disorders and Physiology is the Industry-Academia Collaboration Courses supported by commercial enterprises... **Y. Arakawa:** None. **R. Matsumoto:** 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.; Japan Agency for Medical Research and Development (AMED; Grant Number: JP25wm0625325), JSPS KAKENHI (Grant Numbers: 23KK0146, 23K18275, 25K02548).

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.06/MM7

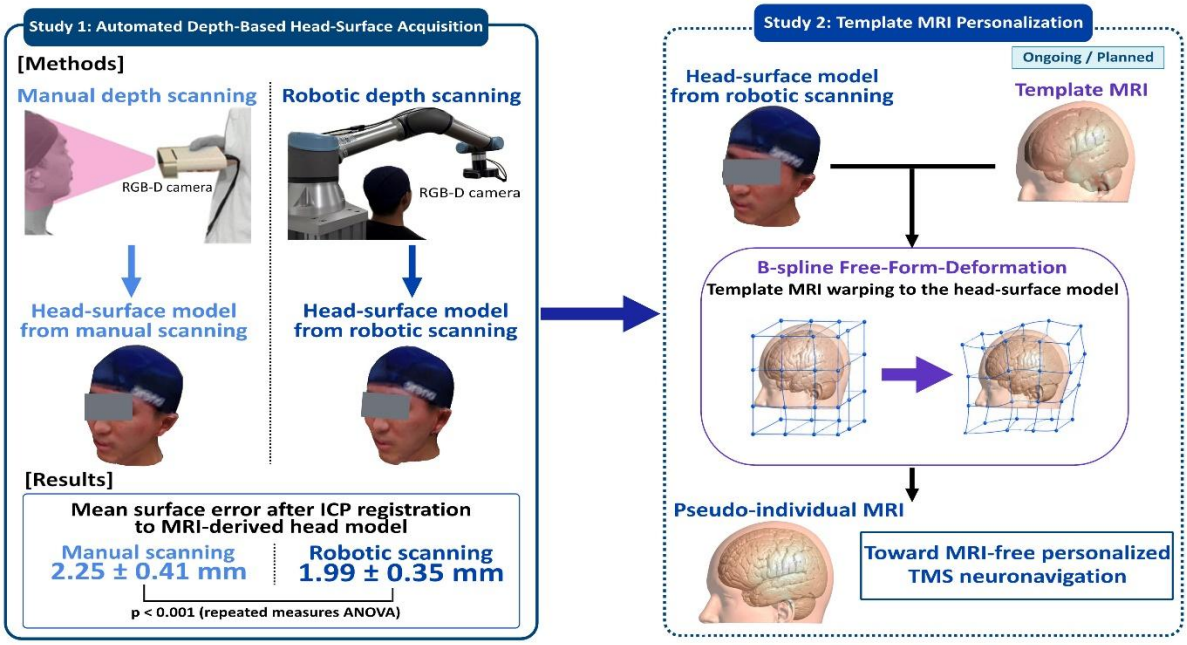
Topic: J.08. Methods to Modulate Neural Activity

Support: JST Moonshot R&D (JPMJMS2012)

Title: Automated Template MRI Personalization for TMS Neuronavigation Using Depth-Based Head Surface Scans

Authors: *S. IKENAGA, M. TAKEMI;
Grad. Sch. of Advanced Sci. and Engin., Hiroshima Univ., Higashi-Hiroshima, Hiroshima, Japan

Abstract: Transcranial magnetic stimulation (TMS) induces electric fields in the cerebral cortex and is widely used in human neuroscience and clinical neurophysiology. Its use requires reproducible coil placement, because differences in coil position and orientation can change the stimulated cortical site. MRI-guided neuronavigation addresses this problem by linking coil position to each person's cortical anatomy, but individual MRI acquisition adds cost and preparation time, and limits use in settings without MRI access. We aimed to develop an MRI-free workflow for TMS neuronavigation that personalizes a template MRI using head surface data acquired by automated depth-based scanning. Study 1 tested whether robotic scanning could acquire head surface data more reproducible than manual depth scanning. Three participants were scanned by five examiners using both methods, with three repeats per method. Depth-based surface models were registered to MRI-derived head models to assess acquisition success, scan time, and surface error. Robotic scanning succeeded on the first attempt in all 45 trials, produced less variable scan times, and reduced surface error compared with manual scanning. Both methods satisfied a predefined 3 mm practical equivalence criterion relative to MRI. Study 2 will use the robot acquired surface to personalize a template MRI. After affine and iterative closest point alignment, B-spline free-form deformation will deform the template to reduce mismatch between the two head surfaces. The pseudo individual MRI will be evaluated against individual MRI using target localization error, electric field distribution similarity, and TMS assessment results (e.g., resting motor threshold and motor hotspot location). This approach may reduce the preparation burden of TMS neuronavigation while retaining anatomical information for cortical targeting beyond the primary motor cortex.



Disclosures: S. Ikenaga: None. **M. Takemi:** A. Employment/Salary (full or part-time):; Neuractice Inc.. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual property rights/patent holder, excluding diversified mutual funds); Neuractice Inc..

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.07/MM8

Topic: J.08. Methods to Modulate Neural Activity

Support: NSERC

Title: When one size doesn't fit all: The effect of personalized tDCS intensity on motor learning

Authors: *T. XIONG, J. CHEN;
Univ. of Toronto, Toronto, ON, Canada

Abstract: Transcranial direct current stimulation (tDCS) applied over the primary motor cortex (M1) may enhance motor learning; however, behavioral findings are inconsistent. Some variability may arise from fixed stimulation parameters despite inter-individual anatomical differences that affect the amount of current delivered to the cortex. Magnetic resonance imaging (MRI)-based current flow modeling (CFM) enables personalized adjustment of stimulation intensity, but its effects on motor performance remain unclear. This study aims to examine whether personalized tDCS intensity improves motor learning compared with fixed and sham

stimulation. Data collection is ongoing. Preliminary data includes 24 right-handed participants (n = 8 per group; 12 females, 12 males; mean age = 23 ± 2.7). In a single-blind design, participants were randomized to personalized tDCS, fixed 2 mA tDCS, or sham stimulation. The personalized group underwent MRI to generate personalized CFM for tailored stimulation. For all participants, the left M1 motor hotspot was localized using single-pulse transcranial magnetic stimulation. On Day 1, participants completed 6 blocks of the Sequential Visual Isometric Pinch Task and received group-specific tDCS during Blocks 2-5. A 24-hour retention test was administered on Day 2 without stimulation. The outcome measure was Skill, a composite of speed and accuracy. Skill acquisition was analyzed using a 3 (Between-Group: personalized, fixed, sham) × 6 (Within-Subject Factor: Block 1-6) mixed-design repeated-measures ANOVA. Separate one-way ANOVAs were used to compare baseline performance, online gain (Block 6-Block 1), retention, and offline gain (Retention-Block 6). Skill improved across practice blocks, $F(5,105)=16.32$, $p<0.001$, with no significant group effect ($p=0.112$) or interaction. However, online gain differed across groups, $F(2,21)=4.02$, $p=0.033$, with greater improvement in the personalized group than the fixed ($p=0.021$) and sham groups ($p=0.025$). At retention, a significant group effect was observed, $F(2,21)=10.30$, $p<0.001$, with the personalized group outperforming both the fixed ($p<0.001$) and sham groups ($p<0.001$). Offline gain also differed across groups, $F(2,21)=7.71$, $p=0.003$, with greater improvement in the personalized group than the fixed ($p=0.004$) and sham groups ($p=0.002$). Overall, preliminary findings suggest that personalized tDCS enhances offline learning and retention relative to fixed and sham stimulation. These results may inform the development of targeted neuromodulation approaches for neurorehabilitation and performance enhancement.

Disclosures: T. Xiong: None. **J. Chen:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.08/Web Only

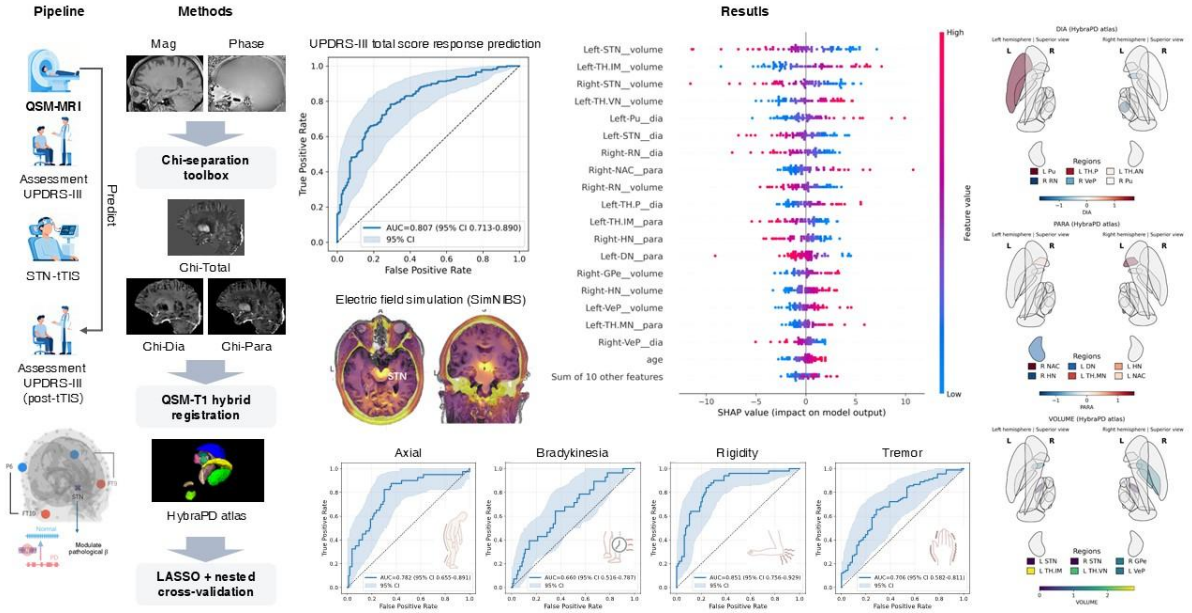
Topic: J.08. Methods to Modulate Neural Activity

Title: Subcortical Quantitative Susceptibility Mapping Predicts Motor Response to Transcranial Temporal Interference Stimulation in Parkinson's Disease

Authors: *S. BAI[1,2], X. GUAN[2], A. LI[2], C. ZHANG[2];
[1]Shanghai Clin. Res. and Trial Ctr., Shanghai, China; [2]Ruijin Hospital, Shanghai Jiao Tong Univ. Sch. of Med., Shanghai, China

Abstract: Clinical response to transcranial temporal interference stimulation (tTIS) in Parkinson's disease (PD) varies substantially, and objective biomarkers for pretreatment stratification are lacking. We tested whether baseline quantitative susceptibility mapping (QSM) can predict single-session motor response to unilateral subthalamic nucleus (STN)-tTIS in 72 patients with PD. Paramagnetic, diamagnetic, and regional volume features were extracted from

deep gray matter regions using QSM source separation and T1-assisted segmentation, then combined with age, sex, and stimulation-target electric field. To improve comparability, paired left/right regional features were aligned to the stimulated side. Response labels were derived from pre-post MDS-UPDRS Part III change after a single session, and candidate thresholds were compared with repeated stratified nested cross-validation. A 5-point improvement threshold yielded the best response definition and was used for stability-based feature selection and final modeling with elastic net logistic regression. The final compact model retained 29 stable features and produced held-out predictions across outer folds, achieving pooled AUC=0.807, AUPRC=0.880, and balanced accuracy=0.741 at the default cutoff, with sensitivity=0.774 and specificity=0.708. Stable predictors spanned paramagnetic, diamagnetic, and volumetric measures in thalamic subregions, subthalamic nucleus, putamen, and related deep nuclei, indicating that iron-related and diamagnetic tissue alterations contribute to responsiveness. When extended to MDS-UPDRS Part III subscores, the same framework yielded encouraging results for rigidity (pooled AUC=0.851), axial symptoms (AUC=0.782), tremor (AUC=0.706), and bradykinesia (AUC=0.660), demonstrating generalization across motor subdomains. These findings support QSM-derived multiregional susceptibility signatures as interpretable imaging biomarkers for predicting STN-tTIS benefit in PD and guiding patient stratification and individualized neuromodulation planning.



Disclosures: S. Bai: None. **X. Guan:** None. **A. Li:** None. **C. Zhang:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.09/MM9

Topic: J.08. Methods to Modulate Neural Activity

Title: Individual variability in autonomic response to non-invasive vagus nerve stimulation

Authors: *M. MCMULLIN, O. MCNEILL, M. DELLAFERA, K. STAMEY, T. M. CENTANNI;
Univ. of Florida, Gainesville, FL

Abstract: Transcutaneous auricular vagus nerve stimulation (taVNS) is a non-invasive neuromodulation technique used to treat depression, epilepsy, post-stroke motor recovery, and opioid withdrawal. taVNS drives activity in the same brain regions as invasive VNS via afferent projections to the nucleus of the solitary tract, releasing acetylcholine, norepinephrine, and serotonin. Heart rate variability (HRV) is a consistently replicated and safe biomarker of VNS; however, HRV responses to taVNS show substantial inter-individual variability, and it is unknown whether medications targeting key VNS neurotransmitters affect taVNS efficacy. HRV data were collected across 5 min windows of baseline, stimulation, and washout (condition), repeated three times (time), while healthy young adults taking no medications (n = 27, M_{age} = 20.74 yrs, 7 males) watched a neutral movie. HRV was indexed using root mean square of successive differences (RMSSD), standard deviation of normal-to-normal intervals (SDNN), and low to high frequency ratio (LF/HF). Repeated-measures ANOVAs quantified effects of condition and time on HRV. Regressions evaluated whether age, sex, sleep, caffeine, physical activity, or stimulation current predicted HRV. RMSSD varied significantly across stimulation condition, driven by reduced values during stimulation relative to baseline. LF/HF showed significant main effects of condition and time, with elevated values during washout relative to stimulation. SDNN showed a significant time effect and condition x time interaction, with higher values at later times. Together, these patterns indicate that taVNS influences HRV beyond active stimulation, with effects persisting into washout and increasing over time. To examine individual variability, regression analyses indicated SDNN was significantly predicted by sex and sleep at baseline and washout, with lower SDNN in females and those reporting more sleep, though sex findings warrant caution given the unequal sample. In an age-matched subsample, a no-medication group (n = 9) was compared to individuals taking medications affecting serotonin (n = 4) or norepinephrine (n = 5). Serotonergic medication users showed lower RMSSD and SDNN than controls across stimulation and washout, while noradrenergic medication users showed lower SDNN than controls during washout. These results suggest that medication status, sex, and sleep may contribute to individual variability in HRV response to taVNS, and that medicated individuals may require more time to return to baseline HRV after stimulation. Collectively, these findings hold important implications for patient selection in clinical taVNS contexts.

Disclosures: M. McMullin: None. **O. McNeill:** None. **M. DellaFera:** None. **K. Stamey:** None. **T.M. Centanni:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.10/MM10

Topic: J.08. Methods to Modulate Neural Activity

Title: Effects of Theta and High-Gamma Temporal Interference Stimulation to the Ventral Striatum on resting EEG

Authors: *M. T. TREADWAY, O. AJE;
Emory Univ., Atlanta, GA

Abstract: Background: Temporal interference (TI) is a relatively novel, non-invasive neuromodulation technique capable of modulating deep brain regions while minimizing stimulation of overlying cortex. Prior neuromodulation studies have linked electroencephalography (EEG) band power modulation to cognitive and clinical outcomes. We previously demonstrated TI stimulation targeting the ventral striatum enhanced the Reward Positivity, a well-validated EEG biomarker of reward processing. Here, we examined whether ventral striatal (VS) TI stimulation modulates resting-state EEG spectral power.Methods: Forty-five healthy participants (M = 24.67 years; SD = 5.59) were recruited across three independent studies using envelope frequencies of 5 Hz (n = 19), 8 Hz (n = 16), and 130 Hz (n = 10). Participants completed both active (4 mA, envelope frequency matched to group) and sham (4 mA/0 Hz) bilateral VS stimulation in a counterbalanced crossover design. During stimulation, participants in the 5 Hz and 130 Hz groups completed an effort-based decision-making task, while the 8 Hz group completed a breath-focused mindfulness task. 3-minute eyes-closed resting-state EEG was recorded pre- and post-stimulation at each visit. Relative spectral power at the FCz electrode was assessed within the delta (1 - 4 Hz), theta (4 - 8 Hz), alpha (8 - 12 Hz), beta (12 - 30 Hz), gamma (30 - 45 Hz), and theta-alpha (7 - 9 Hz) frequency bands. Results: We found a significant omnibus interaction of frequency band x time (pre/post) x stimulation (active/sham) x Group (5/8/130 Hz) ($F(10,78)$= 2.259; p = .022; η^2 = .225). Within-group analyses revealed a significant frequency band x time x stimulation interaction in the 8 Hz group ($F(5,11)$ = 5.224; p = .011; η^2 = .704), a trend-level interaction in the 5 Hz group ($F(5,14)$= 2.330; p = .098; η^2 = .454), and no significant interaction in the 130 Hz group ($F(5,5)$ = 2.899; p = .134; η^2 = .744). Descriptively, post-stimulation spectral power increases were most evident in alpha and theta-alpha bands in the 5 Hz group and in theta and delta bands in the 8 Hz group, suggesting that TI-induced spectral changes may vary by envelope frequency and task context.Conclusions: The significant omnibus interaction suggests that non-invasive subcortical TI stimulation modulates resting-state cortical oscillatory activity differently across spectral bands and envelope-frequency groups. Future work is needed to examine whether TI-induced spectral modulation replicates in larger samples and varies across envelope frequencies and task contexts.

Disclosures: M.T. Treadway: D. Fees for Non-CME Services Received Directly from Commercial Interest or their Agents (e.g., speakers' bureaus); Boehringer Ingelheim, Ono Pharmaceuticals. E. Ownership Interest (stock, stock options, royalty, receipt of intellectual

property rights/patent holder, excluding diversified mutual funds); Neuroprism AG. **O. Aje:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.11/MM11

Topic: J.08. Methods to Modulate Neural Activity

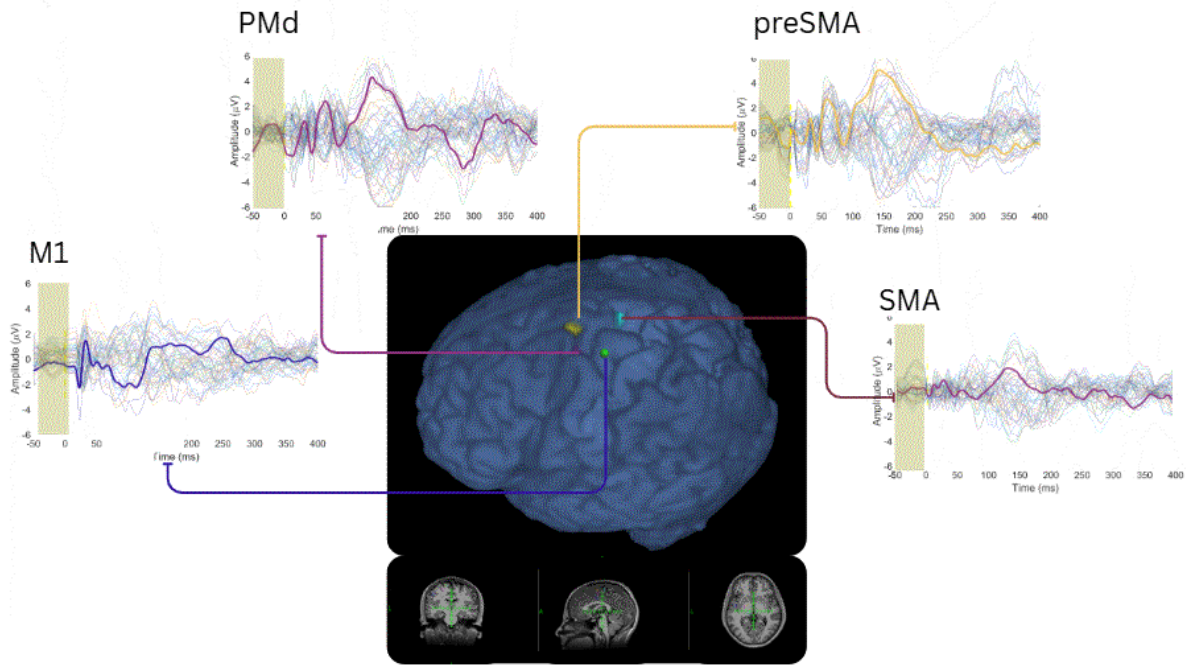
Support: P20GM113109

Title: Exploring the Cortical Excitability of the Motor System: A TMS-EEG Study

Authors: *N. MORA-JIMENEZ[1], C. GEORGE[1], F. FEYISA[2], J. HERNANDEZ-PAVON[1]; [1]Psychological Sci., Kansas State Univ., Manhattan, KS; [2]Psychological Sci., Kansas State Univ., Manhattan, KS

Abstract: Introduction: Transcranial magnetic stimulation combined with electroencephalography (TMS-EEG) enables the study of brain dynamics non-invasively and with a state-of-the-arthigh precisionprecision. The neurophysiological evoked responses derived from TMS-stimulation, or TMS-evoked potentials (TEPs) are an index of cortical excitability (CE). Alterations on CE have been observed in the presence of psychiatric disorders or neurological conditions. In addition, since neuromodulation approaches aim for changes in the neuronal dynamics, characterizing the TEPs in healthy population becomes crucial. So far, TEPs have been well-characterized mainly for the primary motor cortex along with the dorsolateral prefrontal cortex, however how other regions respond to TMS remains to be explored. **Objectives:** The purpose of this study was to explore differences in the TEPs from 5 brain areas that are part of the motor system, namely: the primary motor cortex (M1), dorsal premotor (PMd), ventral premotor cortices (PMv), pre-supplementary (preSMA), and supplementary motor areas (SMA) in both hemispheres. **Methods:** To determine the region of stimulation for the 5 areas in both hemispheres, MRI data was collected and preprocessed for each participant. Targets were identified using HCP-MMP atlas. Single-pulse TMS was delivered to each region at 100% of the rMT, while responses were recorded with a 64-channel EEG system. To assess TEP differences across brain areas, the amplitudes, latencies, and area under the curve of P30, N45, P60, N100 and P180 TEPs components were analyzed. **Results:** We show preliminary data from 6 healthy participants 3 males and 3 females between 18 to 30 years old. Results show that the amplitudes and latencies of the TEPs components obtained vary depending on the region

stimulated.



Disclosures: N. Mora-Jimenez: None. **C. George:** None. **F. Feyisa:** None. **J. Hernandez-Pavon:** None.

Poster

PSTR162: Electrical Manipulation of Human Neuronal Activity

Location: WCC Halls A-C

Time: Monday, November 16, 2026, 8:00 AM - 12:00 PM

Program #/Poster #: PSTR162.12/MM12

Topic: J.08. Methods to Modulate Neural Activity

Support: CNAP: NIH Grant P20GM113109

Title: Optimizing TMS−EEG acquisition: Effects of EEG sampling frequency and stimulation intensity on TMS-evoked responses

Authors: *F. FEYISA[1], N. MORA J[2], C. GEORGE[2], J. HERNANDEZ-PAVON[2];
[1]Dept. of Psychological Sci., kansas state university, Manhattan, KS; [2]Dept. of Psychological Sci., Kansas State Univ., Manhattan, KS

Abstract: Transcranial magnetic stimulation combined with electroencephalography (TMS−EEG) has emerged as a valuable tool for investigating human brain physiology and developing neurophysiological biomarkers. However, TMS−EEG acquisition parameters remain an important methodological challenge. Although high EEG sampling frequencies are routinely used to minimize TMS-induced artifacts, the minimum sampling frequency required to preserve

physiologically meaningful TMS-evoked responses and accurately capture underlying brain dynamics has not been systematically established. Whether these relationships are maintained across different stimulation intensities also remains unclear. Identifying optimal acquisition parameters that preserve reliable sensor- and source-level measures while reducing data storage, computational burden, and processing time could improve the efficiency, scalability, and clinical translation of TMS−EEG. Preliminary analyses were performed on 4 healthy participants (3 males, 1 female; mean age 27.0 ± 5.9 years) who received a single-pulse TMS over the left primary motor cortex (M1) at 90% and 110% of the resting motor threshold, while EEG was recorded at 1, 5, 10, 20, 40, and 80 kHz. An individual T1-weighted MRI was used for MRI-guided neuronavigation and subject-specific electric field (E-field) modeling to estimate the spatial distribution of the induced cortical electric field and characterize the effective stimulation delivered to the targeted cortex. Following preprocessing and artifact correction, the area under the curve (AUC) of the canonical TMS-evoked potential components P60, N100, and P180 was quantified from a predefined motor cortical region of interest (ROI). Preliminary repeated-measures ANOVA revealed no significant effect of EEG sampling frequency on ROI AUC for P60, $F(5,15) = 0.22$, $p = .949$, N100, $F(5,15) = 0.52$, $p = .760$, and P180, $F(5,15) = 1.28$, $p = .325$, with no significant sampling frequency × stimulation intensity interactions ($ps > .14$). These preliminary findings suggest that TMS-evoked responses are preserved across the tested acquisition rates. Data collection is ongoing, and future analyses will investigate whether EEG sampling frequency similarly preserves the time-frequency characteristics of TMS-evoked activity, helping identify optimal acquisition parameters while minimizing storage requirements and computational demands.

Disclosures: F. Feyisa: None. **N. Mora J:** None. **C. George:** None. **J. Hernandez-Pavon:** None.

Poster

SCA01: Beyond the Convention Center

Location:

Time: Monday, November 16, 2026, 8:00 AM - 5:00 PM

Program #/Poster #: SCA01/Web Only

Topic: I.03. Decision Making

Title: Beyond the Convention Center

Authors: *S. NEUROSCIENCE;
Society for Neurosci. (SfN), Washington, DC

Abstract: You've found the scavenger hunt poster! Visit this poster in the virtual component between Monday, November 16 and Wednesday, November 18 to scan the QR code.

Disclosures: S. Neuroscience: None.